Sucrose for analgesia in newborn infants undergoing painful procedures (Review)

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[Intervention Review]

Sucrose for analgesia in newborn infants undergoing painful procedures

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ABSTRACT

Background

Administration of oral sucrose with and without non-nutritive sucking is the most frequently studied non-pharmacological intervention for procedural pain relief in neonates.

Objectives

To determine the efficacy, effect of dose and safety of oral sucrose for relieving procedural pain in neonates.

Search methods

We used the standard methods of the Cochrane Neonatal Review Group. Electronic and manual searches were performed in November 2011 for published randomised controlled trials (RCTs) in MEDLINE (1950 to November 2011), EMBASE (1980 to 2011), CINAHL (1982 to November 2011) and the Cochrane Central Register of Controlled Trials (*The Cochrane Library*). We did not impose language restrictions.

Selection criteria

RCTs in which term, preterm, or both term and preterm neonates (postnatal age maximum of 28 days after reaching 40 weeks' post-menstrual age) received sucrose for procedural pain. Control conditions included no treatment, water, pacifier, positioning/containing or breastfeeding.

Data collection and analysis

Main outcome measures were physiological, behavioural, or both pain indicators with or without composite pain scores. A mean difference (MD) with 95% confidence intervals (CI) using the fixed-effect model was reported for continuous outcome measures. Trial quality was assessed as per The Cochrane Collaboration

Main results

Fifty-seven studies enrolling 4730 infants were included. Results from only a few studies could be combined in meta-analyses. When Premature Infant Pain Profile (PIPP) scores were pooled, sucrose groups had significantly lower scores at 30 seconds (weighted mean difference (WMD) -1.76; 95% CI -2.54 to - 0.97; 4 trials; 264 neonates] and 60 seconds (WMD -2.05; 95% CI -3.08 to -1.02; 3 trials' 195 neonates) post-heel lance. For retinopathy of prematurity (ROP) examinations, sucrose did not significantly reduce PIPP scores (WMD -0.65; 95% CI -1.88 to 0.59; 3 trials; 82 neonates). There were no differences in adverse effects between sucrose and control groups. Sucrose significantly reduced duration of total crying time (WMD -39 seconds; 95% CI -44 to -34; 2 trials; 88 neonates), but did not reduce duration of first cry during heel lance (WMD -9 seconds; 95% CI -20 to 2; 3 trials; 192 neonates). Oxygen saturation (%) was significantly lower in infants given sucrose during ROP examination compared to controls (WMD -2.6; 95% CI -4.9 to - 0.2; 2 trials; 62 neonates). Results of individual trials that could not be incorporated in meta-analyses supported these findings. The effects of sucrose on long-term neurodevelopmental outcomes are unknown.

Authors' conclusions

Sucrose is safe and effective for reducing procedural pain from single events. An optimal dose could not be identified due to inconsistency in effective sucrose dosage among studies. Further investigation on repeated administration of sucrose in neonates and the use of sucrose in combination with other non-pharmacological and pharmacological interventions is needed. Sucrose use in extremely preterm, unstable, ventilated (or a combination of these) neonates needs to be addressed. Additional research is needed to determine the minimally effective dose of sucrose during a single painful procedure and the effect of repeated sucrose administration on immediate (pain intensity) and long-term (neurodevelopmental) outcomes.

PLAIN LANGUAGE SUMMARY

Sucrose for analgesia in newborn infants undergoing painful procedures

Healthcare professionals need strategies to reduce newborn babies' pain. Sucrose (sugar) provides pain relief for newborn babies having painful events such as needles or heel pricks. Pain medicine is usually given for major painful events (such as surgery), but may not be given for more minor events (such as taking blood or needles). Pain medicine can be used to reduce pain but there are several other methods including sucking on a pacifier (dummy) with or without sucrose. Researchers have found that giving sucrose to babies decreases their crying time and behaviours such as grimacing. More research is needed to determine if giving repeated doses of sucrose is safe and effective, especially for very low birthweight infants or infants on respirators.

BACKGROUND

Description of the condition

Management of pain for neonates in the neonatal intensive care unit (NICU) is less than optimal (AAP 2000; Anand 2001; Carbajal 2008). Although strategies to manage pain from surgery, medical illness and major procedures exist, means to prevent or reduce pain from diagnostic procedures including heel lance and venipuncture have, until relatively recently, been lacking (Fernandes 1994; Johnston 1997b; Anand 2007).

Description of the intervention

In recent years, administration of sucrose with or without non-nutritive sucking (NNS) (e.g. pacifiers) has been a frequently studied intervention for relief of procedural pain in neonates. Sucrose has been examined for its calming effects in crying newborns (Smith 1992; Barr 1993; Barr 1994; Haynes 1995) and its pain-relieving effects for invasive procedures in term and preterm neonates (Stevens 1997a).

How the intervention might work

The effects of sucrose and NNS are thought to be mediated by both endogenous opioid and non-opioid systems (Blass 1994) but the underlying mechanisms may differ. These mechanisms

may be additive or synergistic, but most likely depend on normal functioning of central mechanisms. In a systematic review/meta-analysis of the efficacy of sucrose for procedural pain management, Stevens et al (Stevens 1997a) found that the proportion of time crying was decreased with sucrose 0.24 to 0.48 g (i.e. 2 mL of a 12% to 24% solution) administered orally two minutes prior to a painful procedure (e.g. heel lance or venipuncture).

Why it is important to do this review

This systematic review is a substantive update of the original 1998 Cochrane review and the updates completed in 2001, 2004 and 2010 (Stevens 1998; Stevens 2001; Stevens 2004; Stevens 2010).

OBJECTIVES

To determine the efficacy, effect of dose, method of administration and safety of sucrose for relieving procedural pain as assessed by physiological (heart rate (HR), respiratory rate, saturation of peripheral oxygen in the blood (SpO_2), transcutaneous oxygen and carbon dioxide (gas exchange measured across the skin - $TcpO_2$, $TcpCO_2$)), behavioural pain indicators (cry duration, proportion time crying, facial actions), validated composite pain scores, or a combination of these.

For the update in 2012, an additional objective was added: to determine the effects of sucrose used in neonates for relieving procedural pain on long-term neurodevelopmental outcomes (assessed by a standardised and validated assessment tool, a child developmental specialist, or both) at 18 to 24 months or at any later age in childhood.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) that evaluated the effect of sucrose analgesia in newborn infants undergoing painful procedures for this review. We included only published studies. We did not impose language restrictions. We did not include studies published in abstract form.

For this update, we broadened our inclusion criteria to include RCTs in which the efficacy of sucrose was assessed during any minor painful procedure (i.e. other than heel lance and venipuncture) as well as after repeated doses of sucrose.

Types of participants

We included studies assessing term, preterm, or both term and preterm neonates with maximum postnatal age of 28 days after reaching 40 weeks' postmenstrual age.

Types of interventions

Interventions included administration of sucrose via oral syringe, dropper or pacifier for treatment of procedural pain. For this update of the review inclusion criteria were extended to all studies that used sucrose as an intervention for any acute painful procedure including subcutaneous injection, circumcision, bladder catheterisation, eye examination for retinopathy of prematurity (ROP) and heel stroke. Control group conditions included breastfeeding, breast milk or milk formula, water (sterile, tap, distilled, spring), pacifier, positioning/containing or no treatment.

Types of outcome measures

Outcome measures for inclusion were individual behavioural (cry duration, proportion of time crying, facial actions), physiological (HR, respiratory rate, SpO_2, $TcpO_2$, $TcpCO_2$, cortisol levels) pain indicators, composite pain scores (including a combination of behavioural, physiological and contextual indicators) or a combination of these and any adverse effects reported. For the update in 2012, long-term neurodevelopmental outcomes (assessed by a standardised and validated assessment tool, a child developmental specialist, or both) at 18 to 24 months or at any later age in childhood were added.

Search methods for identification of studies

Electronic searches

We used the standard methods of the Cochrane Neonatal Review Group. We carried out electronic searches for relevant RCTs in MEDLINE (1950 to November 2011), EMBASE (1980 to 2011), CINAHL (1982 to November 2011) and the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 10, 2011), all EBM Reviews, ACP Journal Club, DARE, CCTR, CMR, HTA and NHSEED). Key words and MeSH terms included infant/newborn/neonate, pain and sucrose.

Searching other resources

We searched bibliographies, the most recent relevant neonatal and pain journals, and recent major paediatric pain conference proceedings manually or electronically when available. We also searched personal files. We did not include unpublished studies. Additional information from published studies was obtained if

needed. Identified abstracts are listed under excluded studies. We did not include language restrictions.

Data collection and analysis

Selection of studies

We did not include abstracts as we have identified discrepancies in numbers of infants enrolled between abstracts and final publications (Walia 1999). The types of participants were more clearly defined to include maximum postnatal age of 28 days after reaching 40 weeks' postmenstrual age. As sucrose has become more widely evaluated as an analgesic for a variety of different acute painful procedures, we no longer limited our search to those studies evaluating pain due to heel lance and venipuncture.

Data extraction and management

Two review authors extracted data separately. The data were compared and differences were resolved. Additional data were provided by investigators in four studies (Allen 1996; Johnston 1999a; Stevens 1999; Harrison 2003).

Assessment of risk of bias in included studies

The methodological quality of each study was assessed independently by the four review authors, who were not blinded to trial authors or institutions.

For this update the following issues were evaluated and entered into the 'Risk of bias' table.

1. Selection bias (random sequence generation and allocation concealment): for each included study, we categorised the risk of selection bias as:
   i) low risk - adequate (any truly random process, e.g. random number table; computer random number generator);
   ii) high risk - inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
   iii) unclear risk - no or unclear information provided.
2. Allocation concealment: for each included study, we categorised the risk of bias regarding allocation concealment as:
   i) low risk - adequate (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
   ii) high risk - inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
   iii) unclear risk - no or unclear information provided.
3. Performance bias: for each included study, we categorised the methods used to blind study personnel from knowledge of which intervention a participant received. As our study population consisted of neonates they would all be blinded to the study intervention:
   i) low risk - adequate for personnel (a placebo that could not be distinguished from the active drug was used in the control group);
   ii) high risk - inadequate personnel aware of group assignment;
   iii) unclear risk - no or unclear information provided.
4. Detection bias: for each included study, we categorised the methods used to blind outcome assessors from knowledge of which intervention a participant received. (As our study population consisted of neonates they would all be blinded to the study intervention.) Blinding was assessed separately for different outcomes or classes of outcomes. We categorised the methods used with regards to detection bias as:
   i) low risk - adequate follow-up was performed with assessors blinded to group assignment;
   ii) high risk - inadequate assessors at follow-up were aware of group assignment;
   iii) unclear risk - no or unclear information provided.
5. Attrition bias: for each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods with respect to the risk attrition bias as:
   i) low risk - adequate (< 10% missing data);
   ii) high risk - inadequate (> 10% missing data);
   iii) unclear risk - no or unclear information provided.
6. Reporting bias: for each included study, we described how we investigated the risk of selective outcome reporting bias and what we found. We assessed the methods as:
   i) low risk - adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
   ii) high risk - inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
   iii) unclear risk - no or unclear information provided (the study protocol was not available).
7. Other bias: for each included study, we described any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

i) low risk - no concerns of other bias raised;

ii) high risk - concerns raised about multiple looks at the data with the results made known to the investigators, difference in number of patients enrolled in abstract and final publications of the paper;

iii) unclear - concerns raised about potential sources of bias that could not be verified by contacting the authors.

If needed, we planned to explore the impact of the level of bias through undertaking sensitivity analyses.

Measures of treatment effect

We performed statistical analyses were using RevMan 5.1 (RevMan 2011). We analysed categorical data using risk ratio (RR), risk difference (RD) and the number needed to treat for an additional beneficial outcome (NNTB) or additional harmful outcome (NNTH). We analysed continuous data using weighted mean difference (WMD). We reported the 95% confidence interval (CI) on all estimates.

Assessment of heterogeneity

We planned to examine heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic if at least 10 studies were included in a meta-analysis. If we detected statistical heterogeneity, we planned to explore the possible causes (e.g. differences in study quality, participants, intervention regimens or outcome assessments) using post hoc subgroup analyses.

Data synthesis

We used the statistical package (RevMan 2011) provided by The Cochrane Collaboration. For meta-analyses, a mean difference (MD) with 95% CI using a fixed-effect model was reported for continuous outcome measures.

Subgroup analysis and investigation of heterogeneity

Separate comparisons were made for different painful procedures (heel lance, venipuncture, ROP examination, bladder catheterisation, nasogastric (NG) tube insertion, circumcision, subcutaneous injections) and for multiple exposures to sucrose.

RESULTS

Description of studies

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

A total of 57 studies are included in this systematic review. There were 44 studies in the 2010 updated review (Stevens 2010) and 13 additional studies were included in this current update.

For the purpose of the current updated review, the inclusion criteria were expanded to include any minor painful procedure (rather than heel lance and venipuncture only). The updated review criteria included studies that assessed the efficacy of repeated doses of sucrose.

A total of 40 studies were identified for possible inclusion in this current update. Three studies were not RCTs (Joung 2010; Harrison 2011a; Sahebihag 2011). One study examined sucrose use during diaper change (Taddio 2009).

In total, 13 studies were added in the current update (Johnston 2002; Fernandez 2003; Alsaedi 2009; Montoya 2009; Basnet 2010; O'Sullivan 2010; Ozdogan 2010; Slater 2010;Altun-Koroglu 2010; Biran 2011; Kristoffersen 2011; Yilmaz 2011; Taddio 2011). No studies assessing long-term neurodevelopmental outcomes were identified.

Included studies

A total of 57 studies (4730 infants) are included in this systematic review. Of these studies, 29 focused on term infants (Rushforth 1993; Haouari 1995; Allen 1996; Ramenghi 1996b; Blass 1997; Stang 1997; Herschel 1998; Blass 1999; Carbajal 1999; Ors 1999; Overgaard 1999; Isik 2000a; Gormally 2001; Guala 2001; Greenberg 2002; Kaufman 2002; Fernandez 2003; Ogawa 2005; Mathai 2006; Rogers 2006; Codipietro 2008; Taddio 2008; Unceta-Barranechea 2008; Basnet 2010; Ozdogan 2010; Slater 2010; Altun-Koroglu 2010; Taddio 2011; Yilmaz 2011), 27 included preterm infants only (Bucher 1995; Abad 1996; Ramenghi 1996a; Johnston 1997a; Johnston 1999a; Ramenghi 1999; Stevens 1999; Johnston 2002; Storm 2002; Harrison 2003; Acharya 2004; Boyer 2004; Mitchell 2004; Mucignat 2004;Gal 2005; Grabska 2005; Rush 2005; Stevens 2005; Boyle 2006; Okan 2007; Gaspardo 2008; McCullough 2008; Alsaedi 2009; Montoya 2009; O'Sullivan 2010; Biran 2011; Kristoffersen 2011) and one included both preterm and term infants (Gibbins 2002). Details of each study are outlined in the 'Characteristics of included studies' table.

Painful procedures

Heel lance was the most predominant painful procedure, studied in 29 trials (Rushforth 1993; Bucher 1995; Haouari 1995; Ramenghi 1996a; Ramenghi 1996b; Blass 1997; Johnston 1997a; Blass 1999; Johnston 1999a; Ors 1999; Overgaard 1999; Ramenghi 1999; Stevens 1999; Isik 2000a; Gormally 2001; Guala 2001; Gibbins 2002; Greenberg 2002; Storm 2002; Harrison 2003; Stevens 2005; Mathai 2006; Okan 2007; Codipietro 2008; Unceta-Barranechea 2008; Ozdogan 2010; Slater 2010; Altun-Koroglu 2010; Yilmaz 2011). Six studies involved infants

undergoing an examination for ROP (Mitchell 2004; Gal 2005; Grabska 2005; Rush 2005; Boyle 2006; O'Sullivan 2010). In nine studies, infants were observed during venipuncture (Abad 1996; Carbajal 1999; Acharya 2004; Gaspardo 2008; Alsaedi 2009; Montoya 2009; Basnet 2010; Biran 2011;Taddio 2011) and one study assessed both heel lance and venipuncture (Ogawa 2005). In two studies, infants were assessed during subcutaneous injections (Allen 1996; Mucignat 2004) and in three studies (Johnston 2002; Boyer 2004; Taddio 2008) all painful procedures were assessed. Taddio 2008 assessed infants during a combination of intramuscular injections, venipunctures and heel lances. Three studies involved circumcision (Stang 1997; Herschel 1998; Kaufman 2002), one study involved the effectiveness of sucrose for pain during bladder catheterisations (Rogers 2006), two studies were conducted to assess sucrose analgesia during NG tube insertion (McCullough 2008; Kristoffersen 2011) and one study investigated infants response during a heel stroke (Fernandez 2003).

Outcome measures

Cry behaviour was assessed in 35 studies (Rushforth 1993; Bucher 1995; Haouari 1995; Abad 1996; Allen 1996; Ramenghi 1996a; Ramenghi 1996b; Blass 1997; Johnston 1997a; Ramenghi 1999; Blass 1999; Ors 1999; Overgaard 1999; Isik 2000a; Greenberg 2002; Kaufman 2002; Storm 2002; Harrison 2003; Acharya 2004; Mucignat 2004; Grabska 2005; Ogawa 2005; Rush 2005; Mathai 2006; Rogers 2006; Okan 2007; Codipietro 2008; Gaspardo 2008; McCullough 2008; Unceta-Barranechea 2008; Basnet 2010; Ozdogan 2010; Altun-Koroglu 2010; Taddio 2011; Yilmaz 2011). In 31 studies the effect of sucrose on changes in HR/vagal tone was evaluated (Bucher 1995; Haouari 1995; Abad 1996; Ramenghi 1996a; Ramenghi 1996b; Herschel 1998; Blass 1999; Ors 1999; Overgaard 1999; Isik 2000a; Gormally 2001; Guala 2001; Greenberg 2002; Storm 2002; Harrison 2003; Acharya 2004; Mucignat 2004; Grabska 2005; Rush 2005; Mathai 2006; Okan 2007; Codipietro 2008; Gaspardo 2008; McCullough 2008; Alsaedi 2009; O'Sullivan 2010; Ozdogan 2010; Slater 2010; Altun-Koroglu 2010; Taddio 2011; Yilmaz 2011). SpO_2 was reported in 15 studies (Abad 1996; Johnston 1997a; Herschel 1998; Overgaard 1999; Harrison 2003; Acharya 2004; Mucignat 2004; Gal 2005; Grabska 2005; Rush 2005; Mathai 2006; Okan 2007; Codipietro 2008; McCullough 2008; Alsaedi 2009). Respiratory rate was measured in five of these studies (Abad 1996; Grabska 2005; Rush 2005; Alsaedi 2009; Yilmaz 2011) and in one study, $TcpO_2$ and $TcpCO_2$ were reported (Bucher 1995). In one study, the intensity of sucking in infants who received sucrose was compared to those who received water (Ramenghi 1996a). The effect of sucrose on nociceptive-specific brain activity and nociceptive withdrawal activity was assessed in one study (Slater 2010).

Unidimensional and multidimensional behavioural pain measures were reported in 16 studies, while composite pain measures were used in 17 studies. Of the studies that evaluated pain intensity using composite pain measures, 13 used the Premature Infant Pain Profile (PIPP; Stevens 1996) (Johnston 1999a; Stevens 1999; Gibbins 2002; Mitchell 2004; Gal 2005; Grabska 2005; Stevens 2005; Boyle 2006; Codipietro 2008; Taddio 2008; Alsaedi 2009; Slater 2010; Kristoffersen 2011).

In 16 studies, adverse effects were evaluated. In six of these studies, minor and not clinically important adverse effects were observed.

Risk of bias in included studies

Thirty studies (53%) reported that the allocation sequence was adequately generated. In 23 studies (40%), allocation was adequately concealed. Blinding of participants, personnel and outcome assessors was adequately presented in 37 studies (65%). In these studies we reported whether sucrose, water solutions and outcomes were blinded. Incomplete outcome data were adequately addressed in 40 studies (70%).

Few researchers provided a definition of pain or how it was conceptualised in relation to the outcomes. There were differences in study methods. Heel lance was studied as the pain stimulus in the majority of studies. However, little detail about this procedure (e.g. manual versus automated lance) was provided. Therefore, it is impossible to know if the painful stimuli were comparable in intensity, duration or frequency across studies. The length of infant observation following the heel lance was infrequently reported and may have implications for the incidence of reported adverse effects.

The delivery method of sucrose differed between studies (syringe, dropper or sucrose-dipped pacifier). Outcomes were reported inconsistently; as means with standard deviations (SD) or standard errors (SE), medians with ranges and often in graphic form without reporting numerical data.

Effects of interventions

Inconsistencies in outcome measures and differences in the statistical reporting of results existed across studies, preventing the use of comprehensive meta-analytic techniques. In this review update there were no categorical data reported that could be used in a meta-analyses. The results were reported by painful procedure for each accepted study separately. Descriptions of the outcomes for each are presented in Table 1; Table 2; Table 3; Table 4; Table 5; Table 6; Table 7; Table 8; Table 9 and Table 10.

Effectiveness of sucrose for heel lance

1. Crying behaviour

A meta-analysis was performed for three studies (Harrison 2003; Ogawa 2005; Mathai 2006) (192 infants) where the mean duration of first cry (seconds) with heel lance was assessed (Figure

1). Using a fixed-effect approach, no significant heterogeneity was found between studies (I^2 = 0%). Duration of crying was not significantly reduced in infants who were administered sucrose (dose range: 2 mL of 12.5% to 2 mL of 50% sucrose) compared to the control groups (WMD -8.99 seconds; 95% CI -20.07 to 2.10). When combining two studies (Isik 2000a; Mathai 2006) (N = 88) that evaluated total crying time, there was substantial heterogeneity (I^2 = 94%). Mean duration of crying was significantly reduced in infants who received sucrose (dose range 2 mL of 20% to 30% sucrose) (WMD -39.26 seconds; 95% CI -44.29 to -34.24) (Figure 2).

Figure 1. Forest plot of comparison: 3 Heel lance: sucrose 20-50% vs. control (sterile water), outcome: 3.1 Duration of first cry (s).

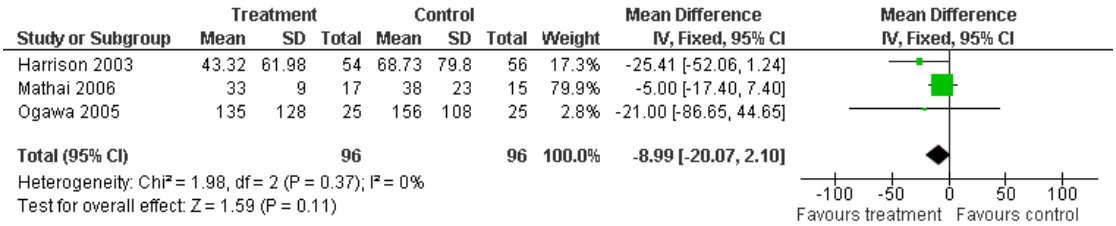
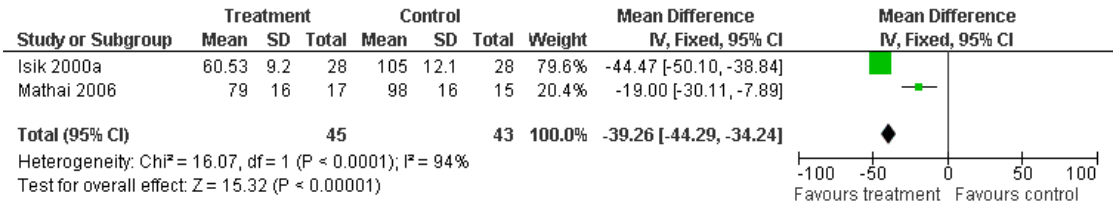


Figure 2. Forest plot of comparison: 3 Heel lance: sucrose 20-50% vs. control (sterile water), outcome: 3.2 Total crying time (s).



Sucrose significantly reduced crying time in 18 studies evaluating pain at heel lance (Bucher 1995; Haouari 1995; Ramenghi 1996a; Ramenghi 1996b; Blass 1997; Blass 1999; Ors 1999; Overgaard 1999; Ramenghi 1999; Isik 2000a; Gormally 2001; Greenberg 2002; Storm 2002; Harrison 2003; Ogawa 2005; Okan 2007; Unceta-Barranechea 2008; Yilmaz 2011).

Significant reductions in crying during the first three minutes following heel lance were found in groups receiving low concentrations (2 mL of 12% sucrose) (Blass 1997; Blass 1999; Greenberg 2002) as well as higher concentrations (2 mL of 50%) of sucrose solution (Ramenghi 1996b).

In a study of 101 term infants who received 1 mL of 25% sucrose solution compared to breastfeeding, Codipietro 2008 reported a statistically significant reduction in the median duration of first cry (P = 0.004), per cent crying during heel lance (P = 0.0003) and per cent crying in the first two minutes after heel lance (P < 0.001) in favour of breastfeeding.

2. Quality of sucking

One study evaluated the quality of sucking as an outcome measure. Ramenghi 1996b reported that the quality of sucking was significantly more intense in infants who received 1 mL of 25% (0.25 g) sucrose compared to those in the control group (P = 0.04) during and after heel lance.

3. Grimace

Blass 1999 evaluated grimacing in term infants undergoing heel lance. In this study, the proportion of time grimacing was significantly reduced in infants who received 2 mL of 12% (0.24 g) sucrose alone compared with water (P = 0.0003), as well as infants in the sucrose with pacifier group compared to water alone (P = 0.001) and pacifier alone (P = 0.04) groups.

4. Physiological outcomes

When results for change in HR were pooled for two studies involving heel lances (Haouari 1995; Isik 2000a) (86 infants), statistically significant heterogeneity (I^2 = 86%) was found between the studies at one minute after heel lance (Figure 3) and no heterogeneity (I^2 = 0) between the studies at three minutes after heel lance (Figure 4). There were no significant differences in per cent change in HR for infants given sucrose (dose range 0.5 g to 0.6 g) compared to the control group at one minute (WMD 0.90; 95% CI -5.81 to 7.61) and three minutes (WMD -6.20; 95% CI -15.27 to 2.88) after heel lance. The results for two additional studies (Guala 2001; Harrison 2003) (154 infants) were combined for HR at three minutes post-heel lance and no heterogeneity was found (I^2 = 0) between the studies. The overall effect of sucrose was not significant (WMD -0.98; 95% CI -8.29 to 6.32) (Figure 5). In 9 studies, sucrose significantly reduced HR or vagal tone at heel lance (Bucher 1995; Haouari 1995; Ramenghi 1996b; Blass 1999; Ors 1999; Isik 2000a; Gormally 2001; Greenberg 2002; Okan 2007).

Figure 3. Forest plot of comparison: 2 Heel lance: sucrose 25-33% vs. control (sterile water), outcome: 2.1 % change in heart rate one minute after heel lance.

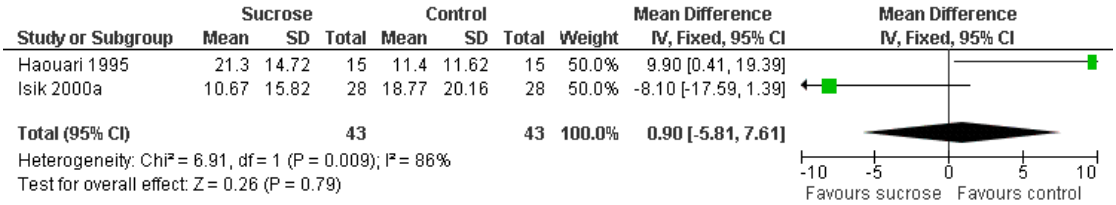


Figure 4. Forest plot of comparison: 2 Heel lance: sucrose 25-33% vs. control (sterile water), outcome: 2.2 % change in heart rate three minutes after heel lance.

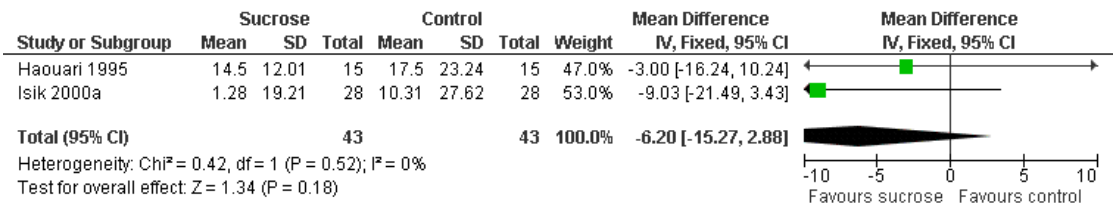
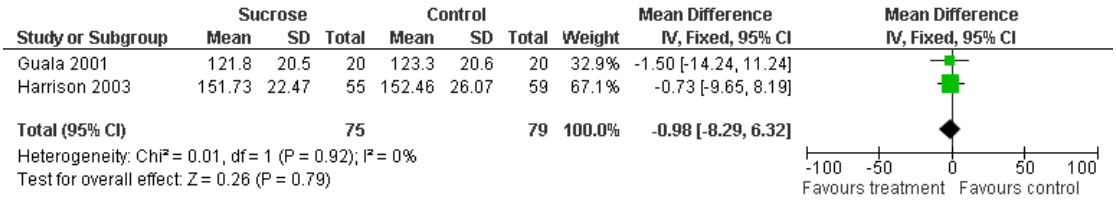


Figure 5. Forest plot of comparison: 2 Heel lance: sucrose 25-33% vs. control (sterile water), outcome: 2.3 Heart rate at three minutes after heel lance.



Findings differed in two studies where vagal tone was assessed (Gormally 2001; Greenberg 2002). Gormally 2001 reported no significant main effects of sucrose whereas Greenberg 2002 found a lower vagal tone during heel lance in the sucrose-dipped pacifier group compared to the control group (P = 0.008) and the oral sucrose group (P = 0.018). The sucrose-dipped pacifier group had a lower vagal tone index than the control group at heel lance (P = 0.019).

Of the six studies where the effects of sucrose on SpO_2 and respiratory rates were assessed at heel lance, there were no significant differences between groups in five studies (Bucher 1995; Overgaard 1999; Harrison 2003; Mathai 2006; Okan 2007). Codipietro 2008 reported that infants who received 1 mL of a 25% sucrose solution had a median decrease in SpO_2 levels from baseline to 30 seconds after the start of a heel lance that was significantly greater (median -3; range -30 to 1) compared to the breastfeeding group (median -1; range -14 to 2) (P = 0.001).

Only Greenberg 2002 measured salivary cortisol levels as markers of pain/stress in infants during heel lance. There were no significant differences between treatment and control groups in cortisol levels.

5. Unidimensional single and multiple domain pain measures

In 8 out of 9 studies utilising unidimensional pain scales to assess pain at heel lance, sucrose was statistically favoured when measuring pain with the Neonatal Facial Coding System (NFCS) (Johnston 1997a; Harrison 2003; Ogawa 2005; Okan 2007), and a pain scale using four facial expressions and the presence of cry (Ramenghi 1996a; Ramenghi 1996b; Ramenghi 1999). In one study using a multidimensional pain scale, the Douler Aigue Du Nouveau-ne (DAN) (Mathai 2006), sucrose was also statistically favoured.

In one study (Gormally 2001) using pain concatenation scores for facial activity pre-heel lance, and at one, two and three minutes post-heel lance, there was no significant effect of sucrose reported (test of main effect F[1,65] 0.17, P = 0.68).

6. Multidimensional composite pain measure

Seven of eight studies assessing pain intensity with composite measures at heel lance favoured sucrose. Six studies used PIPP (Johnston 1999a; Stevens 1999; Gibbins 2002; Stevens 2005; Codipietro 2008; Slater 2010), which is a validated pain measure that includes behavioural (three facial expressions), physiological (HR and SpO_2) and contextual (gestational age and behavioural state) indicators (Stevens 1996). Sucrose doses in these studies ranged from 0.05 to 2 mL of a 24% or 25% solution. In all five studies, sucrose significantly reduced PIPP scores.

When PIPP scores were pooled across four studies involving heel lances (Johnston 1999a; Stevens 1999; Gibbins 2002; Slater 2010), no statistically significant heterogeneity (I^2 = 0%) was found. PIPP scores were significantly reduced in infants who received sucrose (dose range 0.012 to 0.12 g) compared to the control group at 30 seconds (WMD -1.76; 95% CI -2.54 to - 0.97; 264 infants) and 60 seconds (WMD -2.05; 95% CI -3.08 to -1.02; 195 infants) after heel lance in three studies (Johnston 1999a; Stevens 1999; Gibbins 2002) (Figure 6; Figure 7).

Figure 6. Forest plot of comparison: 1 Heel lance: sucrose (sucrose or sucrose+NNS) vs. control (NNS+water, water or positioning and containing intervention), outcome: 1.1 Premature Infant Pain Profile (PIPP) at 30 seconds after heel lance.

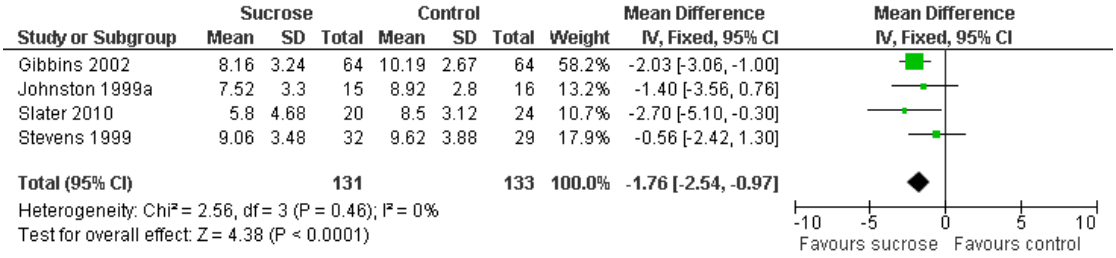
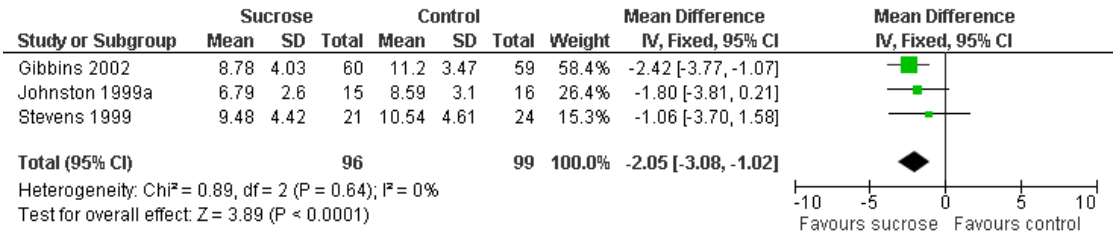


Figure 7. Forest plot of comparison: 1 Heel lance: sucrose (sucrose or sucrose+NNS) vs. control (NNS+water, water or positioning and containing intervention), outcome: 1.2 Premature Infant Pain Profile (PIPP) at 60 seconds after heel lance.



Overgaard 1999 and Yilmaz 2011 used the Neonatal Infant Pain Scale (NIPS), which is composed of behavioural and physiological indicators, to assess pain intensity in infants. Significantly lower NIPS scores were reported in infants who received sucrose versus the comparison group(s).

7. Cortical pain Indicators

Slater 2010 found no significant differences in the nociceptive brain activity measured with neonatal electroencephalography (EEG) or magnitude or latency of the spinal nociceptive reflex withdrawal measured with electromyography (EMG) between neonates given sucrose versus sterile water.

Effectiveness of sucrose for ROP examinations

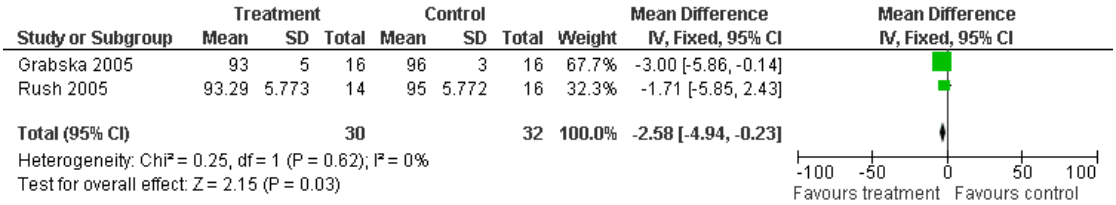
1. Crying behaviours

Grabska 2005 and Rush 2005 assessed the effect of administering 24% sucrose on crying behaviour during ROP examinations. Grabska 2005 adjusted sucrose doses by the weight of the infants, while Rush 2005 administered pacifier dipped in 24% sucrose. In both studies, no significant differences in crying behaviour were found between treatment and control groups.

2. Physiological outcomes

Results from two studies (Grabska 2005; Rush 2005) (N = 62) measuring SpO_2 during ROP examinations were pooled (Figure 8). No statistically significant heterogeneity was found between the studies (I^2 = 0%). Twenty-four per cent sucrose was adjusted by weight in one study (Grabska 2005) and administered on a pacifier dipped in sucrose in another study (Rush 2005). SpO_2 was significantly reduced in infants given sucrose compared to the control group (WMD -2.58; 95% CI -4.94 to -0.23).

Figure 8. Forest plot of comparison: 7 ROP examination: sucrose 24-33% (sucrose or sucrose+NNS) vs. control (water or water+NNS), outcome: 7.1 Oxygen saturation (%) during eye examination.



Two studies assessed changes in HR during and after ROP examinations (Grabska 2005; Rush 2005). There were no significant differences between sucrose and control groups in either study.

In three studies, SpO_2 was measured during and after ROP examinations (Gal 2005; Grabska 2005; Rush 2005). Only Grabska 2005 found significant differences in SpO_2 between sucrose and control groups during the examination; however, the differences were not significant at two minutes after the examination.

3. Multidimensional composite pain measure

Four of the five studies assessing pain using composite measures used the PIPP as an outcome measure (Mitchell 2004; Gal 2005; Grabska 2005; Boyle 2006). Boyle 2006 and Grabska 2005 found no significant difference between sucrose and control groups regarding PIPP scores. Gal 2005 and Mitchell 2004 found that sucrose significantly reduced PIPP scores during ROP examinations (P = 0.001 and 0.0077, respectively), but the analgesic effects were not sustained after the examination. Significantly lower Neonatal Pain, Agitation and Sedation Scale (N-PASS) scores (6.5 versus 5.0) at speculum insertion in sucrose compared to control groups (P = 0.02) and during the procedure (9.5 versus 7.5; P = 0.03) were reported in one study (O'Sullivan 2010).

PIPP scores were pooled in two studies (N = 52) where infants who received either water or sucrose (24% to 33%) via syringe prior to ROP examinations were observed (Grabska 2005; Boyle 2006). There was no heterogeneity between the studies (I^2 = 0%) and the overall effect of sucrose was not significant (WMD -0.65; 95% CI -1.88 to 0.59).

Effectiveness of sucrose for venipuncture

1. Crying Behaviours

Crying duration was assessed at venipuncture in six studies (Abad 1996; Acharya 2004; Ogawa 2005; Gaspardo 2008; Basnet 2010; Taddio 2011); Abad 1996 and Acharya 2004 reported that sucrose significantly reduced crying duration (P < 0.05 and < 0.001, respectively). In the study by Ogawa 2005, there were no significant differences in sucrose and control groups for infants undergoing venipuncture.

2. Physiological outcomes

In five studies, HR during and after venipuncture was evaluated as an outcome measure (Abad 1996; Acharya 2004; Gaspardo 2008; Basnet 2010; Taddio 2011). In two studies (Abad 1996; Acharya 2004) there was a significant reduction in HR in groups receiving 2 mL of 12% to 25% sucrose up to five minutes post-venipuncture. However, in Abad 1996, groups receiving 2 mL of 12% sucrose had lower HR than those receiving 2 mL of 24% sucrose or water. Four studies assessed SpO_2 during and after venipuncture (Abad 1996; Acharya 2004; Rush 2005; Taddio 2011). All studies reported no significant differences between sucrose and control groups.

3. Unidimensional single and multiple domain pain measures

The NFCS was used in three studies (Acharya 2004; Ogawa 2005; Gaspardo 2008), and the DAN was used in three studies (Carbajal 1999; Basnet 2010; Biran 2011) evaluating pain at venipuncture. One study favouring sucrose assessed grimace using three facial expressions (brow bulge, eye squeeze and nasolabial furrow) (Taddio 2011). Six studies reported that sucrose (dose range of 0.5 mL to 2 mL of 12% to 30% solution with or without pacifier significantly reduced pain scores (Carbajal 1999; Acharya 2004; Ogawa 2005; Basnet 2010; Biran 2011; Taddio 2011).

4. Multidimensional composite pain measure

Two studies included composite pain measures. Alsaedi 2009 used the PIPP and Montoya 2009 used the NIPS. In both studies, sucrose reduced pain scores versus the comparison groups.

Effectiveness of sucrose for bladder catheterisation

1. Crying behaviours

Rogers 2006 examined the use of 24% sucrose during bladder catheterisation and found that a subgroup of infants (1 to 30 days of age) who received sucrose were significantly less likely to cry during maximal catheterisation insertion compared to infants who received water (29% versus 78%; P = 0.008). Infants older than 30 days did not show significant differences in crying when given sucrose versus water.

2. Unidimensional single and multiple domain pain measures

In the same study by Rogers 2006, infants one to 30 days of age receiving 2 mL of 24% sucrose had significantly lower DAN scores than the group receiving water.

Effectiveness of sucrose for circumcision

1. Crying behaviours

Kaufman 2002 assessed infants who were given a pacifier dipped in 24% sucrose as an adjunct therapy for circumcision pain for two different circumcision clamping methods (Gomco and Mogen). The cumulative crying time in the Gomco-sucrose group was significantly lower than the Gomco-water group (53 seconds versus 86 seconds; P = 0.0001).

2. Grimace

Kaufman 2002 observed the time spent grimacing by infants undergoing circumcision by two different clamping methods (Gomco and Mogen). A significant reduction in grimacing was found in the Gomco-sucrose group compared to the Gomco-water group (P = 0.0001).

3. Physiological outcomes

When Herschel 1998 administered pacifiers dipped in 50% sucrose for circumcision, HRs were significantly higher by 10 to 15 beats per minute in the control group compared to the sucrose group (P < 0.03) during dorsal clamping of the foreskin using the Gomco method. Herschel 1998 also reported that the use of pacifiers dipped in 50% sucrose resulted in lower changes in baseline SpO_2 compared to the control group (P = 0.05); however, this difference was not clinically significant.

Stang 1997 measured plasma cortisol levels a marker of pain/stress in infants during circumcision. No significant differences between treatment and control groups in cortisol levels were reported.

Effectiveness of sucrose for subcutaneous injections

1. Crying behaviours

Crying time was significantly lowered (P = 0.002) in a study of infants who were administered a combination of EMLA (eutectic mixture of local anaesthetics; contains lidocaine 2.5% and prilocaine 2.5%), sucrose and pacifier compared to groups who were given a pacifier alone, pacifier plus EMLA, and pacifier plus sucrose for subcutaneous injections (Mucignat 2004). Another study assessing pain during subcutaneous injections found that 2 mL of 12% sucrose significantly reduced crying time compared to water and no treatment (P < 0.01 for both comparisons) (Allen 1996).

2. Physiological outcomes

Mucignat 2004 did not find a significant difference in HR between treatment and control groups. In the same study, SpO_2 during subcutaneous injections in the pacifier only group was significantly lower than infants who were given 0.5 mL of a 30% sucrose solution plus pacifier, EMLA plus pacifier and sucrose plus EMLA plus pacifier (P = 0.02).

3. Unidimensional single and multiple domain pain measures

Mucignat 2004 found significant results for the effectiveness of sucrose during subcutaneous injection using both the DAN and NFCS scales; however, P values were not reported.

Effectiveness of sucrose for NG-tube insertion

1. Physiological outcomes

In two studies (McCullough 2008; Kristoffersen 2011), pain was assessed during and after NG-tube insertion. McCullough 2008 reported no significant differences in HR and SpO_2 between sucrose and water groups during and after NG-tube insertion.

2. Unidimensional single and multiple domain pain measures

In the study by McCullough 2008, the NFCS was used to assess pain during NG-tube insertion; 0.5 to 2 mL of 24% sucrose (dose administered according to weight) was reported to significantly reduce NFCS scores compared to sterile water (P = 0.004).

3. Multidimensional composite pain measure

Kristoffersen 2011 reported a significant reduction in PIPP scores in preterm infants who were given 0.2 mL 30% sucrose plus pacifier compared to no treatment.

Effectiveness of sucrose for multiple procedures

1. Multidimensional composite pain measures

Taddio 2008 assessed infants during intramuscular injections, venipunctures and heel lances and reported that overall, PIPP scores were significantly lower among newborns given sucrose (mean 6.8; SD 2.9) compared to placebo (mean 8.1; SD 2.5) (MD -1.3; 95% CI -2.0 to -0.6; P < 0.001).

Adverse effects

Sixteen studies (Ramenghi 1996a; Carbajal 1999; Stevens 1999; Guala 2001; Gibbins 2002; Acharya 2004; Gal 2005; Grabska 2005; Stevens 2005; Rogers 2006; Codipietro 2008; McCullough 2008; Taddio 2008; O'Sullivan 2010; Biran 2011; Taddio 2011) evaluated adverse effects of sucrose compared to placebo. Six of these studies (Gibbins 2002; Grabska 2005; Stevens 2005; McCullough 2008; Taddio 2008; O'Sullivan 2010) observed minor side effects in infants. Gibbins 2002 described minor adverse effects in six infants, none of which occurred in the sucrose with pacifier group. One neonate who received water with pacifier choked when administered the water and stabilised within 10 seconds. Three infants randomised to the sucrose group and two infants randomised to the water with pacifier groups experienced oxygen desaturation when the study intervention was administered. Each neonate recovered spontaneously with no medical interventions required. Grabska 2005 confirmed choking and oxygen desaturation as possible adverse effects of administering sucrose for pain. McCullough 2008 reported that there was no significant difference between the sucrose and control groups regarding adverse effects; the investigators observed brief apnoea or self-limiting bradycardia in some infants, but none required clinical intervention. Stevens 2005 reported that the adverse events related to repeated use of sucrose over the first 28 days of life were "low" and all immediate adverse events resolved spontaneously. Taddio 2008 reported no significant differences between groups in blood glucose levels monitored during the study as well as the incidence of spitting up the sucrose solution. Lastly, O'Sullivan 2010 reported that four neonates in the water group and one neonate in the sucrose group experienced oxygen desaturation or bradycardia.

Repeated doses of sucrose

Repeated dosing of sucrose was addressed in five studies (Boyer 2004; Mucignat 2004; Stevens 2005; Gaspardo 2008; Taddio 2008). Boyer 2004 studied infants who received 0.1 to 0.3 mL of 24% sucrose or sterile water for every painful procedure over the first week of life. No significant differences were found in salivary cortisol levels in infants who received sucrose compared to sterile water. Gaspardo 2008 assessed 17 preterm infants receiving 0.5 mL/kg of 25% sucrose prior to every minor painful procedure over a period of four days. Infants in the sucrose group had significantly fewer facial expressions than the control group (N = 16) on the second and third assessment days and less crying on the second, third and fourth day of assessment compared to the control group. The authors concluded that sucrose was efficacious and safe when administered over a three-day period. Mucignat 2004 reported that in 33 preterm infants who received 265 subcutaneous injections of erythropoietin over a six-week period, that the use of 0.2 to 0.5 mL of 30% sucrose solution with pacifier and EMLA was more effective than each of the interventions alone. Stevens 2005 reported that administration of 24% sucrose for all painful procedures over the first 28 days of life was more effective compared to standard care (positioning and swaddling) in preterm infants. Taddio 2008 studied newborns of diabetic and non-diabetic mothers who received 2 mL of 24% sucrose for intramuscular injection of vitamin K, venipunctures for newborn screening tests and the first three heel lances for glucose testing. Sucrose was found to be effective during venipunctures only when compared to control groups.

Effects of sucrose on long-term neurodevelopmental outcomes

No studies reporting on long-term neurodevelopmental outcomes (assessed by a standardised and validated assessment tool, a child developmental specialist, or both) at 18 to 24 months or at any later age in childhood were identified.

DISCUSSION

In this systematic review update that included 13 new studies, the efficacy of sucrose analgesia was assessed on a broad range of painful procedures undertaken on infants hospitalised in the NICU including heel lance, venipuncture, bladder catheterisation, circumcision, ophthalmology examination, NG-tube insertion and subcutaneous injection.

The strength of the studies reviewed was in their design. Most studies were carefully planned prospective RCTs with a control group and one or more treatment interventions. Several studies were excluded as the method of allocation, the number of infants in each condition (intervention group), or both were not clearly stated. Attempts were made to decrease heterogeneity in meta-analyses by pooling studies that were similar in terms of type of painful procedure and volume and concentration of solution used. Within and between-study variability is inherent in the performance of a painful procedure. Other sources of heterogeneity might include volume and concentration of the solution administered, neonatal age and methodological differences across studies. Subgroup analysis to explore heterogeneity was not performed as there were too few studies to conduct such analyses.

Sucrose was effective in reducing crying behaviours, grimacing, vagal tone, and unidimensional, multidimensional and composite pain scores during heel lance in volumes and concentrations ranging from 0.5 to 2 mL of 12% to 50% solution. Some effectiveness

of sucrose administration was evident during venipuncture with respect to reducing HR, unidimensional and multidimensional composite pain scores. The effectiveness of sucrose use for ROP examinations was less clear. Based on existing data, sucrose does not appear to be effective for ROP. In fact, SpO_2 was reduced as a result of sucrose administration during ROP examinations. For other painful procedures, such as bladder catheterisation, subcutaneous injections, N/G tube insertions and circumcision, there were few studies and conflicting results. For procedures of longer duration, such as ROP examinations, bladder catheterisation, N/G tube insertions and circumcision, multiple doses of sucrose or sucrose combined with other pharmacological and non-pharmacological interventions may be required to achieve an effect. Some support exists for the use of repeated doses of sucrose for painful procedures within the first several days of life up to the first seven weeks of life; however, further studies are required to determine which procedures and at what concentration and dose would be effective on repeated occasions.

Crying remains the most widely used indicator for pain intensity in infants, followed by changes in HR, composite pain measures, unidimensional behavioural pain measures and SpO_2. The NFCS and DAN were the most commonly used validated unidimensional and multidimensional behavioural pain assessment measures (respectively), while the PIPP was the most frequently used composite (including physiological, behavioural and contextual indicators) measure. The wide variety of outcome measures and differences in the timing of outcome assessments precluded inclusion of most studies in meta-analyses. Meta-analyses resulted in statistically significant reductions in crying but also SpO_2 (which is a negative result); however, these results should be interpreted with caution as there was significant heterogeneity between studies (crying) or the combined sample in the treatment and control groups was small (SpO_2).

In our previous reviews (Stevens 2001; Stevens 2004; Stevens 2010), we reported inconsistency in effective sucrose dosage, although a dose range of 0.012 to 0.12 g was identified. Johnston 1997a and Stevens 1999 identified that very small volumes of 24% sucrose (estimated at 0.01 to 0.02 g) significantly reduced pain. However, in the meta-analyses by Stevens (Stevens 1997a), 0.18 g of sucrose was ineffective in reducing crying and did not differ from the control solution (water). Doses of 0.24 g or greater were most effective; there was some additional benefit of administering 0.48 to 0.50 g sucrose, but effectiveness did not increase when sucrose doses greater than 0.50 g were administered. In this updated review, there was a significant reduction in PIPP scores using sucrose doses 0.012 to 0.12 g (0.05 to 0.5 mL of 24% sucrose solution) at 30 and 60 seconds after heel lance and 0.12 g (0.5 mL) prior to ROP examinations. In these studies, there was a 1- to 2-point reduction in the PIPP score. Shah 2004 report that clinicians and researchers consider a 20% reduction in pain as the minimal clinically important difference, although other researchers suggest a 10% reduction may suffice for this difference (Powell 2001). Lemyre 2006 used a 3-point reduction on the PIPP scale as being clinically meaningful; however, a rationale for this decision was not reported. Determining the level of clinical improvement is challenging to measure in infants, given their inability to self report their pain and what level of improvement could truly make significant differences either in treatment strategy or the affective component of pain (i.e. how bad pain makes you feel). Only minor adverse events that resolved spontaneously have been reported (Gibbins 2002).

The greatest analgesic effect occurs when sucrose is administered approximately two minutes before the painful stimulus. This interval is thought to coincide with the release of endogenous opioids (Blass 1994). Johnston 1999a reported increased analgesia when sucrose solution was repeatedly administered in small aliquots (i.e. 0.05 mL of 24% sucrose) at two-minute intervals throughout the painful procedure. The peak effect appears to occur at two minutes and lasts approximately four minutes; therefore, the analgesic effect may wear off if procedures are prolonged. Factors such as the infant's postnatal age may influence the effectiveness of sucrose (Taddio 2008).

Adverse effects of sucrose were evaluated in 16 studies. In the study that most carefully observed for adverse events (Gibbins 2002), only six infants (3%) experienced minor side effects (e.g. oxygen desaturation, choking), which resolved spontaneously without intervention. It is not clear whether investigators in other studies carefully monitored for adverse effects and for how long. Reporting on the incidence of any adverse effects of single or repeated administration of sucrose needs to be undertaken in both term and preterm infants. Willis 1977 reported that frequent (eight to 12 times per day) small volumes (0.5 to 1 mL) of 20% sucrose concentration (mixed with calcium lactate and given 20 minutes prior to gavage feeding) could contribute to necrotising enterocolitis (NEC) in very low birthweight infants. Since the sample size and methodological rigor of this study was limited, specific attention to the efficacy and safety of sucrose administration in extremely-low birthweight preterm infants needs to be further investigated.

Stevens 2005 found no significant differences in incidence rates for NEC between infants who received repeated doses of sucrose over 28 days of life compared to control groups. Johnston 2002 studied 107 preterm infants less than 31 weeks' postmenstrual age where 1 mL of 24% sucrose or sterile water was administered to infants up to three times, two minutes apart, for all painful procedures over a seven-day period. Johnston indicated that higher frequency of sucrose doses was predictive of lower awareness, orientation, motor development and vigour at 36 weeks, and lower motor development and vigour at 40 weeks. At two weeks' postnatal age, a higher number of doses of sucrose were predictive of higher Neuro-Biological Risk Score (NBRS) scores. Proposed explanations were that: (a) low neurodevelopmental scores could be

related to infants receiving sucrose during the one-week study period only, and ongoing exposure to painful procedures might have resulted in heightened sensitivity to pain; or (b) the sample size was inadequate to identify other explanatory variables. However, on further analysis of these data, 10 or fewer doses of sucrose over a 24-hour period were less likely to be related to poorer neurodevelopmental scores (Johnston 2007). Stevens 2005 reported no statistically significant differences between sucrose plus pacifier, water plus pacifier, or the standard care group on neurobiological risk status outcomes.

Generally, infants in this review were healthy and very few were less than 27 weeks' gestational age at birth. Although the preterm infant's pain response is generally consistent with that of the term infant, it is often more subtle, less sustained and affected by the infant's behavioural state and severity of illness (Gibbins 2008). There was no significant difference found in this systematic review between the crying outcomes in term and preterm infants; however, the incidence of crying following painful stimuli is reported to be 50% less in preterm infants compared to term infants (Stevens 1994); therefore, crying is questioned as a reliable indicator of pain in the preterm infant population and is precluded as an indicator in many validated infant pain measures.

Few researchers provided a definition or conceptualisation of pain in relation to the outcomes. If the reported outcomes reflect the investigators' conceptualisation of pain, then we can assume that most investigators considered proportion, percentage or duration of time crying to be the most valid indicator of pain in neonates. Few investigators used validated pain measures or multidimensional approaches to pain assessment that reflect a more comprehensive conceptualisation of pain. Although research on infant crying has delineated certain crying characteristics, such as pitch, intensity, melody and harmonics, as being good indicators of pain, these were not assessed in the sucrose studies reviewed. Cry duration may give some indication of distress. However, cry duration does not necessarily confirm or deny that the infant is in pain. For unstable and ventilated infants who do not cry following painful procedures, cry may be an inappropriate outcome. Attempts at cry or a silent cry in ventilated infants may be more reasonable to consider. A multivariate approach or composite pain score would be a more valid approach (Stevens 1997c).

The majority of researchers studied heel lance as the painful procedure. However, little detail about this procedure (e.g. type of lancet used, number of attempts, number of squeezes, duration of the procedure) was provided. Therefore, it was impossible to determine if the painful stimuli (or painful procedures) were comparable in intensity, duration or frequency between studies. Similarly, details on other procedures (e.g. subcutaneous injections, ROP examinations, bladder catheterisations and circumcision) and comforting interventions (e.g. containment, bundling, tucking or positioning) that could provide comfort to the infant and act as co-interventions would be desirable. The length of observation and return to baseline parameters (e.g. HR) of infants following the procedures was also not reported frequently.

The delivery method of sucrose varied between studies. Sucrose was delivered by syringe, dropper or pacifier. The pacifier promotes NNS and calming that may contribute to reducing pain-elicited distress (Campos 1994). Blass 1994 suggests that sucking exerts a profound behavioural effect and induces feelings of calm. Other researchers have found that NNS reduces HR and metabolic rate, causes infants to self-soothe and elevates the pain threshold. However, contact has not been shown to affect cortisol response, HR, vagal tone and SpO_2 (DiPietro 1994; Gunnar 1992). The calming effects are not sustained following cessation of the contact. This is in contrast to sucrose administration where the effects persist beyond the cessation of contact for several minutes. Blass and Hoffmeyer (Blass 1991) examined the combined effectiveness of sucrose and pacifiers and reported that physiological and behavioural changes resulted from both sucrose and non-nutritive interventions. Results from this update indicate that the use of sucrose with pacifier appears to have a synergistic effect with both single and repeated doses of sucrose.

Codipietro 2008 concluded that breastfeeding was more effective than sucrose for reducing pain from heel lance in term neonates. Shah 2006 recommended that breastfeeding, when available, should be used to reduce procedural pain in neonates who are exposed to single painful procedures; breast milk alone in small volumes is shown to be as effective as water for the relief of procedural pain (much less so than sucrose), and its effectiveness for repeated painful procedures has not yet been established.

Harrison 2010 conducted a systematic review of 14 RCTs with 1674 injections to compare the efficacy of oral sweet solutions to water or no treatment in infants aged one to 12 months. They concluded that infants administered sucrose or glucose before immunisation had moderately reduced incidence and duration of crying. Harrison 2011b conducted a Cochrane systematic review on sweet solutions for needle-related procedural pain in children aged one to 16 years and reported that in four studies (330 participants), two studies focused on toddlers and pre-school children receiving sucrose for immunisation pain compared with water or no treatment. Two studies included school-aged children receiving sweetened or unsweetened chewing gum before, or, before and during immunisation and blood collection. Results for the toddlers/pre-school children were conflicting.

Slater 2010 demonstrated no significant differences in the nociceptive brain activity measured with neonatal EEG or magnitude or latency of the spinal nociceptive reflex withdrawal measured with EMG between neonates given sucrose versus sterile water. A number of methodological issues in the study by Slater et al (Slater 2010) included (a) the small sample size and, therefore, the study might have been underpowered, (b) moderate attrition rates (i.e. 25% in EEG analysis; 42% in EMG analysis), (c) questionable

methods used to measure and analyse EEG and EMG recordings (Heaton 2011; Stevens 2011; Vanhatalo 2011), and (d) potentially insufficient doses of sucrose (i.e. 0.5 mL) administered to relieve pain in these full-term infants (Linhares 2011). Therefore, methodological issues need to be addressed, and new evidence generated in light of the existing evidence.

There is a need to assess the long-term effects of sucrose administration to neonates. Long-term neurodevelopmental outcomes should be assessed by a standardised and validated assessment tool, a child developmental specialist, or both at 18 to 24 months or at any later age in childhood.

AUTHORS' CONCLUSIONS

Implications for practice

The results of the 57 studies included in this review provide further evidence supporting the efficacy and safety of sucrose for reducing pain from single and to a lesser extent, repeated heel lances. Additional studies report the use of sucrose for ROP examinations, bladder catheterisation, venipuncture, circumcision, NG-tube insertion and subcutaneous injections in hospitalised neonates; however, further studies for these painful procedures are required due to conflicting evidence on the effect of sucrose in reducing pain. Sucrose reduces procedural pain with minimal to no side effects. Small doses of 24% sucrose (0.01 to 0.02 g) are efficacious in very-low birthweight infants while larger doses (0.24 to 0.50 g) reduce the proportion of time crying in term infants. This evidence has been integrated into evidence-based sucrose consensus protocols from which guidelines have been developed (Dunbar 2006; Lefrak 2006; Sharek 2006). However, in a cross-sectional survey of painful procedures in NICUs, procedural pain was managed using sweet solutions only 3.5% of the time (Carbajal 2008). Based on the meta-analyses of 4 studies (Johnston 1999a; Stevens 1999;Gibbins 2002;Slater 2010), we would recommend the routine use of sucrose 0.012 to 0.12 g (0.05 ml of 24% sucrose to 0.5 ml of 24% sucrose) be administered approximately two minutes prior to single heel lances and venipunctures. However, given the broad range of effectiveness of sucrose doses and the heterogeneity of studies in this review, further research is needed to identify a more precise dose for the different gestational ages. Other methods of pain relief, including NNS and skin-to-skin/kangaroo care should be considered in combination with sucrose to reduce or eliminate pain significantly in this population. Effective knowledge translation strategies are required to translate research evidence on sucrose into practice effectively (Dunbar 2006). These strategies could include the use of reminders, interactive education of health professionals, and regular audit and feedback sessions.

Implications for research

The optimal dose of sucrose for term and preterm infants has not yet been established. Researchers should consider establishing more precise and tailored doses based on context in which it is to be used (e.g. gestational age of the infant, severity of illness). Optimal sucrose doses could be further assessed using sensitivity/meta-regression techniques. More research is needed addressing the analgesic and calming effects of sucrose and its interaction with other behavioural (e.g. facilitated tucking, kangaroo care) and pharmacological (e.g. morphine, fentanyl) interventions for more invasive procedures. Strategies need to be initiated to increase understanding of the underlying mechanisms of sucrose and pain relief in infants. The use of repeated administrations of sucrose in neonates needs to be investigated further in terms of clinical, developmental and economic outcomes.

Investigators embarking on further research should utilise existing evidence to answer questions on efficacy and safety when used with other painful procedures that have been minimally addressed to date (e.g. intravenous starts, lumbar punctures, peripherally inserted central catheter (PICC) insertions, endotracheal intubation, suctioning, chest tube insertions). Strengthened study design and methods are required regarding descriptions of the painful procedures, adequacy of sample size, acknowledgment of a multidimensional conceptualisation of pain, use of validated pain measures to determine outcomes, and consideration of variation in the infant's response and context in which the pain is experienced. Use of sucrose in neonates that are extremely-low birthweight, unstable, ventilated, or a combination of these needs to be addressed.

Replication of existing studies of high methodological quality and using identical validated outcomes would allow for further combination of results in meta-analyses. Researchers should report on means and SDs in addition to medians and ranges if the data are not normally distributed to allow for the use of meta-analytic techniques. Future research should also focus on long-term effects of repeated sucrose administration with other behavioural and pharmacological interventions in sick and very-preterm neonates; and the relationship between validated pain measures and indicators of nociceptive brain activity. Overall, there needs to be broader consensus on valid physiological, behavioural, cortical and composite measures to evaluate pain in neonates, especially when evaluating pain-relieving interventions that form the basis for clinical decision-making. Sucrose effectively reduced composite pain scores (PIPP) in neonates for acute procedural pain. Future research should focus on the repeated use of sucrose across a wider age range and broader repertoire of painful procedures that differ in pain intensity. The relationship between validated pain measures and individual physiological and cognitive indicators of nociceptive brain activity should be further explored.

Additional research is needed on determining the minimally effective dose of sucrose during a single painful procedure and the effect of repeated sucrose administration on immediate (pain intensity) and long-term (neurodevelopmental) outcomes.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abad 1996

Methods	Double-blind, randomised controlled trial
Participants	28 (29 to 36 weeks' gestational age) infants, postnatal age 1 to 26 days
Interventions	2 mL of 12% sucrose via syringe (N = 8) 2 min prior to venipuncture (N = 8) 2 mL of 24% sucrose via syringe (N = 8) 2 min prior to venipuncture (N = 8) 2 mL of spring water via syringe (N = 12) 2 min prior to venipuncture (N = 12)
Outcomes	Oxygen saturation, respiratory rate, heart rate (just before and just after administering the solution and 5 min after venipuncture), time spent in audible crying for 3 min following venipuncture
Notes	1-way and 2-way ANOVA used to evaluate outcomes Data were reported as means and standard deviations for the 3 physiological outcomes and as medians and interquartile ranges for cry duration. Data were collected at 3 time points; just before the administration of the solution, just after the solution and 5 min after venipuncture Adverse effects were not evaluated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Selected from randomisation table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Interventions and outcomes blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Acharya 2004

Methods	Double-blind, randomised controlled cross-over trial
Participants	39 preterm neonates (mean 30.5 weeks' gestational age), mean postnatal age 27.2 days
Interventions	2 mL of 25% (0.5 g) sucrose (N = 39) via syringe over 2 min into infant's mouth 2 mL of water (N = 39) via syringe over 2 min into infant's mouth
Outcomes	Rise in heart rate, O_2 saturation (SpO_2), duration of first cry, total duration of crying, Neonatal Facial Coding System (NFCS) at the 3 phases of the venipuncture
Notes	Data were reported using means, standard deviations over the 3 phases of the venipuncture Adverse effects were evaluated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Selected from random number table
Allocation concealment (selection bias)	Low risk	Allocation controlled by hospital pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Interventions and outcomes blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Inconsistent number of infants reported in methods section versus discussion section
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Allen 1996

Methods	Randomised controlled trial
Participants	285 infants aged between 2 weeks and 18 months; 50 included in this review (only neonates at 2 weeks of age)
Interventions	2 mL of 12% sucrose (N = 16) 2 mL of sterile water (N = 15) No treatment (N = 19)
Outcomes	Mean cry duration and % time crying during and 3 min after subcutaneous injection

Allen 1996 (*Continued*)

Notes	Data for % time crying were presented in graphical form only. Data were requested and obtained directly from the author for this review	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Low risk	Solutions in coded syringes prepared by pharmacist
Blinding (performance bias and detection bias) All outcomes	High risk	Low risk for sucrose and water; high risk for no intervention group Low risk for blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	285 infants recruited from a continuous sample. Unsure of the number included in analysis
Selective reporting (reporting bias)	Low risk	Data was provided to the authors of the sucrose systematic review
Other bias	Low risk	

Alsaedi 2009

Methods	Randomised controlled trial	
Participants	36 infants - median (range): 32 weeks' gestational age (GA) (27 to 46), mean (SD) GA: 32.4 (2.0) - 2 different mean GA reported in the article	
Interventions	0.5 mL sterile water with pacifier 0.5 mL sterile water without pacifier 0.5 mL sucrose 24% with pacifier 0.5 mL sucrose 24% without pacifier Pacifier alone and control group	
Outcomes	Duration of cry, Premature Infant Pain Profile (PIPP), heart rate, respiratory rate, glucose check	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Alsaedi 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	A paper was randomly picked so that assignments were random and double-blinded for the sucrose and water solutions
Allocation concealment (selection bias)	Unclear risk	Consecutive numbered envelopes, but did not specify whether it's opaque or sealed
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, personnel and outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Altun-Koroglu 2010

Methods	
Participants	75 full-term infants undergoing heel lance
Interventions	3 mL of hind milk (N = 25) 3 mL of 12.5% sucrose solution (N = 25) 3 mL of distilled water (N = 25)
Outcomes	NFCS, crying time, duration of crying, HR
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Did not mention sequence
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes were used, however, there was no mention as to whether envelopes were opaque and sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Sample sizes were not provided in Tables 2 and 3

Altun-Koroglu 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Basnet 2010

Methods	Randomised controlled trial
Participants	50 term infants aged between 12 h to 8 days; aged 59.92 h non-sucrose group, 68.76 h sucrose group
Interventions	No treatment (N = 25) Treatment group: did not say method of administration (i.e. pacifier/syringe; N = 25)
Outcomes	Douler Aigue Du Nouveau-ne (DAN) score, duration of cry, number of babies crying
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used random numbers from 1 to 50 developed from a random number table
Allocation concealment (selection bias)	Unclear risk	Authors did not report whether the envelopes use to allocate participants were sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant, personnel and outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reported for all randomised infants
Selective reporting (reporting bias)	Low risk	One rating scale (DAN) listed in methods section and is reported in results table
Other bias	Low risk	Does not appear to have any other bias

Biran 2011

Methods	Randomised controlled trial
Participants	76 preterm infants, mean gestational age: S group (N = 37): 32.6 (2.33) weeks; S + E group: (N = 39): 32.3 (2.01) weeks

Biran 2011 (*Continued*)

Interventions	S group: 0.5 mL of 30% sucrose solution orally and placebo cream S + E group: received 30% sucrose solution orally and EMLA (eutectic mixture of local anaesthetics; contains lidocaine 2.5% and prilocaine 2.5%) on the skin
Outcomes	Douleur Aigue du Nouveau-ne (DAN) scale
Notes	Discussed adverse effects observed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation done in advance in blocks of 8 using a random number table
Allocation concealment (selection bias)	Low risk	Used opaque, sealed and sequentially numbered envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, personnel and outcome assessors all blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Blass 1997

Methods	Randomised controlled trial
Participants	72 newborn infants (postnatal age 22 to 40 h)
Interventions	2 mL of 12% sucrose (N = 8) 2 mL of protein solution (provimin) (N = 8) 2 mL of lactose (N = 8) 2 mL of dilute fat (coconut and soy oil blend) (N = 8) 2 mL of concentrated fat (N = 8) 2 mL of fat and lactose solution (N = 8) 2 mL of Ross Special Formula (RSF) - artificial milk (N = 8) 2 mL of Similac (N = 8) Solutions were given via syringe over a 2-min period
Outcomes	Crying time (% procedure time spent crying, % time spent crying during 3-min recovery period, number of infants that cried 20% or more during each recovery minute)

Blass 1997 (*Continued*)

Notes	Sucrose vs. water, Similac vs. water and RSF vs. water were compared using Mann-Whitney U test. Results were presented in graph form and means were reported in text Adverse events were not evaluated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	High risk	Similac group could not be concealed because appearance differed from other intervention solutions
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments. However, similac group is high risk as its appearance differed from sucrose or water
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	High risk	Results reported incompletely (only in figures) and cannot be combined in meta-analysis
Other bias	Unclear risk	Several test solutions were gifts from Ross Laboratories

Blass 1999

Methods	Randomised controlled trial
Participants	40 term newborn infants 34 to 55 h old
Interventions	2 mL of 12% sucrose over 2 min via syringe (N = 10) 2 mL of water via syringe over 2 min (N = 10) Pacifier dipped every 30 s in 12% sucrose solution for 2 min (N = 10) Pacifier dipped in water every 30 s for 2 min (N = 10) prior to heel lance
Outcomes	Percentage of time spent crying 3 min after heel lance, percentage of time spent grimacing, change in mean heart rate
Notes	Data were reported in graph forms only Results of ANOVA reported as P -values only (we have contacted the authors to obtain additional information) Adverse effects were not evaluated

Risk of bias

Blass 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water alone groups blinded; pacifier + water, pacifier + sucrose groups were blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	High risk	Results reported incompletely (only in figures) and could not be combined in meta-analysis
Other bias	Low risk	

Boyer 2004

Methods	Double-blind randomised controlled trial (repeated doses of sucrose)
Participants	105 preterm neonates (< 31 weeks' gestational age), postnatal age ≤ 48 h
Interventions	0.1 mL of sterile water up to 3 times for each painful procedure 0.1 mL of 24% sucrose up to 3 times for each painful procedure Intervention was given prior to all painful procedures for a duration of 7 days
Outcomes	Pulse rate (over 1 day), cortisol level (change in cortisol levels before/after procedure)
Notes	This paper assessed physiological stability over 1 full day of the 7-day study period Subset analyses were conducted. Results were reported as means and standard deviations Adverse events were not evaluated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Did not specify method of allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of intervention - nurses were aware of the group assignment but treating clinicians were not

Boyer 2004 (*Continued*)

		Low risk for blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete physiological data for majority of infants but rationale provided
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Boyle 2006

Methods	Randomised controlled trial
Participants	40 preterm infants < 32 weeks' gestational age (GA) Sterile water group: mean GA 27 weeks; postnatal age mean 45 days Sucrose group: mean GA 29 weeks; postnatal age mean 43 days Water + pacifier group: mean GA 30 weeks; postnatal age mean 41 days Sucrose + pacifier group: mean GA 29 weeks; postnatal age mean 42 days
Interventions	2 min before start of eye examination: 1 mL of sterile water (N = 10) 1 mL of sucrose 33% (N = 10) 1 mL of sterile water + pacifier (N = 9) 1 mL sucrose 33% + pacifier (N = 11) *water or sucrose was given by mouth using a syringe
Outcomes	Premature Infant Pain Profile (PIPP) during eye examination
Notes	Data were presented in graph form and reported as means and standard deviations Results of ANOVA and independent t-tests reported as P values Adverse events were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Yes as sucrose and water alone groups blinded; pacifier + water, pacifier + sucrose groups were blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reported for all randomised infants

Boyle 2006 (*Continued*)

Selective reporting (reporting bias)	Low risk	1 rating scale (PIPP) listed in methods and is reported in results section
Other bias	Low risk	

Bucher 1995

Methods	Randomised, double-blind, placebo-controlled cross-over trial
Participants	16 preterm infants (27 to 34 weeks' gestational age), postnatal age approximately 42 days
Interventions	2 mL of 50% sucrose via syringe into the mouth 2 min before heel lance 2 mL of distilled water via syringe into the mouth 2 min before heel lance (N = 16, cross-over design)
Outcomes	Increase in heart rate (HR) (beats per minute); recovery time for HR (sec); recovery time for respirations (sec); crying (% of total intervention); recovery time until crying stopped (sec); $TcpO_2$ (maximum increase in kPa); $TcpO_2$ (maximum decrease in kPa); $TcpO_2$ (difference between baseline and 10 min after end of intervention in kPa); $TcpCO_2$ (maximum decrease in kPa); $TcpCO_2$ (difference between baseline and 10 min after the end of intervention)
Notes	Results were presented in graph forms without mean values and standard deviations, in tables with medians with interquartile ranges, or both. Wilcoxon signed rank test Adverse effects were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generated from random number table
Allocation concealment (selection bias)	Low risk	Vials containing solutions were coded and contents could not be identified
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reported for all randomised infants
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Carbajal 1999

Methods	Randomised controlled trial
Participants	150 term newborn infants, 3 to 4 days old
Interventions	No treatment (N = 25) 2 mL of sterile water via syringe over 30 s (N = 25) 2 mL of 30% glucose via syringe (N = 25) 2 mL of 30% sucrose (N = 25) Pacifier alone (N = 25) 2 min prior to venipuncture 2 mL of 30% sucrose via syringe followed by sucking a pacifier (N = 25)
Outcomes	Douleur Aigue du Nouveau-ne (DAN) scale
Notes	Mann-Whitney U test used to evaluate pain scores Adverse effects were evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generated by random number table
Allocation concealment (selection bias)	Low risk	Allocated by sequentially numbered, opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Low risk for sucrose and water solutions High risk for pacifier group
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Codipietro 2008

Methods	Randomised controlled trial
Participants	51 term infants, mean gestational age (GA) 39.3 (standard deviation (SD) 1.2) in breastfeeding group, GA 39.4(SD 1.1) in sucrose group
Interventions	1 mL of 25% sucrose (N = 50) Breastfeeding (N = 51)

Codipietro 2008 (*Continued*)

Outcomes	Premature Infant Pain Profile (PIPP) during blood sampling, 2 min after heel lance, Heart rate increase from baselines at 30 s following commencement of procedure, O_2 saturation decrease, duration of first cry, % crying time in first 2 min and % in crying time during blood sampling
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence created by statistician and masked to investigators
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Breastfeeding could not be blinded. Nurses and parents not blinded to assignment Only assistants listening to voice recordings of cry for PIPP scoring were blind to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Fernandez 2003

Methods	Randomised, prospective controlled study
Participants	34 term infants, mean (standard deviation) gestational age (GA): 38 weeks (2) in sucrose group; GA 39 (1) in water group
Interventions	Water group: 2 mL of water Sucrose group: 2 mL of 12% sucrose The pipette containing the liquid was placed towards the front and centre of the mouth, and the solution was then released in small amounts
Outcomes	Electroencephalography (EEG), electrocardiography (ECG), crying and facial expressions
Notes	

Risk of bias

Fernandez 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Newborns were randomly assigned using a flip of a coin; uneven distribution of infants in each group (sucrose: N = 20, water: N = 14)
Allocation concealment (selection bias)	Unclear risk	Did not specify method of allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Low risk for participants Unclear risk for personnel - did not specify whether the experimenter was blinded Low risk for outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reported for all randomised infants - explained exclusion of 9 infants from EEG data due to crying and movement artefacts
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Gal 2005

Methods	Randomised, double-blind, placebo-controlled, cross-over study
Participants	23 preterm infants mean gestational age 26.4 weeks (range 24 to 29), postnatal age 28 to 93 days
Interventions	2 mL of sterile water via syringe (N = 23) 2 mL of 24% sucrose via syringe (N = 23) Mydriatic eye drops (phenylephrine HCl 1%, cyclopentolate HCl 0.2%) and local anaesthetic eye drops (proparacaine HCl 0.5%: 2 drops) were given to both groups prior to examination
Outcomes	Premature Infant Pain Profile (PIPP) score at 5 min and 1 min pre-examination, PIPP score at eye speculum insertion, PIPP score 1 min and 5 min post-examination
Notes	Results were reported as means and standard deviations Results of paired t-tests were reported as P values Adverse events - no adverse events experienced

Risk of bias

Bias	Authors' judgement	Support for judgement

Gal 2005 (*Continued*)

Random sequence generation (selection bias)	Low risk	Dice roll used to allocate to 6 groups
Allocation concealment (selection bias)	Low risk	Allocation centrally controlled by pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported to have 23 neonates in study but only 22 neonates included in demographic information and PIPP Scores in Table 1
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Stopped at 23 neonates due to change in ophthalmologist in order to maintain consistency in examinations; however, statistical power calculated determined that 24 neonates were needed for the study. This does not seem to have affected the results

Gaspardo 2008

Methods	Randomised double-blind controlled trial
Participants	33 preterm infants, median gestational age 30 weeks
Interventions	0.5 mL/kg of 25% sucrose before every minor painful procedure (venipuncture, arterial puncture, heel-lance, intravenous cannulation, endotracheal tube introduction, endotracheal tube suctioning, gavage insertion for feeding, removal of electrode leads and tape) (N = 17) 0.5 mL/kg of sterile water (N = 16)
Outcomes	Incidence of cry (% neonates crying), heart rate (HR) (% neonates with HR $\geq$ 160 beats per minute), Neonatal Facial Coding System (NFCS) (% neonates with score $\geq$ 3), Activated Behavioural State (% neonates with score $\geq$ 4)
Notes	Pain was assessed over 4 days during morning blood collection (heel lance) On day 1, no treatment was given to any neonate in order to collect baseline data. Solutions were administered to neonates before every painful procedure (listed above) on days 2 to 4 The Mann-Whitney U test was used to calculate the difference between sucrose and water groups for continuous variables. The Chi^2 test was used to calculate the difference between sucrose and water groups for categorical variables No means or standard deviations reported

Gaspardo 2008 (*Continued*)

	Adverse events were assessed	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	Solutions prepared by pharmacist called 'A' or 'B' to keep identity from investigators. Co-ordinator kept identities of solutions in sealed and opaque envelopes until after analysis
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Gibbins 2002

Methods	Randomised controlled trial	
Participants	190 preterm and term infants, mean gestational age 33.7 weeks, under 7 days' postnatal age	
Interventions	0.5 mL of 24% sucrose via syringe to the anterior surface of the tongue followed by pacifier (N = 64) 0.5 mL 24% sucrose without pacifier (N = 62) 0.5 mL sterile water with pacifier (N = 64) 2 min prior to heel lance	
Outcomes	Premature Infant Pain Profile (PIPP) at 30 and 60 s after heel lance	
Notes	1-way ANOVA to evaluate mean pain scores Results were reported as means and standard deviations Adverse effects were evaluated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Gibbins 2002 (*Continued*)

Random sequence generation (selection bias)	Low risk	Sequence generated using a centralised randomisation table
Allocation concealment (selection bias)	Low risk	Centrally allocated by pharmacist. Pharmacist labelled all solutions as "study drug" and delivered it to neonate's bedside
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Facial coders were uninformed as to the purpose of the study, phases of the heel lance and group allocation for the 2 pacifier groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Gormally 2001

Methods	Randomised controlled trial, factorial design	
Participants	94 normally developing newborns, mean gestational age 39.4 weeks on 2nd or 3rd day of life 9 infants did not complete the study due to early discharge, nurse or testing room unavailability to obtain heel stick, infant removed from study prior to start date, technical difficulties	
Interventions	No holding and sterile water given by pipette (N = 21) No holding and 0.25 mL of 24% sucrose Solution (0.06 g) given by pipette (N = 22) Holding and sterile water given by pipette (N = 20) Holding and 0.25 mL of 24% sucrose solution (0.06 g) by pipette (N = 22) All solutions given 3 times at 30-second intervals	
Outcomes	Percentage of time crying, pain concatenation scores for facial activity, mean heart rate, mean vagal tone index, measurements at pre-intervention and 1, 2, and 3 min after heel lance	
Notes	Factorial ANOVA to assess effects on behavioural and physiological measures No means or standard deviations reported Adverse effects were not evaluated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Gormally 2001 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Facial coders were blind to solution assignment only
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Grabska 2005

Methods	Prospective randomised, blinded, placebo controlled study
Participants	32 preterm infants with birthweight < 1.5 kg or gestational age (GA) < 28 weeks GA (mean ± standard deviation) 28 ± 1.6 weeks, postnatal age (mean ± standard deviation) 50.8 ± 20.3 days
Interventions	Sterile water (N = 16) 24% sucrose (N = 16) Dose was adjusted by weight: < 1 kg = 0.5 cm^3 (0.12 g) 1 to 1.5 kg = 1.0 cm^3 (0.24 g) > 1.5 to 2 kg = 1.5 cm^3 (0.36 g) > 2 kg = 2.0 cm^3 (0.48 g)
Outcomes	Heart rate, respiratory rate and oxygen saturation at baseline, post-mydriatic, post-study drug, during eye examination, post eye examination; Premature Infant Pain Profile (PIPP) at baseline, during eye examination, post eye examination; Crying time during eye examination; Blood pressure at baseline, post-mydriatics, during eye examination and post-eye examination
Notes	Results were reported as means and standard deviations Results of t-tests and ANOVAs were reported as P values where a value of < 0.05 was considered significant Adverse events were evaluated-choking, transient O_2 desaturation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Grabska 2005 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Pharmacy provided solutions in sealed envelopes after randomisation but did not specify whether envelopes were sequentially numbered and opaque
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Although not explicitly stated, it can be inferred that nurses administering solutions and those assessing videotapes were blinded to assigned solution
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reported for all randomised infants
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Greenberg 2002

Methods	Randomised controlled trial
Participants	84 term newborns, approximately 17 to 19 h old
Interventions	Sugar-coated pacifier held in infant's mouth before procedure to 3 min after procedure (N = 21) Water-moistened pacifier (N = 21) 2 mL of 12% sucrose via syringe into side of infant's mouth (N = 21) Routine care (N = 21)
Outcomes	Salivary cortisol levels, duration of cry, vagal tone
Notes	Analysis using MANOVA to evaluate outcomes by groups Results were presented in graph forms without mean values and standard deviations Adverse effects were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described

Greenberg 2002 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Use of pacifier precluded blinding. No blinding between pacifier groups either, as 1 was moistened with water and 1 dipped in sugar packet No blinding of outcome measurement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement indicating how many were recruited and how many dropped out
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Guala 2001

Methods	Randomised controlled trial
Participants	140 term (38 to 41 weeks' gestational age)
Interventions	Nothing (N = 20) Water (N = 20) 5% glucose (N = 20) 33% glucose (N = 20) 50% glucose (N = 20) 33% sucrose (N = 20) 50% sucrose (N = 20) Administered via syringe into infant's mouth over 30 s
Outcomes	Heart rate before, during and 3 min after heel lance
Notes	ANOVA to evaluate heart rate across groups at each phase of the heel lance. Means and standard deviations provided Adverse effects were evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generated by random number table
Allocation concealment (selection bias)	Low risk	Allocated by sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement indicating how many were recruited and how many dropped out

Guala 2001 (*Continued*)

Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Haouari 1995

Methods	Randomised, double-blind placebo-controlled trial
Participants	60 term (37 to 42 weeks' gestation) infants, 1 to 6 days of age
Interventions	2 mL of 12.5% sucrose 2 min prior to heel lance (N = 15) 2 mL of 25% sucrose 2 min prior to heel lance (N = 15) 2 mL of 50 % sucrose 2 min prior to heel lance (N = 15) 2 mL of sterile water 2 min prior to heel lance (N = 15) All solutions were given by syringe on the tongue over less than 1 min
Outcomes	Total time (s) crying over 3 min following heel lance, time of first cry (s) following heel lance, % change in heart rate (HR) after heel lance (at 1, 3 and 5 min)
Notes	Analysis of non-parametric data was by the Mann-Whitney U test or a trend test. Total time crying in the first 3 min after heel lance was reported as medians and interquartile ranges. Changes in HR were expressed in means and standard deviations as a percentage of resting HR Adverse effects were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Low risk	Pre-prepared solutions in coded bottles
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Harrison 2003

Methods	Randomised, blinded, controlled trial
Participants	Our sample was a subset of a larger study (N = 128) that included older infants Authors provided us with data for a subset of infants that fulfilled our inclusion criteria The subset included 99 hospitalised infants Mean (standard deviation (SD)) gestational age (GA) of placebo group: 36.7 weeks (3.3) Mean (SD) GA of treatment group: 36.8 weeks (3.7)
Interventions	1 mL of water 2 min prior to heel lance (N = 46) 1 mL of 25% sucrose 2 min prior to heel lance (N = 53) *For infants weighing ≤ 1500 g the dose was reduced to 0.5 mL
Outcomes	Neonatal Facial Coding System (NFCS) at baseline, upon heel lance, during heel squeeze and completion of heel squeeze at 1, 2 and 3 min of recovery Duration of cry until 5-s pause, percentage of crying time during heel lance and squeeze, percentage of crying time during 3 min recovery period Heart rate and O_2 saturation (SpO_2)
Notes	Results were presented in graphs Results of Student's t-test, Pearson's Chi^2 test, Fisher's exact test and Mann-Whitney U test were reported as P values Adverse events were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	Pharmacy-prepared solutions in consecutively numbered syringes. Contents of syringes obscured
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Non-nutritive sucking with pacifier was provided as comfort measure if part of regular infant care. This was addressed by the authors and adjusted analyses were performed to assess the effect of pacifier across groups

Herschel 1998

Methods	Randomised controlled trial
Participants	119 full-term male neonates undergoing circumcision, gestational age ≥ 38 weeks, postnatal age ≥ 12 h
Interventions	No treatment (N = 40) Dorsal penile nerve block (DPNB) - 0.8 mL of 1% lidocaine (N = 40) Pacifier dipped in and packed with gauze soaked in 50% sucrose (N = 39)
Outcomes	Heart rate (HR) and oxygen saturation (change from baseline and means for each interval of circumcision)
Notes	Results of change in HR and oxygen saturation for each group was reported as mean and standard deviation. Mean HR for each interval of circumcision were presented in graph form Mean HR and oxygen saturation were compared between groups using ANOVA. Characteristics of infants in the 3 groups were compared using Chi^2 test, Fisher exact test or ANOVA Adverse events were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Shuffled envelopes to generate sequence
Allocation concealment (selection bias)	Unclear risk	Group assignments contained in opaque unmarked envelopes but did not say whether it was sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Intervention was not blinded; however, the outcome assessment was blinded. Outcome not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Did not report data for all 120 infants as suggested in methods section
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Isik 2000a

Methods	Randomised controlled trial
Participants	113 healthy newborns gestational age: 37 to 42 weeks, median postnatal age: 2 days (range 2 to 5 days)
Interventions	2 mL of 30% sucrose (N = 28) 2 mL of 10% glucose (N = 29) 2 mL of 30% glucose (N = 28) 2 mL of distilled water (N = 28) Syringed into the anterior third of the tongue for 1 min 2 min prior to heel lance
Outcomes	Mean cry time during 3 min after heel lance; mean maximum heart rate (HR) 3 min after heel lance; mean recovery time for HR; % change in HR at 1, 2, 3 min after heel lance
Notes	1-way ANOVA was used to evaluate mean cry time, recovery time and % change in HR Results reported as means and standard errors of the mean Adverse effects were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Cannot tell if intervention was blinded. Also cannot tell if heart rate assessment was blinded; however, it is stated that assessment of crying was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No clear statement given. Indicate that any baby that cried was excluded, but number in methods is same as number in results, so unsure if there were more recruited but dropped out/excluded for results
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Johnston 1997a

Methods	Randomised controlled trial
Participants	85 preterm infants (25 to 34 weeks' gestational age), 2 to 10 days of age
Interventions	0.05 mL of 24% sucrose via syringe into the mouth just prior to heel lance (N = 27) 0.05 mL of 24% sucrose via syringe into the mouth just prior to heel lance and simulated rocking 15 min prior to heel lance (N = 14) 0.05 mL of sterile water via syringe into the mouth just prior to heel lance and simulated rocking 15 min prior to heel lance (N = 24) 0.05 mL of sterile water via syringe into the mouth just prior to heel lance
Outcomes	Heart rate, oxygen saturation, behavioural facial actions, behavioural state; Neonatal Facial Coding System (NFCS) baseline and at 3 x 30-second blocks
Notes	Data were analysed using MANOVA (facial action). For heart rate repeated measures ANOVA was used with mean values but no standard deviations presented in graph form. For state repeated measures ANOVA was performed and no univariate means and standard deviations were presented O_2 saturation (SpO_2) was dropped from analysis Adverse effects were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence
Allocation concealment (selection bias)	Unclear risk	Sequentially numbered envelopes but did not specify whether envelopes were opaque
Blinding (performance bias and detection bias) All outcomes	High risk	Not clear as to whether solutions were blinded Outcome assessments blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	In the original design it called for 28 infants/group based on anticipated effect size; however it shows in table 1 that sample size of each group varied from 14 to 27; not equal groups
Selective reporting (reporting bias)	High risk	Data reported as significance levels only and in figures only
Other bias	Low risk	

Johnston 1999a

Methods	Randomised controlled trial
Participants	48 preterm neonates mean gestational age of 31 weeks (range 25 to 34 weeks) within 10 days of birth
Interventions	0.05 mL of 24% sucrose as a single dose, followed by 2 doses of sterile water (N = 15) 3 doses of 0.05 mL of 24% sucrose (N = 17) 3 doses of 0.05 mL of sterile water (N = 16) given by syringe to anterior surface of the tongue at: 2 min prior to heel lance, just prior to lancing 2 min after lancing
Outcomes	Premature Infant Pain Profile (PIPP), measured over 5 x 30 second blocks of time
Notes	Repeated measures ANOVA was used to evaluate the effect of single versus repeated doses of sucrose Means and standard deviations for pain scores were obtained from the author Adverse effects were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random assignment
Blinding (performance bias and detection bias) All outcomes	High risk	Sucrose and water solutions blinded for research nurses but not the research assistants as they prepared the solutions
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Johnston 2002

Methods	Randomised controlled trial
Participants	103 infants sucrose group: N = 51, mean (standard deviation) gestational age: 28.18 weeks (1.72) Water (control) group: N = 52, mean (standard deviation) gestational age 28.05 weeks (2.06)
Interventions	Sucrose group: solutions of 0.1 mL of 24% sucrose were drawn up into sterile syringes and placed in the unit medicine refrigerator Water group: solutions of 0.1 mL of water were drawn up into sterile syringes and placed in the unit medicine refrigerator

Johnston 2002 (*Continued*)

Outcomes	Neurobehavioural development assessed by the subscales of alertness and orientation and motor development and vigour of the Neurobehavioral Assessment of the Preterm Infant (NAPI), Score for Neonatal Acute Physiology (SNAP) and Neuro-Biological Risk Score (NBRS)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random computer-generated program
Allocation concealment (selection bias)	Unclear risk	Did not specify how allocation was done
Blinding (performance bias and detection bias) All outcomes	High risk	Impossible to blind personnel to the rocking in enhanced kangaroo mother care (EKMC) condition versus no rocking in the kangaroo mother care (KMC) condition Research assistants not blinded to group but blinded to purpose of study
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Kaufman 2002

Methods	Randomised controlled trial
Participants	57 infants undergoing circumcision
Interventions	Mogen method and water (N = 15) Mogen method and 24% sucrose (N = 14) Gomco method and 24% sucrose (N = 14) Gomco method and water (N = 14) Solutions were given via a dipped pacifier
Outcomes	Cry and grimacing during real-time 10-second intervals
Notes	Results were reported graphically. A 2-factor analysis of variance evaluated raw and % duration of crying and grimacing. The Kolmogorov-Smirnov test for the equivalence of empiric distribution functions was used to evaluate differences in the distribution of cumulative crying and grimacing Adverse events were not evaluated

Kaufman 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not adequately described
Allocation concealment (selection bias)	Low risk	Solutions prepared and coded by pharmacy and stored in dark vials to deem them indistinguishable
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	High risk	Data reported incompletely in graphical form only and therefore cannot be meta-analysed
Other bias	Low risk	

Kristoffersen 2011

Methods	Randomised controlled trial, cross-over design
Participants	24 preterm infants, 28 to 32 weeks' gestational age
Interventions	Pacifier, no pacifier, combined, with no fluid, sterile water, or 30% sucrose
Outcomes	Premature Infant Pain Profile (PIPP) scores
Notes	Infants acted as own control groups

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random list generated by computer
Allocation concealment (selection bias)	Low risk	Used a unique sequence from list - only the study leader had access to the list
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Nurses doing PIPP scores were asked to "turn away" before solution was given but authors did not mention how to control for

Kristoffersen 2011 (*Continued*)

		that
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Did not specify number of infants in each group in table 1
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Mathai 2006

Methods	Randomised study (blinded for cry but not for Douler Aigue Du Nouveau-ne (DAN))
Participants	104 term neonates > 24 h of life Sucrose group mean postnatal age: 48 h Distilled water group mean postnatal age: 44 h
Interventions	2 mL of 20% sucrose (N = 17) 2 mL of distilled water (N = 15) 2 mL of expressed breast milk (EBM) (N = 18) Non-nutritive sucking (NNS) (N = 20) Rocking (N = 17) Massage (N = 17)
Outcomes	DAN before heel prick and 30 s and 1, 2 and 4 min after heel prick; time of first cry in seconds (until baby took first inspiration after beginning of cry), total cry in seconds; heart rate and O_2 saturation (SpO_2) before heel prick and 2 and 4 min after heel prick
Notes	Results were graphed and reported as means and standard deviations (2 SD) ANOVA, Fischer's exact 't' test, multivariate analysis, Pearson's correlation test - some P values were reported Adverse events were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generated by random number table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Interventions could not be blinded. One observer left the room during the intervention to be able to assess the DAN score blindly. The second observer was in the room during the interventions and was not blinded

Mathai 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Physiological parameters (heart rate, oxygen saturation) not reported
Selective reporting (reporting bias)	Unclear risk	Physiological parameters (heart rate, oxygen saturation) not reported
Other bias	Low risk	

McCullough 2008

Methods	Randomised, double-blind controlled trial
Participants	20 preterm infants, mean gestational age 30 weeks Sucrose group: mean postnatal age 23 days Water group: mean postnatal age 27 days
Interventions	(0.5 to 2 mL) of 24% sucrose (N = 26) (0.5 to 2 mL) of sterile water (N = 25) *Note: a total of 51 nasogastric tube insertions were performed. Each baby was randomised to either the control or treatment group prior to each insertion. This was not a cross-over study
Outcomes	Incidence of crying, heart rate, oxygen saturation, Neonatal Facial Coding System (NFCS) (median)
Notes	Incidence of crying reported as percentage of neonates who cried. Heart rate and oxygen saturation measured as change (in beats per minute and % saturation, respectively) from baseline Adverse events were evaluated; brief apnoea and self-limiting bradycardia reported in a few neonates, but no clinical intervention needed. No statistically significant differences between sucrose and control groups regarding incidence of adverse events

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Low risk	Used sealed opaque envelopes to allocate to groups
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments

McCullough 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided about why enrolled infants did not participate in the study
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Several infants have been randomised several times - could they be "remembering" their previous experience, which may affect the results?

Mitchell 2004

Methods	Randomised, double-blind, placebo-controlled trial
Participants	30 preterm infants Water group: mean gestational age 27.3 weeks, mean postnatal age 8.2 weeks Sucrose group: mean gestational age 26.5 weeks, mean postnatal age 8.5 weeks
Interventions	Water group: pacifier and 3 doses of 0.1 mL sterile water drops (N = 15) Sucrose group: pacifier and 3 doses of 0.1 mL 24% sucrose drops (N = 15) *Both groups received proparacaine hydrochloride 0.5% and were swaddled before the eye examination
Outcomes	Premature Infant Pain Profile (PIPP) at baseline; eye drops instillation; examination of left eye and 30, 60, 90 and 120 s after completion of the eye examination
Notes	Results were in graph form and reported as means and standard errors of the means. A series of t tests were conducted and their P values reported Adverse events were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Allocated using sealed envelopes but did not specify whether envelopes were opaque or sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Nurse administering interventions was aware of group allocation. All other personnel and investigators were blinded. Outcome assessment was blinded

Mitchell 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reported for all randomised infants
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Montoya 2009

Methods	Randomised double-blind controlled trial
Participants	111 infants included - 55 in experimental group, 56 in control group
Interventions	1 cm^3 of 12% sucrose 1 cm^3 of water
Outcomes	Neonatal Infant Pain Scale (NIPS) score
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table used
Allocation concealment (selection bias)	Low risk	Coded solutions
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Did not mention blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Mucignat 2004

Methods	Randomised, prospective study
Participants	33 preterm neonates, < 33 weeks' gestation Mean (standard deviation (SD)) gestational age at birth 30 ± 6 weeks Mean (SD) gestational age at injection 32 ± 6 weeks

Mucignat 2004 (*Continued*)

Interventions	Non-nutritive pacifier (NNS) 0.2 to 0.5 mL of 30% sucrose with pacifier local application of eutectic mixture of local anaesthetics (EMLA) with pacifier 0.2 to 0.5 mL of sucrose with EMLA and pacifier
Outcomes	Douler Aigue Du Nouveau-ne (DAN) and Neonatal Facial Coding System (NFCS) scores; heart rate, respiratory rate and oxygen saturation measured before, during and after injection
Notes	Fisher test, ANOVA of fixed effect and the Tukey method was used to compare groups Results were reported as means and SD Adverse effects were not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Interventions could not be blinded. Did not state that outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	High risk	Unequal distribution of allocated and received treatments amongst injections: NNS = 41, EMLA = 71, sucrose = 86, EMLA + sucrose = 67

O'Sullivan 2010

Methods	Randomised, prospective placebo-controlled study
Participants	40 preterm infants Water group: mean gestational age ± standard deviation (SD) 29.5 ± 2.3 weeks, mean corrected age at first eye examination ± SD 33.1 ± 1.2 weeks Sucrose group: mean gestational age ± SD = 29.8 ± 2.4 weeks, mean corrected age at first eye examination ± SD = 33.0 ± 1.1 weeks

O'Sullivan 2010 (*Continued*)

Interventions	Water group: 0.2 mL of sterile water given by mouth using a syringe and a pacifier (N = 20) Sucrose group: 0.2 mL of sucrose 24% given by mouth using a syringe and a pacifier (N = 20) Both groups were swaddled
Outcomes	Neonatal Pain, Agitation and Sedation Scale (N-PASS); heart rate and O_2 saturation (SpO_2) at baseline; # of bradycardia, desaturation
Notes	Recorded number of adverse events

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-based randomisation process used
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque and sealed envelopes used
Blinding (performance bias and detection bias) All outcomes	Low risk	Only pharmacist was aware of the identify of solutions All other personnel and outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reported for all randomised infants
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Ogawa 2005

Methods	Randomised, double-blind, placebo-controlled trial
Participants	100 healthy, full-term infants $\geq$ 37 weeks' gestation
Interventions	1 mL of sterile water 2 min before heel lance (N = 25) 1 mL of 50% sucrose 2 min before heel lance (N = 25) 1 mL of sterile water 2 min before venipuncture (N = 25) 1 mL of 50% sucrose 2 min before venipuncture (N = 25)
Outcomes	Neonatal Facial Coding System (NFCS) score after skin puncture, during blood sampling and during compression to stop bleeding; duration of first cry, ratio of crying to no crying, total procedure time

Ogawa 2005 (*Continued*)

Notes	Intergroup comparisons were performed by the Kruskal-Wallis test Mann Whitney U test for continuous variables or by the Chi^2 test for categorical data Results were reported as medians and ranges and means and standard deviations. P values were also reported Adverse effects were evaluated for the procedure itself, not sucrose

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	100 sealed envelopes. Unsure if they were opaque or sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Okan 2007

Methods	Randomised, blinded, cross-over trial
Participants	31 preterm infants, mean (standard deviation (SD)) gestational age 30.5 weeks (2.7), postnatal age of 20 days (16)
Interventions	2 mL of sterile water 2 mL of 20% sucrose 2 mL of 20% glucose All solutions were given 2 min before heel lance
Outcomes	Heart rate, respiratory rate, oxygen saturation and Neonatal Facial Coding System (NFCS) score at baseline, heel lance and 1, 2, 3 and 4-min post heel lance; duration of first cry and total crying time
Notes	The differences in duration of crying time and blood collection were analysed using the Friedman test Results were reported as means and SDs Adverse effects were not evaluated

Okan 2007 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Envelopes drawn randomly to determine sequence
Allocation concealment (selection bias)	Unclear risk	Allocated by sealed envelopes. Solutions contained in identical bottles coded by nurse who was not a part of the study. Did not mention whether envelopes were opaque or sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Ors 1999

Methods	Randomised controlled trial
Participants	102 healthy term infants, gestational age 37 to 42 weeks, median postnatal age 1.6 days (range 1 to 15 days)
Interventions	2 mL of 25% sucrose (N = 35) 2 mL of human milk (N = 33) 2 mL of sterile water (N = 34) syringed to anterior part of tongue for 1 min Heel prick done 2 min after intervention
Outcomes	Median crying time 3 min after heel lance; % change in heart rate 1, 2, 3 min after heel lance
Notes	Kruskal-Wallis 1-way ANOVA used to assess differences between groups Medians and interquartile ranges reported for outcomes Adverse effects were not evaluated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Ors 1999 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Overgaard 1999

Methods	Double-blind randomised controlled trial
Participants	100 newborn term infants, mean age 6 days (range 4 to 9)
Interventions	2 mL of 50% sucrose solution via syringe into the mouth over 30 s, 2 min prior to heel lance 2 mL of sterile water via syringe into the mouth over 30 s, 2 min prior to heel lance
Outcomes	Neonatal Infant Pain Scale (NIPS) score, crying time (duration of first cry, crying time during heel lance, fraction of crying during sampling, crying time during first minute after end of sampling, total crying time), NIPS 1 min after heel lance and 1 min after blood sampling, change in heart rate at 0 and 1 min. change in O_2 saturation (SpO_2) at 0 and 1 min
Notes	Results were reported as medians and 5% and 95% percentiles Statistical testing used Mann Whitney U and Fisher's exact test Adverse effects were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Low risk	100 syringes manufactured at random to contain sucrose or water. Numbered and administered consecutively. Contents were unknown to investigators and parents

Overgaard 1999 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Ozdogan 2010

Methods	Prospective randomised controlled trial
Participants	142 healthy term newborns
Interventions	Single dose breast milk Single dose sterile water Single dose 12.5% sucrose 2 doses of breast milk 2 doses of sterile water 2 doses of 12.5% sucrose
Outcomes	Median crying time, Neonatal Facial Coding System (NFCS) scores
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Did not specify randomisation method
Allocation concealment (selection bias)	Unclear risk	Did not specify allocation method
Blinding (performance bias and detection bias) All outcomes	High risk	Cannot be blinded to breast milk group
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Ramenghi 1996a

Methods	Randomised, double-blind, placebo-controlled cross-over study
Participants	15 (32 to 34 weeks' gestation) infants > 24 h of age
Interventions	1 mL of 25% sucrose via syringe into mouth 2 min prior to heel lance 1 mL of sterile water via syringe into mouth via syringe 2 min before heel lance Cross-over design)
Outcomes	Duration of first cry (sec) following heel lance, percentage of time crying 5 min after heel lance, heart rate (at -2, 0, 1, 3, 5 min from heel lance), behavioural scores (4 facial expressions and the presence of cry at -2, 0, 1, 3, 5 min from heel lance)
Notes	Medians and ranges were reported for duration of first cry, % cry over 5 min and heart rate. For composite behavioural outcome scores data were presented in graph form only with no indication if data represent medians or means. Wilcoxon matched pairs signed rank test used to evaluate outcomes Adverse effects were evaluated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Unsure if sucrose and water solutions blinded Unsure of whether outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Ramenghi 1996b

Methods	Randomised, single-blind, placebo-controlled trial
Participants	60 (37 to 42 weeks' gestational age) 2 to 5 days old infants
Interventions	2 mL of 25% sucrose via syringe into mouth 2 min prior to heel lance (N = 15) 2 mL of 50% sucrose via syringe into mouth 2 min prior to heel lance (N =15) 2 mL of commercial sweet-tasting solution (Calpol) via syringe into mouth 2 min prior

Ramenghi 1996b (*Continued*)

	to heel lance (N = 15) 2 mL of sterile water via syringe into mouth 2 min prior to heel lance (N = 15)
Outcomes	Duration of first cry (seconds) following heel lance, % time crying over 3 min following heel lance, % change in heart rate over 5 min (-2, 0, 1, 3, 5 min from heel lance), behavioural scores (4 facial expressions and the presence of cry (-2, 0, 1, 3, 5 min after heel lance)
Notes	Results were presented as medians and interquartile ranges for the pain score. For cry duration and % crying over 3 min the data were presented as medians and interquartile ranges. % change in heart rate was reported in graph form without indicating if data represent means or medians with standard deviations or errors. Mann-Whitney U test used to evaluate outcomes Adverse effects were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Outcome assessment were blinded

Ramenghi 1999

Methods	Randomised double-blind placebo-controlled cross-over trial
Participants	30 preterm infants (gestational age 32 to 36 weeks, postnatal age < 24 h)
Interventions	25% sucrose solution (volume not reported) was given via syringe into the mouth or via nasogastric (NG) tube 2 min prior to first heel lance (N = 15), and via the alternate route for the second heel lance within 48 h Sterile water via syringe into the mouth or via NG tube 2 min prior to first heel lance and for the second heel lance the alternate route within 48 h Cross-over design
Outcomes	% crying over 5 min after sampling, behavioural scores (4 facial expressions and the presence of cry) at 1, 3 and 5 min after the lance for a total behavioural score
Notes	Mann Whitney-U and Wilcoxon matched pairs signed ranked test used to evaluate outcomes Results reported as median and interquartile and total range Adverse effects were not evaluated

Ramenghi 1999 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Do not describe measures taken to ensure blinding of intervention and outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Rogers 2006

Methods	Randomised double-blind trial
Participants	80 infants ≤ 90 days old, born at least 34 weeks' gestational age Separated into 3 age groups: 1) 1 to 30 days, 2) 31 to 60 days, 3) 61 to 90 days
Interventions	2 mL of sterile water via syringe 2 min before bladder catheterisation (N = 40) 2 mL of 24% sucrose via syringe 2 min before bladder catheterisation (N = 40)
Outcomes	Douleur Aigue du Nouveau-ne (DAN) scale, % cry, time to return to behavioural baseline
Notes	Post hoc subgroup analyses, t-tests, Chi^2 tests, Mann-Whitney test, ANOVA and Breslow-Day (BD) test for homogeneity used to evaluate outcomes Results were reported as means and standard deviations. P values were also reported Adverse events were evaluated; no adverse effects experienced

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence generated by random number table

Rogers 2006 (*Continued*)

Allocation concealment (selection bias)	Low risk	Syringes were coded by pharmacy and solutions were indistinguishable
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Rush 2005

Methods	Prospective randomised controlled trial
Participants	30 infants < 32 weeks' gestational age or weighing < 1500 g Control group mean gestational age of 28.8 weeks (range 25 to 31) Treatment group mean gestational age of 29.57 weeks (range 26 to 32)
Interventions	Control: no swaddling, no sucrose and not held by nurse Treatment: swaddled in a warm blanket, pacifier packed with gauze soaked in 24% sucrose and held by a nurse until 15 min after the eye examination *All infants received eye drop instillation of 0.5% proparacaine and 1% tropicamide, then 15 min later eye drop instillation of 0.5% tropicamide, 2.5% phenylephrine and 0.5% tropicamide. Eye drops were all instilled into both eyes before the ROP examination
Outcomes	Pulse rate, respiratory rate and oxygen saturation at baseline (30 min before instillation of proparacaine), 5 min before eye examination, 3 different times during eye examination and 5 min after the completion of the examination; total crying time; time required to return to baseline value
Notes	ANOVA and Wilcoxon signed rank test and the Pearson test were used to evaluate outcomes Results were reported as medians, means and standard errors of the means (SEM). P values were also reported Adverse events were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described

Rush 2005 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding to interventions Outcome assessments blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Pulse rate, respiratory rate data not reported
Selective reporting (reporting bias)	Unclear risk	Pulse rate, respiratory rate data not reported
Other bias	Low risk	

Rushforth 1993

Methods	Randomised, double-blind, placebo-controlled study
Participants	52 infants, 37 to 42 weeks' gestational age, 2 to 7 days of age
Interventions	2 mL of 7.5% sucrose administered by a dropper into the mouth over a 1-min period prior to heel lance (N = 26) 2 mL of sterile water administered by dropper into the mouth over a 1-min period prior to heel lance (N = 26)
Outcomes	Percentage time crying during sampling and 3 min following the completion of the heel lance recorded on a standard audio tape recorder and analysed blindly at a later date
Notes	Results are presented as medians only with no ranges Mann Whitney U test to evaluate duration of cry Adverse effects were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Not clear as to whether sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	

Other bias	Low risk	

Slater 2010

Methods	Randomised prospective study
Participants	44 term infants 37 to 43 weeks' gestational age, < 8 days old
Interventions	Treatment group: 0.5 mL of 24% sucrose given via syringe (N = 20) Control group: 0.5 mL of sterile water (N = 24)
Outcomes	Heart rate change, Premature Infant Pain Profile (PIPP) score, nociceptive-specific brain activity, latency to change in facial expression(s), facial non-responders, nociceptive reflex withdrawal activity
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomised code
Allocation concealment (selection bias)	Low risk	Only the hospital pharmacy had access to the randomisation codes that could be used to identify the solution. A sealed copy of the randomisation chart was also stored in the neonatal unit in case an adverse event was reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, personnel and outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Stang 1997

Methods	Prospective, randomised, double-blind, placebo-controlled trial
Participants	80 healthy term male newborns, mean gestation age 39.5 weeks, mean postnatal age 31.5 h
Interventions	Dorsal Penile Nerve Block (DPNB) with non-buffered lidocaine (0.8 mL lidocaine, 0.2 mL saline), new padded restraint chair and pacifier dipped in water (N = 20) DPNB with buffered lidocaine (0.8 mL lidocaine, 0.2 mL sodium bicarbonate), rigid plastic restraint chair and pacifier dipped in water (N = 20) DPNB with non-buffered lidocaine (0.8 mL lidocaine, 0.2 mL saline), rigid plastic restraint chair and pacifier dipped in 24% sucrose (N = 20) DPNB with non-buffered lidocaine (0.8 mL lidocaine, 0.2 mL saline), rigid plastic restraint chair and pacifier dipped in water (N = 20)
Outcomes	Behavioural Distress Scale (BDS) (scores at pre-injection, at injection for DPNB, 2 min post injection, 4 min post injection and at circumcision); plasma cortisol level (30 min after start of circumcision); percentage of sleep during circumcision
Notes	Results were reported as mean and standard deviation ANOVA with repeated measures were used to compare distress scores. 1-way ANOVAs were used to examine plasma cortisol and sleep data Adverse effects were not evaluated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data results do not include number of infants with data
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Stevens 1999

Methods	Randomised, cross-over, controlled trial
Participants	122 neonates, 27 to 31 weeks' gestational age, < 28 days of age Johnston 1999b Subsample of 25 preterm neonates, 27 to 31 weeks' gestational age, < 28 days of age (refer to Stevens 1999)
Interventions	Prone positioning 30 min prior to heel lance. Pacifier dipped in sterile water and placed into the mouth 2 min prior to heel lance Pacifier dipped in 24% sucrose and placed into the mouth 2 min prior to heel lance No treatment. (N = 122, cross-over design)
Outcomes	Premature Infant Pain Profile (PIPP)
Notes	Repeated measures ANOVA and ANCOVA used to evaluate efficacy of treatment interventions Means and standard deviations provided for pain scores Adverse effects were evaluated

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of solutions and outcome assessment unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Stevens 2005

Methods	Prospective, randomised, controlled trial
Participants	66 preterm infants, 26 to 30 weeks' gestational age, < 72 h' postnatal age
Interventions	Control - no intervention (N = 22) 0.1 mL of sterile water via syringe and pacifier (N = 21) 0.1 mL of 24% sucrose via syringe and pacifier (N = 23) Solutions were given 2 min before every procedure during the first 28 days of life
Outcomes	Premature Infant Pain Profile (PIPP), Neonatal clinical outcomes and Neurobiological risk scores (NRBS)

Notes	Actual PIPP scores (mean, standard deviation) were not reported. PIPP scores were analysed by RMANOVA. Chi^2 analyses were used to compare the incidence of immediate and long-term adverse events Adverse events were evaluated-adverse events were "low" and all immediate adverse events resolved spontaneously

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated table of random numbers
Allocation concealment (selection bias)	Low risk	Delivered to baby by pharmacist. Solutions carried in dark glass bottles. Water and sucrose solutions appeared to be the same
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Storm 2002

Methods	Randomised, controlled trial
Participants	48 preterm, median gestational age 32 week, median postnatal age 14 days
Interventions	2 mL of 15% sucrose, N = 12 1 mL of 25% sucrose, N = 12 Milk via nasogastric (NG) tube, N = 12 Milk via NG tube + 25% sucrose, N = 12 All infants were given water prior to a second heel lance Oral solutions were administered via syringe into infant's mouth 2 min prior to heel lance Milk was given during the last hour prior to heel lance
Outcomes	Changes from before heel lance to during heel lance for: crying time, changes in behavioural state, skin conductance, heart rate

Storm 2002 (*Continued*)

Notes	Paired non-parametric tests (Wilcoxon test) used to compare the infant's intervention and control session No median or interquartile range reported for each outcome Adverse effects were not evaluated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	2 groups fasting, 2 groups fed up to 1 h prior to intervention with NG-tube. Did not provide any information about blinding of assessor
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on number of participants included in the methods or results section
Selective reporting (reporting bias)	High risk	Results in figures and P values only. No data that can be meta-analysed presented
Other bias	Low risk	

Taddio 2008

Methods	Double-blinded, randomised-controlled trial
Participants	240 newborns, mean gestational age 38.7 to 39.9 weeks, mean postnatal age 0.5 to 0.8 h
Interventions	2 mL of 24% sucrose given to newborns of non-diabetic mothers, N = 60 2 mL of sterile water given to newborns of non-diabetic mothers, N = 60 2 mL of 24% sucrose given to newborns of diabetic mothers, N = 60 2 mL of sterile water given to newborns of diabetic mothers, N = 60 Solutions were given before all intramuscular injections, venipunctures and heel lances during the first 2 days of birth
Outcomes	Premature Infant Pain Profile (PIPP) score during procedure
Notes	Student t-test used to compare average PIPP scores between groups. Post-hoc analyses was performed after adjusting for baseline characteristics by use of a general linear model for intramuscular injection and venipuncture and linear mixed-model analysis for heel lances. Adverse events were analysed using the Chi^2 test or the Student t-test Adverse effects were reported - no significant differences between groups in the incidence of adverse events, which included spitting up and blood glucose levels

Taddio 2008 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table. 1:1 allocation
Allocation concealment (selection bias)	Low risk	Centralised at the hospital pharmacy. Solutions carried in identical bottles only labelled with patient identification
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Taddio 2011

Methods	Randomised controlled trial
Participants	330 infants mean gestational age (standard deviation (SD)) 39.5 (1.2) Liposomal lidocaine group (N = 110) mean gestational age (SD) 39.6 (1) Sucrose group (N = 110) mean gestational age (SD) 39.6 (1.3) Sucrose liposomal lidocaine group (N = 110) mean gestational age (SD) 39.6 (1.3)
Interventions	Liposomal lidocaine group: 1 g of liposomal lidocaine 4% cream to the dorsum of the hand, occluded by a dressing (Tegaderm) for 30 to 40 min Sucrose group: 2 mL of 24% sucrose solution, administered by mouth using a syringe over 1 to 2 min Sucrose liposomal lidocaine group: both sucrose and liposomal lidocaine Placebos were used for liposomal lidocaine and sucrose (i.e. double-dummy design), so that all infants received a topically administered cream (liposomal lidocaine or placebo cream) and oral solution (sucrose or placebo water)
Outcomes	Facial grimacing, cry duration (seconds), observer-rated pain using a visual analogue scale (VAS) (0 to 10 cm), heart rate (beats per minute), oxygen saturation (%)
Notes	Reported no significant adverse effects
Risk of bias	

Taddio 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used
Allocation concealment (selection bias)	Low risk	Concealment of treatment allocation was achieved by carrying out randomisation and dispensing functions offsite
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, personnel and outcome assessors all blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Unceta-Barranechea 2008

Methods	Prospective randomised controlled trial
Participants	150 term infants
Interventions	Control - facilitated tucking Non-nutritive sucking (NNS) with water 2 mL 24% sucrose with NNS
Outcomes	Modified Neonatal Facial Coding System (NFCS), mean crying time
Notes	Paper translated from Spanish to English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions blinded Blinding of outcome assessments

Unceta-Barranechea 2008 (*Continued*)

Other bias	Unclear risk	Not enough details in the paper to determine whether there were other risks of bias

Yilmaz 2011

Methods	Randomised controlled trial
Participants	120 infants gestational age (GA) 37 to 42 weeks Control group (N = 30): mean GA (standard deviation (SD)) 39.67 (0.80) Mother's milk group (N = 30): mean GA (SD) 39.10 (1.03) Sucrose group (N = 30): mean GA (SD) 39.10 (0.71) Pacifier group (N = 30): mean GA (SD) 39.20 (0.93)
Interventions	Control group: newborns were in their mothers' lap; no interventions were made before the painful procedure Mother's milk group: 2 mL mother's milk 2 min before the procedure by using a syringe with the needle removed and avoiding contact of the syringe with the mouth and lips Sucrose group: 2 mL sucrose of 20% by using a syringe 2 min before the procedure Pacifier group: given a pacifier
Outcomes	Neonatal Infant Pain Scale (NIPS) score, heart rate, respiratory rate, crying time
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Did not specify method of randomisation
Allocation concealment (selection bias)	High risk	Did not specify method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Did not report blinding of personnel or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

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

Study	Reason for exclusion
Abad 1993	Abstract
Abad 2001	Although this was a randomised controlled trial, 4 newborns were included twice (i.e. there were 55 events recorded for 51 participants), therefore, it was not possible to separate data for 51 newborns
Ahuja 2000	This was a non-randomised study. A single cohort was studied. The intervention was a non-sucrose sweetener
Barbier 1994	Study did not include the use of sucrose
Barr 1993	Although a randomised controlled trial, the authors do not provide information on the number of infants in each group. Results were presented in graph form without indicating whether means or medians were used. No standard deviations are presented
Barr 1995	Excluded based on postnatal age (PNA) (2 and 4 months PNA)
Bilgen 2001	This manuscript was published previously in the *European Journal of Pediatrics* ("Comparison of sucrose and human milk on pain response in newborns" by Ors et al, Eur J Pediatr, 158:63-66, 1999) and therefore, this article has been retracted by the Journal of Pain The editor of the Journal of Pain states that "Anyone citing this article must cite from the European Journal of Pediatrics and not from the Journal of Pain"
Blass 1991	Although this is a randomised controlled trial the number of neonates in each group is not stated
Blass 1995	This is a controlled trial without randomisation. The number of patients in each group is not stated
Blass 2001	Study not fully randomised
Bucher 2000	This study used an artificial sweetener, glycine or breast milk as the intervention
Curtis 2007	Postnatal age 0 to 6 months
Efe 2007	Study not fully randomised
Gibbins 2000	Abstract
Gormally 1996	Abstract
Graillon 1997	A randomised controlled cross-over study. 60 crying infants were randomised to receive 250 μL of 24% sucrose solution, 0.25% quinine hydrochloride solution, or corn oil as well as water in a mixed parallel cross-over design. Relative to water, sucrose persistently reduced crying, and transiently increased mouthing and hand-mouth contact. No painful stimulus was applied to the neonates
Harrison 2011a	Not a randomised controlled trial
Isik 2000b	Abstract

(*Continued*)

Johnston 2000	Abstract
Joung 2010	Non-randomised groups
Lewindon 1998	The infants in this study were older than the inclusion criteria for this review (mean age 17.1 weeks)
Mellah 1999	Randomised double blind cross-over study. Data analysed by paired t-test. Results from the first exposure to sucrose or placebo could not be isolated
Mohan 1998	Control group was not randomised
Ramenghi 2002	Immunisations performed at 2, 3 or 4 months
Razmus 2004	Study not fully randomised
Reis 2003	Mean postnatal age 9.5 weeks
Sahebihag 2011	Infants were too old for this review
Skogsdal 1997	This study used glucose and breast milk as the interventions
Stevens 1997b	Abstract
Stevens 2000	Abstract
Taddio 2000	Not a randomised controlled trial and postnatal age included older infants
Taddio 2003	Infants did not receive painful procedure
Taddio 2009	Population subset of a larger study already included in the review
Vederhus 2006	Sucrose was not used as an intervention
Yoon 2001	Not fully randomised

Characteristics of studies awaiting assessment *[ordered by study ID]*

Akman 2002

Methods	Unknown I Blinding of randomisation - unclear II Blinding of intervention -unclear III Complete follow-up - unclear IV Blinding of outcome measurement - unclear

Akman 2002 (*Continued*)

Participants	138 neonates, 37 to 42 weeks' postmenstrual age, > 24 h' postnatal age Mean age of 2 days for all groups
Interventions	2 mL of 12.5% glucose plus pacifier 2 mL of 12.5% sucrose plus pacifier 2 mL of 12.5% glucose 2 mL of 12.5% sucrose 2 mL of sterile water
Outcomes	Crying behaviours, Neonatal Facial Coding System (NFCS)
Notes	Cry duration measured up to 3 min after heel lance in seconds Adverse effects: not reported

Dilli 2009

Methods	Randomised controlled trial
Participants	243 children aged 0 and 48 months receiving their routine vaccinations; unknown number for 0 to 6 months
Interventions	Unknown
Outcomes	Neonatal Infant Pain Scale (NIPS) score, crying behaviours
Notes	Methods and results not reported for 0 to 6 months age group

Singh 2001

Methods	Unknown
Participants	Unknown
Interventions	Unknown
Outcomes	Unknown
Notes	Unknown

DATA AND ANALYSES

Comparison 1. Heel lance: sucrose (sucrose or sucrose+NNS) vs. control (NNS+water, water or positioning and containing intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Premature Infant Pain Profile (PIPP) at 30 s after heel lance	4	264	Mean Difference (IV, Fixed, 95% CI)	-1.76 [-2.54, -0.97]
2 Premature Infant Pain Profile (PIPP) at 60 s after heel lance	3	195	Mean Difference (IV, Fixed, 95% CI)	-2.05 [-3.08, -1.02]

Comparison 2. Heel lance: sucrose 25-33% vs. control (sterile water)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 % change in heart rate 1 min after heel lance	2	86	Mean Difference (IV, Fixed, 95% CI)	0.90 [-5.81, 7.61]
2 % change in heart rate 3 min after heel lance	2	86	Mean Difference (IV, Fixed, 95% CI)	-6.20 [-15.27, 2.88]
3 Heart rate at 3 min after heel lance	2	154	Mean Difference (IV, Fixed, 95% CI)	-0.98 [-8.29, 6.32]

Comparison 3. Heel lance: sucrose 12.5-50% vs. control (sterile water)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of first cry (s)	3	192	Mean Difference (IV, Fixed, 95% CI)	-8.99 [-20.07, 2.10]
2 Total crying time (s)	2	88	Mean Difference (IV, Fixed, 95% CI)	-39.26 [-44.29, -34.24]

Comparison 4. ROP examination: sucrose 24-33% (sucrose or sucrose+NNS) vs. control (water or water+NNS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PIPP score during (L) eye examination	3	82	Mean Difference (IV, Fixed, 95% CI)	-1.27 [-2.29, -0.25]
1.1 Sucrose via syringe vs. control (sterile water via syringe)	2	52	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-1.88, 0.59]
1.2 Sucrose + pacifier vs. control (sterile water + pacifier)	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-4.41, -0.79]
2 PIPP score for ROP examinations	2	52	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-1.88, 0.59]

Comparison 5. ROP examination: sucrose 24-33% (sucrose or sucrose+NNS) vs. control (water or water+NNS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oxygen saturation (%) during eye examination	2	62	Mean Difference (IV, Fixed, 95% CI)	-2.58 [-4.94, -0.23]

Analysis 1.1. Comparison 1 Heel lance: sucrose (sucrose or sucrose+NNS) vs. control (NNS+water, water or positioning and containing intervention), Outcome 1 Premature Infant Pain Profile (PIPP) at 30 s after heel lance.

Review: Sucrose for analgesia in newborn infants undergoing painful procedures

Comparison: 1 Heel lance: sucrose (sucrose or sucrose+NNS) vs. control (NNS+water, water or positioning and containing intervention)

Outcome: 1 Premature Infant Pain Profile (PIPP) at 30 s after heel lance

Study or subgroup	Sucrose N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gibbins 2002	64	8.16 (3.24)	64	10.19 (2.67)		58.2 %	-2.03 [-3.06, -1.00]
Johnston 1999a	15	7.52 (3.3)	16	8.92 (2.8)		13.2 %	-1.40 [-3.56, 0.76]
Slater 2010	20	5.8 (4.68)	24	8.5 (3.12)		10.7 %	-2.70 [-5.10, -0.30]
Stevens 1999	32	9.06 (3.48)	29	9.62 (3.88)		17.9 %	-0.56 [-2.42, 1.30]
Total (95% CI)	**131**		**133**			**100.0 %**	**-1.76 [-2.54, -0.97]**

Heterogeneity: $Chi^2 = 2.56$, df = 3 (P = 0.46); $I^2 = 0.0\%$

Test for overall effect: Z = 4.38 (P = 0.000012)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Heel lance: sucrose (sucrose or sucrose+NNS) vs. control (NNS+water, water or positioning and containing intervention), Outcome 2 Premature Infant Pain Profile (PIPP) at 60 s after heel lance.

Review: Sucrose for analgesia in newborn infants undergoing painful procedures

Comparison: 1 Heel lance: sucrose (sucrose or sucrose+NNS) vs. control (NNS+water, water or positioning and containing intervention)

Outcome: 2 Premature Infant Pain Profile (PIPP) at 60 s after heel lance

Study or subgroup	Sucrose N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gibbins 2002	60	8.78 (4.03)	59	11.2 (3.47)		58.4 %	-2.42 [-3.77, -1.07]
Johnston 1999a	15	6.79 (2.6)	16	8.59 (3.1)		26.4 %	-1.80 [-3.81, 0.21]
Stevens 1999	21	9.48 (4.42)	24	10.54 (4.61)		15.3 %	-1.06 [-3.70, 1.58]
Total (95% CI)	**96**		**99**			**100.0 %**	**-2.05 [-3.08, -1.02]**

Heterogeneity: Chi^2 = 0.89, df = 2 (P = 0.64); I^2 =0.0%

Test for overall effect: Z = 3.89 (P = 0.000099)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Heel lance: sucrose 25-33% vs. control (sterile water), Outcome 1 % change in heart rate 1 min after heel lance.

Review: Sucrose for analgesia in newborn infants undergoing painful procedures

Comparison: 2 Heel lance: sucrose 25-33% vs. control (sterile water)

Outcome: 1 % change in heart rate 1 min after heel lance

Study or subgroup	Sucrose N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Haouari 1995	15	21.3 (14.72)	15	11.4 (11.62)		50.0 %	9.90 [0.41, 19.39]
Isik 2000a	28	10.67 (15.82)	28	18.77 (20.16)		50.0 %	-8.10 [-17.59, 1.39]
Total (95% CI)	**43**		**43**			**100.0 %**	**0.90 [-5.81, 7.61]**

Heterogeneity: Chi^2 = 6.91, df = 1 (P = 0.01); I^2 =86%

Test for overall effect: Z = 0.26 (P = 0.79)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Heel lance: sucrose 25-33% vs. control (sterile water), Outcome 2 % change in heart rate 3 min after heel lance.

Review: Sucrose for analgesia in newborn infants undergoing painful procedures

Comparison: 2 Heel lance: sucrose 25-33% vs. control (sterile water)

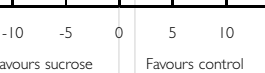
Outcome: 2 % change in heart rate 3 min after heel lance

Study or subgroup	Sucrose N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Haouari 1995	15	14.5 (12.01)	15	17.5 (23.24)		47.0 %	-3.00 [-16.24, 10.24]
Isik 2000a	28	1.28 (19.21)	28	10.31 (27.62)		53.0 %	-9.03 [-21.49, 3.43]
Total (95% CI)	**43**		**43**			**100.0 %**	**-6.20 [-15.27, 2.88]**

Heterogeneity: Chi^2 = 0.42, df = 1 (P = 0.52); I^2 =0.0%

Test for overall effect: Z = 1.34 (P = 0.18)

Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2 Heel lance: sucrose 25-33% vs. control (sterile water), Outcome 3 Heart rate at 3 min after heel lance.

Review: Sucrose for analgesia in newborn infants undergoing painful procedures

Comparison: 2 Heel lance: sucrose 25-33% vs. control (sterile water)

Outcome: 3 Heart rate at 3 min after heel lance

Study or subgroup	Sucrose N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Guala 2001	20	121.8 (20.5)	20	123.3 (20.6)		32.9 %	-1.50 [-14.24, 11.24]
Harrison 2003	55	151.73 (22.47)	59	152.46 (26.07)		67.1 %	-0.73 [-9.65, 8.19]
Total (95% CI)	**75**		**79**			**100.0 %**	**-0.98 [-8.29, 6.32]**

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0.0\%$

Test for overall effect: Z = 0.26 (P = 0.79)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Heel lance: sucrose 12.5-50% vs. control (sterile water), Outcome 1 Duration of first cry (s).

Review: Sucrose for analgesia in newborn infants undergoing painful procedures

Comparison: 3 Heel lance: sucrose 12.5-50% vs. control (sterile water)

Outcome: 1 Duration of first cry (s)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Harrison 2003	54	43.32 (61.98)	56	68.73 (79.8)		17.3 %	-25.41 [-52.06, 1.24]
Mathai 2006	17	33 (9)	15	38 (23)		79.9 %	-5.00 [-17.40, 7.40]
Ogawa 2005	25	135 (128)	25	156 (108)		2.8 %	-21.00 [-86.65, 44.65]
Total (95% CI)	**96**		**96**			**100.0 %**	**-8.99 [-20.07, 2.10]**

Heterogeneity: Chi^2 = 1.98, df = 2 (P = 0.37); I^2 =0.0%

Test for overall effect: Z = 1.59 (P = 0.11)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Heel lance: sucrose 12.5-50% vs. control (sterile water), Outcome 2 Total crying time (s).

Review: Sucrose for analgesia in newborn infants undergoing painful procedures

Comparison: 3 Heel lance: sucrose 12.5-50% vs. control (sterile water)

Outcome: 2 Total crying time (s)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Isik 2000a	28	60.53 (9.2)	28	105 (12.1)		79.6 %	-44.47 [-50.10, -38.84]
Mathai 2006	17	79 (16)	15	98 (16)		20.4 %	-19.00 [-30.11, -7.89]
Total (95% CI)	**45**		**43**			**100.0 %**	**-39.26 [-44.29, -34.24]**

Heterogeneity: Chi^2 = 16.07, df = 1 (P = 0.00006); I^2 =94%

Test for overall effect: Z = 15.32 (P < 0.00001)

Test for subgroup differences: Not applicable

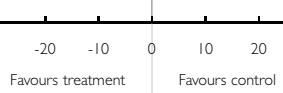
Analysis 4.1. Comparison 4 ROP examination: sucrose 24-33% (sucrose or sucrose+NNS) vs. control (water or water+NNS), Outcome 1 PIPP score during (L) eye examination.

Review: Sucrose for analgesia in newborn infants undergoing painful procedures

Comparison: 4 ROP examination: sucrose 24-33% (sucrose or sucrose+NNS) vs. control (water or water+NNS)

Outcome: 1 PIPP score during (L) eye examination

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 Sucrose via syringe vs. control (sterile water via syringe)							
Boyle 2006	10	14.3 (1.6)	10	15.3 (1.9)		43.9 %	-1.00 [-2.54, 0.54]
Grabska 2005	16	14 (3)	16	14 (3)		24.1 %	0.0 [-2.08, 2.08]
Subtotal (95% CI)	**26**		**26**			**68.0 %**	**-0.65 [-1.88, 0.59]**
Heterogeneity: Chi^2 = 0.57, df = 1 (P = 0.45); I^2 =0.0%							
Test for overall effect: Z = 1.02 (P = 0.31)							
2 Sucrose + pacifier vs. control (sterile water + pacifier)							
Mitchell 2004	15	8.8 (2.71)	15	11.4 (2.32)		32.0 %	-2.60 [-4.41, -0.79]
Subtotal (95% CI)	**15**		**15**			**32.0 %**	**-2.60 [-4.41, -0.79]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.82 (P = 0.0048)							
Total (95% CI)	**41**		**41**			**100.0 %**	**-1.27 [-2.29, -0.25]**
Heterogeneity: Chi^2 = 3.64, df = 2 (P = 0.16); I^2 =45%							
Test for overall effect: Z = 2.44 (P = 0.015)							
Test for subgroup differences: Chi^2 = 3.06, df = 1 (P = 0.08), I^2 =67%							



Analysis 4.2. Comparison 4 ROP examination: sucrose 24-33% (sucrose or sucrose+NNS) vs. control (water or water+NNS), Outcome 2 PIPP score for ROP examinations.

Review: Sucrose for analgesia in newborn infants undergoing painful procedures

Comparison: 4 ROP examination: sucrose 24-33% (sucrose or sucrose+NNS) vs. control (water or water+NNS)

Outcome: 2 PIPP score for ROP examinations

Study or subgroup	Sucrose N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Boyle 2006	10	14.3 (1.6)	10	15.3 (1.9)		64.6 %	-1.00 [-2.54, 0.54]
Grabska 2005	16	14 (3)	16	14 (3)		35.4 %	0.0 [-2.08, 2.08]
Total (95% CI)	**26**		**26**			**100.0 %**	**-0.65 [-1.88, 0.59]**

Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² =0.0%

Test for overall effect: Z = 1.02 (P = 0.31)

Test for subgroup differences: Not applicable

Analysis 5.1. Comparison 5 ROP examination: sucrose 24-33% (sucrose or sucrose+NNS) vs. control (water or water+NNS), Outcome 1 Oxygen saturation (%) during eye examination.

Review: Sucrose for analgesia in newborn infants undergoing painful procedures

Comparison: 5 ROP examination: sucrose 24-33% (sucrose or sucrose+NNS) vs. control (water or water+NNS)

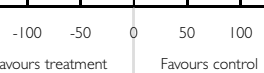
Outcome: 1 Oxygen saturation (%) during eye examination

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Grabska 2005	16	93 (5)	16	96 (3)		67.7 %	-3.00 [-5.86, -0.14]
Rush 2005	14	93.29 (5.773)	16	95 (5.772)		32.3 %	-1.71 [-5.85, 2.43]
Total (95% CI)	**30**		**32**			**100.0 %**	**-2.58 [-4.94, -0.23]**

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² =0.0%

Test for overall effect: Z = 2.15 (P = 0.031)

Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Trials assessing pain during heel lances

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Altun-Koroglu 2010	75 full-term infants	Heel lance	3 mL of hind milk (N = 25) 3 mL of 12.5% sucrose solution (N = 25) 3 mL of distilled water (N = 25)	NFCS, crying time, duration of crying, HR	Median and IQR	Median crying time, duration of first cry and tachycardia, and time needed to return to baseline = longest in the distilled water group. Significantly shorter in the hind milk group when compared to distilled water group (P = 0.022, P = 0.008, P 0.009 and P = 0.038, respectively) No statistically significant differences observed between the hind milk and sucrose group Maximum HR in hind milk group was significantly lower than distilled water group (184 bpm vs. 196 bpm, P = 0.031) Significant reduction in average NFCS score. 1st minute NFCS score and 5th minute NFCS score in the hind

Table 1. Trials assessing pain during heel lances (*Continued*)

						milk group compared to the distilled water group (P = 0.006, P = 0.017 and P = 0.021, respectively)
Blass 1997	72 infants, 22 to 40 h old	Heel lance	2 mL of either of the following solutions: water 12% sucrose protein mixture 7% lactose dilute fat (coconut and soy oil) concentrated fat fat and lactose mixture RSF (water, protein, lactose, fat) milk N = 8 for all groups	Crying time (%) during blood collection and 1, 2 and 3 min after heel lance Mean % of crying time per min at 1, 2 and 3 min after heel lance (recovery period)	Mean proportions Graphically reported	Significantly less crying time during blood collection in the sucrose group (47%) compared to the water group (92%, P = 0.015)
Blass 1999	40 term newborn infants, 34 to 55 h old	Heel lance	2 mL of 12% sucrose over 2 min via syringe (N = 10) 2 mL of water via syringe over 2 min (N = 10) Pacifier dipped every 30 s in 12% sucrose solution for 2 min (N = 10) Pacifier dipped in water every 30 s for 2 min (N = 10) prior to heel lance	% time crying 3 min after heel lance Mean change in HR % time grimacing	Mean percentage Mean change (bpm) Mean percentage	2 mL of 12% (0.24 g) sucrose alone diminished cry duration from heel lance compared to water (8% vs. 50%, P = 0.003) and water with pacifier (8% vs. 35%, P = 0.002). Pacifier with 12% sucrose more effective in reducing cry duration compared to water with pacifier (5% vs. 35%, P = 0.001) or water alone (50%, P = 0.002)

Table 1. Trials assessing pain during heel lances (*Continued*)

						Mean HR increased significantly from treatment to heel lance in infants receiving water alone (mean increase of 17 bpm, P = 0.002) and water with pacifier (mean increase of 20 bpm, P = 0.005). Mean increase in HR also increased for the 2 mL of 12% (0.24 g) sucrose and pacifier group (mean difference of 7.4 bpm, P = 0.05) but not for infants receiving 2 mL of 12% (0.24 g) sucrose alone (mean difference of 5.9 bpm, P = 0.142) 2 mL of 12% (0.24 g) sucrose reduced grimacing compared to water (P = 0.0003). 12% (0.24 g) sucrose with pacifier reduced grimacing compared to water (P = 0.001) and pacifier alone (P = 0.04)
Bucher 1995	16 preterm infants, 27 to 34 weeks' GA, postnatal age approximately 42 days	Heel lance	2 mL of 50% sucrose via syringe into the mouth 2 min before heel lance 2 mL of distilled water via syringe into the mouth 2 min before heel	% time crying Recovery time until crying stopped Increase in HR Recovery time for HR $TcpO_2$ (max increase - kPa); $TcpO_2$	Not reported Median, IQR Median, IQR	Cry duration (% of total duration of intervention) significantly reduced in 2 mL of 50% (1.0 g) sucrose group (71.5%) compared to control

Table 1. Trials assessing pain during heel lances (*Continued*)

			lance (N = 16, cross-over design)	(max decrease - kPa); $TcpO_2$ (difference between baseline and 10 min after end of intervention - kPa) ; $TcpCO_2$ (max decrease - kPa); $TcpCO_2$ (difference between baseline and 10 min after the end of intervention), recovery time for respirations		group (93.5%, P = 0.002) Median increase in HR (bpm) after heel lance were significantly reduced in the 2 mL of 50% (1.0 g) of sucrose group (35 bpm) compared to water (51 bpm), P = 0.005 No significant differences between groups with respect to measures for $TcpO_2$ (P = 0.05) and $TcpCO_2$ (P = 0.21)
Codipietro 2008	101 term infants, 39.3 to 39.4 weeks GA	Heel lance	Breastfeeding prior to heel lance (N = 51) 1 mL 25% sucrose via syringe (N = 50)	Duration of first cry, % crying time in first 2 min, and % crying time during blood sampling HR increase from baselines at 30 s following commencement of procedure SpO_2 decrease PIPP during blood sampling, 2 min after heel lance	Median, range	Median duration of first cry: breastfeeding group (3 (0 to 12)) compared to sucrose (21 (0 to 120)), P = 0.004 % crying during first 2 min: breastfeeding group (4 (0 to 100) compared to sucrose (45 (0 to 100) (P < 0.001) % crying during sampling: breastfeeding group (8 (0 to 100) compared to sucrose (56.5 (0 to 100) (P = 0.0003) Median increase in HR from baseline to 30 s after start of heel lance was significantly

Table 1. Trials assessing pain during heel lances (*Continued*)

						lower in breastfeeding group (13 (-12 to 54)) compared to sucrose group (22 (-32 to 65)) (P = 0.005) Median decrease in SpO_2 from baseline to 30 s after start of heel lance was significantly greater in sucrose group (-3 (-30 to 1)) compared to breastfeeding group (-1 (-14 to 2)) (P= 0.001) Median PIPP scores significantly lower in breastfeeding group (3.0) compared to sucrose group (8.5) (P < 0.0001)
Gibbins 2002	190 preterm and term infants, mean GA of 33.7 weeks, < 7 days postnatal age	Heel lance	0.5 mL of 24% sucrose via syringe to the anterior surface of the tongue followed by pacifier (N = 64) 0.5 mL 24% sucrose without pacifier (N = 62) 0.5 mL sterile water with pacifier (N = 64) 2 min prior to heel lance	PIPP scores at 30 and 60 s after heel lance	Reported means, SD	Statistically significant difference in mean PIPP scores at both 30 s (F = 8.23, P < 0.001) and 60 s (F = 8.49, P < 0.001) after heel lance in favour of 0.5 mL of 24% (0.12 g) sucrose group and 0.5 mL of 24% (0.12 g) sucrose with pacifier group. Post-hoc Tukey tests showed infants who received sucrose and pacifier had significantly lower PIPP scores

Table 1. Trials assessing pain during heel lances (*Continued*)

						after heel lance at 30 s (mean 8.16, SD 3.24) compared to infants receiving sucrose alone (mean 9.77, SD 3.04, P = 0.007) and water with pacifier (mean 10.19, SD 2.67, P < 0.001). At 60 s after heel lance, PIPP scores were significantly lower for 0.5 mL of 24% (0.12 g) sucrose with pacifier group (mean 8.78, SD 4.03) compared to the 0.5 mL of 24% (0.12 g) sucrose alone group (mean 11.20, SD 3.25, P = 0.005) and water with pacifier group (mean 11.20, SD 3.47, P = 0.007). No significant differences in PIPP scores found between 0.5 mL of 24% (0.12 g) sucrose alone group or water with pacifier group at both follow-up times
Gormally 2001	94 term newborns, mean GA 39.4 weeks on 2nd or 3rd day of life	Heel lance	No holding and sterile water given by pipette (N = 21) No holding and 0.250 mL of 24% sucrose solution given by	% time crying 1, 2, 3 min after heel lance Mean HR before intervention, 1, 2, 3 min after heel lance, mean vagal tone index before	Not reported	Crying decreased over time (F(2, 80) = 10.0, P < 0.001) but no significant interaction noted for time with holding, taste or hold-

Table 1. Trials assessing pain during heel lances (*Continued*)

			pipette (N = 22) Holding and sterile water given by pipette (N = 20) Holding and 0.250 mL of 24% sucrose solution by pipette (N = 22) All solutions given 3 times at 30-s intervals	intervention, 1, 2, 3 min after heel lance Pain concatenation scores for facial activity before intervention, 1, 2, 3 min after heel lance		ing and taste. Effect of taste on crying was significant (F(1,81) = 4.1, P < 0.05) in favour of 0.25 mL of 24% (0.18 g) sucrose. Effect of holding not statistically significant (F(1,81) = 3.0, P = 0.09)). No statistically significant interaction between taste and holding to reduce crying (F(1,81) = 0.80, P = 0.37). Effect of combined interventions was additive Although no significant differences in mean HR due to holding or sucrose as main effects, there was significant interaction between holding and taste (F(1,61) = 8.89, P < 0.004), indicating synergistic effect that was also dependent on pre-intervention HR (F(1, 61) = 9.23, P < 0.004). No significant main effects noted for vagal tone; as with HR, effect of vagal tone was de-

Table 1. Trials assessing pain during heel lances (*Continued*)

						pen- dent on pre-intervention vagal tone for both holding and taste interventions (F(1,60) = 4.82, P < 0.03) . Pre-intervention levels interacted to decrease HR and vagal tone in infants who had higher rates before interventions Pain concatenation scores measuring facial expressions of pain decreased over time (F(1,65) = 28.5, P < 0. 001). Only the effect of holding reduced pain scores (F(1,65) = 5.6, P <0.02). No difference as to whether infant received sucrose (taste main effect F(1,65) 0. 17, P = 0.68
Greenberg 2002	84 term newborns, approximately 17 to 19 h old	Heel lance	Sugar-coated pacifier (N = 21) water-moistened pacifier (N = 21) 2 mL of 12% sucrose (n =21) routine care (N = 21)	Duration of cry from procedure phase to 3 min post-procedure Vagal tone and vagal tone index Salivary cortisol levels	Not reported	Significant decrease in duration of cry for the sugar-coated pacifier group compared to the control group (P = 0. 001) and the water-moistened pacifier group (P = 0.001) Lower vagal tone during heel lance in the sugar-coated paci-

Table 1. Trials assessing pain during heel lances (*Continued*)

						fier group compared to the control group (P = 0.008) and oral sucrose group (P = 0.018). Lower vagal tone index in the sugar-coated pacifier group compared to control group at heel lance (P = 0.019), and 6 to 10 min after (P = 0.007) and 11 to 15 min (P = 0.049) after heel lance No significant differences were found in salivary cortisol levels across groups (no P value reported)
Guala 2001	140 term, 38 to 41 weeks' GA	Heel lance	Nothing (N = 20) Water (N = 20) 5% Glucose (N = 20) 33% Glucose (N = 20 50% Glucose (N = 20) 33% Sucrose (N = 20) 50% Sucrose (N = 20)	HR before, during and 3 min after heel lance	Mean, SD	No significant differences were found between groups for differences in HR at each of the 3 phases of the heel lance (P value reported for 3 min after heel lance, P = 0.087; the difference between 3 min after heel lance and during heel lance, P = 0.068)
Haouari 1995	60 term infants, 37 to 42 weeks' gestation, 1 to 6 days of age	Heel lance	2 mL of 12.5% sucrose 2 min prior to heel lance (N = 15) 2 mL of 25% sucrose 2 min prior to heel lance (N = 15)	Total time crying over 3 min. Time of first cry after lance % change in HR at 1, 3, 5 min after heel lance	Median, IQR Reported Means and SEM	After heel lance, significant decreases in total crying time and duration of first cry in 2 mL of 50% (1.0 g) sucrose group com-

Table 1. Trials assessing pain during heel lances (*Continued*)

			2 mL of 50 % sucrose 2 min prior to heel lance (N = 15) 2 mL of sterile water 2 min prior to heel lance (N = 15) All solutions were given by syringe on the tongue over < 1 min			pared with water (P = 0.02). Significant reduction in median time crying at end of first minute (P < 0.02) in 2 mL of 50% (1.0 g) sucrose group (35 s; range 14 to 60) compared with water (60 s; range 50 to 60). In second minute, duration of cry was significantly less in 2 mL of 50% (1.0 g) sucrose group (0 s; range 0 to 25) and in 2 mL of 25% (0.5 g) sucrose group (18 s; range 0 to 55) compared to water (60 s; range 40 to 60), P = 0.003 and P = 0.02, respectively Significant decrease in % change in HR 3 min after heel lancing (P = 0.02) in the 2 mL of 50% (1.0 g) sucrose group (mean 0.1%, SEM 3.3) compared to water group (mean 17.5%, SEM 6.0)
Harrison 2003	99 sick hospitalised infants, mean (SD) gestation age 36.7 weeks (3.3) (treatment), 36.8 weeks (3.	Heel lance	1 mL of water (N = 46) 1 mL of 25% sucrose (N = 53) For infants weighing ≤ 1500 g the dose was reduced	Duration of cry until 5 second pause, incidence and duration of crying time during the heel lance and	Mean, SD (collected from authors)	Mean length of first cry was higher in the water group (70.5 (83.6)) compared to the sucrose group (46.

Table 1. Trials assessing pain during heel lances (*Continued*)

	7) (control) (author provided data on a subset of infants from a larger study (N = 128) that fulfilled our inclusion criteria)		to 0.5 mL	squeeze and during the 3-minute recovery period HR at baseline, heel lance, during heel lance and 1, 2, 3 min post heel lance SpO_2 at baseline, heel lance, during heel lance and 1, 2, 3 min post heel lance 4-point subset of the NFCS (brow bulge, eye squeeze, nasolabial furrow, stretch mouth) at heel lance, during heel lance and 1, 2, 3 min post heel lance		8 (63.1)). The sucrose group cried 57.1% of the procedure time compared to 58.8% in the water group. The mean total duration of cry during the heel lance was 84.7 s (68.8) in the sucrose group and 87.4 s (87.1) in the water group The mean (SD) HR upon heel lance was 163. 0 (17.9) bpm in the sucrose group and 159.5 (19.2) bpm in the water group. HR at 30 s from the beginning of the procedure was 175.4 (22.2) and 172.8 (23.6) bpm in the sucrose and water groups, respectively. The HR in both groups decreased after the procedure to 152. 1 (22.5) bpm in the sucrose group and 154.2 (29.1) bpm in the water group 2 min post heel lance Results of SpO_2 were similar between the 2 groups Mean facial scores were significantly

Table 1. Trials assessing pain during heel lances (*Continued*)

						reduced at heel lance (2.74 (1.8)) in the sucrose group compared to the water group (2.94 (1.6)) (P = 0.02) and at 1 min (P = 0.04) and 2 min (P = 0.046) post-heel lance. No significant differences occurred at 3 min post heel lance
Isik 2000a	113 healthy term newborns GAs 37 to 42 weeks, median post natal age 2 days, range 2 to 5 days	Heel lance	2 mL of 30% sucrose (N = 28) 2 mL of 10% glucose (N = 29) 2 mL of 30% glucose (N = 28) 2 mL of distilled water (N = 28) syringed into the anterior third of the tongue for 1 and 2 min prior to heel lance	Mean cry time during 3 min after lance Mean maximum HR 3 min from heel lance Mean recovery time for HR % change in HR at 1, 2, 3 min after heel lance	Reported means, SD Reported means and SEM	Infants who received 2 mL of 30% (0.6 g) sucrose (mean crying time of 61 s) cried significantly less than those who received 30% glucose (mean crying time of 95 s), 10% glucose (mean crying time of 103 s) or sterile water (mean crying time of 105 s) (P = 0.02) No significant difference between groups with respect to maximum HR after heel lance (P = 0. 71), or mean recovery time (P = 0.09). No significant difference found in % change in HR at 1 or 3 min after heel lance (P

Table 1. Trials assessing pain during heel lances (*Continued*)

						= 0.14, P = 0. 53, respectively). At 2 min after heel lance, % change in HR favoured group receiving sucrose (P = 0.05) compared to other groups
Johnston 1997a	85 preterm infants, 25 - 34 weeks' GA, 2 to 10 days of age	Heel lance	0.05 mL of 24% sucrose via syringe into the mouth just prior to heel lance (N = 27) 0.05 mL of 24% sucrose via syringe into the mouth just prior to heel lance and simulated rocking 15 min prior to heel lance (N = 14) 0.05 mL of sterile water via syringe into the mouth just prior to heel lance and simulated rocking 15 min prior to heel lance (N = 24) 0.05 mL of sterile water via syringe into the mouth just prior to heel lance	HR at baseline and 3 x 30-second blocks Behavioural facial actions (NFCS) at baseline and 3 x 30-second blocks	Not reported	Although HR increased across all phases of procedure (F(3,59) = 2.94, P < 0.04) , there was no significant differences noted between groups (F (3,59) = 0.682, P = 0.566) Decrease in % facial action in 0. 05 mL of 24% (0.012 g) sucrose alone group and combined 0.05 mL of 24% (0.012 g) sucrose and rocking group compared to water group (F (6, 150) = 2.765, P < 0.02)
Johnston 1999a	48 preterm neonates mean GA of 31 weeks, range 25 to 34 weeks, within 10 days of birth	Heel lance	0.05 mL of 24% sucrose as a single dose, followed by 2 doses of sterile water (N = 15) 3 doses of 0.05 mL of 24% sucrose (N = 17) 3 doses of 0.05 mL of sterile water (N = 16) given by syringe	PIPP scores in 5 x 30 second blocks	Reported means, SD	Statistically significant difference between groups (F = 9.143, P < 0.0001) for mean PIPP scores. Post-hoc analysis found significantly lower PIPP scores with repeated doses of

Table 1. Trials assessing pain during heel lances (*Continued*)

			to anterior surface of the tongue at: 2 min prior to heel lance, just prior to lancing and 2 min after lancing			0.05 mL of 24% (0.012 g) sucrose compared to placebo groups across all blocks of time, P < 0.05. PIPP scores for repeated doses of 0.05 mL of 24% (0.012 g) sucrose were significantly lower compared to single doses of 0.05 mL of 24% (0.012 g) sucrose (8.25 vs. 6.25) only at last block of time, P < 0.05. PIPP scores for single doses of 0.05 mL of 24% (0.012 g) sucrose compared to placebo showed trend towards statistical significance in favour of 0.05 mL of 24% (0.012 g) sucrose (F = 3.465, P = 0.07)
Mathai 2006	104 term neonates, postnatal age > 24 h, sucrose group mean postnatal age 48 h, distilled water groups mean postnatal age 44 h	Heel lance	2 mL 20% sucrose instilled into mouth via a dropper (N = 17) 2 mL distilled water instilled into mouth via a dropper (N = 15) Rocking (N = 17) Massage (N = 17) Expressed breast milk (N = 18) NNS (N = 18)	Time of first cry in seconds, total cry in seconds HR before heel lance, 2 min after heel lance and 4 min after heel lance SpO_2 before heel lance, 2 min after heel lance and 4 min after heel lance DAN scale before the heel lance and 30 s, 1 min, 2	Reported means, SD Not reported Mean, SD	No significant difference between sucrose group and any other group for time of first cry NNS and rocking significantly reduced total duration of cry, P < 0.05 No significant difference in HR between the groups at any time point No significant difference

Table 1. Trials assessing pain during heel lances (*Continued*)

				min, 4 min after heel lance		in SpO_2 between the groups at any time point Significantly reduced DAN scores at 30 s after the heel lance for the sucrose group (mean 7.6, SD 14, P < 0.05); however, this was not sustained at 1, 2 and 4 min NNS and rocking signif- icantly decreased the DAN scores at 2 and 4 min post heel lance, P < 0.05
Okan 2007	31 healthy preterm newborns, mean GA 30.5 weeks, mean postmenstrual age 32.3 weeks	Heel lance	2 mL of 20% sucrose 2 mL of 20% glucose 2 mL of water Infants received all 3 interventions at different times	Duration of first cry and total crying time HR at baseline, during heel lance and 1, 2, 3, 4 and 5 min post heel lance SpO_2 and respiratory rate at baseline, during heel lance and 1, 2, 3, 4 and 5 min after heel lance NFCS scores during heel lance and 1, 2, 3, 4 and 5 min post heel lance	Mean, SD	Significantly increased duration of first cry and total crying time in the water group compared to the sucrose and glucose groups (P = 0.005 and P = 0.007, respectively). No significant differences in cry characteristics were observed between the sucrose and glucose groups Sig- nificantly higher HR in the water group (mean 175, SD 20.8) compared to the sucrose (mean 166, SD 17.6) and glucose groups

Table 1. Trials assessing pain during heel lances (*Continued*)

						(mean 165, SD 17.5) at 1 min following heel lance (P = 0.007). No significant differences between the sucrose and glucose groups Significantly higher NFCS score in the placebo group in the 4th minute following heel lance (mean 1.3, SD 2.0) and 5th minute following heel lance (mean 1.0, SD 1.0) compared to the sucrose (mean 0.5, SD 1.7; mean 0.3, SD 1.3, respectively) and glucose groups (mean 0.2, SD 0.5; mean 0.1, SD 0.3, respectively) (P = 0.009 at 4th minute and P = 0.049 at 5th minute. There were no significant differences between the sucrose and glucose groups
Ors 1999	102 healthy term infants, GA 37 to 42 weeks, median postnatal age 1.6 days, range 1 to 15 days	Heel lance	2 mL of 25% sucrose (N = 35) 2 mL of human milk (N = 33) 2 mL of sterile water (N = 34) All solutions syringed onto anterior part of tongue for 1 min Heel prick per-	Median cry time during 3 min after lance % change HR 1, 2 and 3 min after heel lance	Median, IQR	Significant decrease in crying times for 2 mL of 25% (0.5 g) sucrose group (median 36, IQR 18 to 43) compared to human milk (median 62, IQR 29 to 107)

Table 1. Trials assessing pain during heel lances (*Continued*)

			formed 2 min after intervention			and sterile water [(median 52, IQR 32 to 158) (P = 0.0009). Recovery time for crying was significantly reduced in 2 mL of 25% (0.5 g) sucrose group (median 72, IQR 48 to 116) compared to human milk (median 112, IQR 72 to 180) and sterile water (median 124, IQR 82 to 180) (P = 0.004) % change in HR after heel lance was significantly lower in the group receiving 2 mL of 25% (0.5 g) sucrose compared to groups receiving human milk and sterile water at 1, 2 and 3 min (P = 0.008, P = 0.01, P = 0.002, respectively)
Overgaard 1999	100 newborn term infants, mean age 6 days, range 4 to 9	Heel lance	2 mL of 50% sucrose solution via syringe into the mouth over 30 s 2 min prior to heel lance 2 mL of sterile water via syringe into the mouth over 30 s 2 min prior to heel lance	Median crying time during heel lance, fraction of crying during sampling, crying time during first minute after end of sampling, total crying time Change HR 0 and 1 min SpO_2 at 0 and 1 min NIPS scores 1 min	Median, 5th and 95th percentiles	Median duration of first cry in group receiving 2 mL of 50% (1 g) sucrose was significantly lower (18 s (2 to 75)) compared to placebo group (22 s (11 to 143)) (P = 0.03). Median crying time during heel lance in the sucrose group was lower (26 s

Table 1. Trials assessing pain during heel lances (*Continued*)

				after heel lance and 1 min after blood sampling		(2 to 183)) compared to placebo group (40 s (12 to 157)) (P = 0. 07). Median fraction of crying during sampling in 2 mL of 50% (1 g) sucrose group was significantly lower (43% (4 to 100)) com- pared to placebo group (83% (20 to 100)) (P = 0. 004). Median crying time during first minute after end of sampling in 2 mL of 50% (1 g) sucrose group was significantly lower (3 s (0 - 58)) compared to placebo group (16 s (0 to 59)) (P = 0.004). Median total time crying in 2 mL of 50% (1 g) sucrose group was significantly lower (30 s (2 to 217)) compared to placebo group (71 s (13 to 176)) (P = 0.007) No significant in HR differences between groups (P = 0.05) No significant differences between groups with respect to changes in SpO_2 (P = 0.8)

Table 1. Trials assessing pain during heel lances (*Continued*)

						Median NIPS scores 1 min after heel lance were lower in 2 mL of 50% (1.0 g) sucrose group compared to placebo group (3 (0 to 7) and 6 (0 to 7), respectively; P = 0.04). Median NIPS scores 1 min after end of blood sampling were lower in 2 mL of 50% (1.0 g) sucrose group (0 (0 to 7)) compared to placebo group (2 (0 to 7)) (P = 0.05)
Ozdogan 2010	142 healthy term newborns	Heel lance	6 groups Single-dose breast milk Single-dose sterile water Single-dose 12.5% sucrose 2 doses breast milk 2 doses sterile water 2 doses 12.5% sucrose	Median crying time; NFCS	Medians	Significant difference between single-dose sucrose vs. water (P = 0.002) in favour of sucrose. Double doses of sucrose were not superior to single doses; single doses or double doses of breast milk were not effective in reducing pain No significant differences between groups on crying time
Ramenghi 1996a	15 preterm infants, 32 to 34 weeks' gestation, > 24 h of age	Heel lance	1 mL of 25% sucrose 1 mL of sterile water	Duration of first cry and % time crying 5 min after lance HR (at -2, 0, 1, 3 and 5 min from heel lance) Behavioural	Median, IQR Not reported Not reported	Significant decrease in total % of time crying over 5 min (median 6%, IQR 3.3 to 15.3) in the 1 mL of 25% (0.25 g) sucrose

Table 1. Trials assessing pain during heel lances (*Continued*)

				scores (4 facial expressions and the presence of crying) -2, -1 , 0, 1, 2, 3 and 5 min Quality/intensity of sucking		group compared with water group (median 16.6%, range 5 to 27.3) (P = 0.018). Duration of first cry was significantly decreased in the 1 mL of 25% (0.25 g) sucrose group (median 12 s, IQR 8 to 22) compared to control group (median 23 s, IQR 15 to 45) (P = 0.004) No significant differences in HR between groups, P value not reported Mean pain scores were significantly lower in the groups receiving 1 mL of 25% sucrose (0.25 g) of sucrose at both 1 and 3 min after heel lance (P = 0.01, P = 0.03, respectively) The clinical interpretation of the quality of sucking was significantly more intense in the 1 mL of 25% (0.25 g) sucrose group than in the water group (P = 0.04)
Ramenghi 1996b	60 term infants, 37 to 42 weeks GA, 2- to 5-day old	Heel lance	2 mL of 25% (0.5 g) sucrose 2 mL of 50% (1.0 g) sucrose Calpol Single-dose sterile water	Duration of first cry after lance, % time crying over 3 min after heel lance % change in HR over 5 min (at -2,	Median, IQR Not reported Median, IQR	Significant decrease in duration of first cry and % crying during 3 min after heel lance in the 2 mL of 25%

Table 1. Trials assessing pain during heel lances (*Continued*)

				0, 1, 3 and 5 min from heel lance) Behavioural scores (4 facial expressions and the presence of crying) -2, -1, 0, 1, 2, 3 and 5 min		(0.5 g) sucrose, 2 mL of 50% (1. 0 g) sucrose and Calpol groups (P = 0.02) (data in graph form only) Signif- icant increase in HR for 3 min after heel lance in water group compared with 2 mL of 50% (1.0 g) sucrose group and Calpol group (P = 0.009) Pain score (0 to 5) was significantly higher in water group (score = 2, range 1 to 5) than in other 3 groups: 2 mL of 50% (1 g) sucrose group (score = 0, range 0 to 3); 2 mL of 25% (0.5 g) sucrose group (score = 0, range 0 to 2); Calpol group (score = 0, range 0 to 1) (P = 0.05)
Ramenghi 1999	30 preterm infants, GA 32 to 36 weeks, postnatal age < 24 h	Heel lance	25% sucrose solution (volume not reported) was given via syringe into the mouth or via NG tube 2 min prior to first heel lance (N = 15), and via the alternate route for the second heel lance within 48 h Sterile water via syringe into the mouth or via NG	% cry over 5 min after sampling Behavioural scores (4 facial expressions and the presence of cry) at 1, 3 and 5 min after the lance for a total behavioural score	Median, IQR	Median % cry in intraoral water group was 22% (IQR 10.6 to 40) and 27% (IQR 11.6 to 47) for infants in NG tube water group. Median % cry in intraoral 25% sucrose group was 6% (IQR 0.6 to 15) and 18.3% (IQR 11.6 to 41.6) for

Table 1. Trials assessing pain during heel lances (*Continued*)

			tube 2 min prior to first heel lance and for the second heel lance the alter- nate route within 48 h (cross-over design, N = 30)			NG tube 25% sucrose group. Significant reduction in crying time (P = 0.006) noted in the 25% sucrose group compared with water group when infants received 25% sucrose intraorally, not via NG-tube route. For infants in 25% sucrose group, significant reduction in crying time noted (P = 0.008) when solution given intraorally compared to NG tube route Behavioural scores for the intraoral water group was 9 (IQR 6 to 12) and 10 (IQR 6 to 14) for NG tube water group. Behavioural scores for intraoral 25% sucrose group was 5 (IQR 3 to 6) and 9 (IQR 8 to 10) for NG tube sucrose group. Significant reduction in behavioural scores noted in 25% sucrose group (P = 0.002) compared with water group when infants re-

Table 1. Trials assessing pain during heel lances (*Continued*)

						ceived 25% sucrose intraorally but not via NG route. For infants in 25% sucrose group, there was significant reduction in behavioural score (P = 0.001) when solution was given intraorally compared to via NG tube
Rushforth 1993	52 term infants, 37 to 42 weeks, GA, 2 to 7 days of age	Heel lance	2 mL of 7.5% sucrose administered by a dropper into the mouth over a 1-minute period prior to heel lance (N = 26) 2 mL of sterile water administered by dropper into the mouth over a 1-minute period prior to heel lance (N = 26)	% cry over 3 min after sampling	Median only	No significant differences in median % time crying between group receiving 2 mL of 7.5% (0.15 g) sucrose (74.3%) compared to group receiving water (73.2%). No significant differences between groups in duration of cry after 1 min (P = 0.65), 2 min (P = 0.52) and 3 min (P = 0.72). No difference in time to cessation of crying (P = 0.16)
Slater 2010	44 term infants, 37 to 43 GA, < 8 days old	Heel lance	0.5 mL of 24% sucrose given via syringe (N = 20) 0.5 mL of sterile water (N = 24)	HR change, PIPP score, nociceptive-specific brain activity, latency to change in facial expression (s), facial non-responders, nociceptive reflex withdrawal activity	Mean, SD, mean weight	Only mean baseline HR given: 0.5 mL of 24% sucrose 132.6 bpm (124.3 to 140.9); 0.5 mL of sterile water 131.8 (122.2 to 141.5) (P = 0.90) Only mean baseline SpO_2 given: 0.5 mL of 24%

Table 1. Trials assessing pain during heel lances (*Continued*)

						sucrose 99.4 (98.8 to 100.1); 0.5 mL of sterile water 97.4 (95.0 to 99.8) (P = 0.13) PIPP score during insertion: baseline PIPP score: 0.5 mL of 24% sucrose 1.3 (0.8 to 1.7), 0.5 mL of sterile water 1.3 (0.8 to 1.8) (P = 0.13); PIPP during procedure: 0.5 mL of 24% sucrose 5.8 (3.7 to 7.8), 0.5 mL of sterile water 8.5 (7.3 to 9.8) (P = 0.02) No significant differences in nociceptive-specific brain activity (P = 0.46) latency to change in facial expression (P = 0.86), mean nociceptive reflex withdrawal activity (P = 0,49) or mean latency to nociceptive reflex withdrawal activity (P = 0.56); significant difference in facial non-responder (P < 0.0001)
Stevens 1999	122 neonates, 27 to 31 weeks' GA, < 28 days of age	Heel lance	Prone positioning 30 min prior to heel lance Pacifier dipped in sterile water and placed into the mouth 2 min prior to heel lance	PIPP scores at 30 and 60 s	Reported means, SD	Main effect of treatment for mean PIPP scores (F(16.20), P < 0.0001). Post-hoc analysis revealed significant reduction in PIPP scores 30

Table 1. Trials assessing pain during heel lances (*Continued*)

			Pacifier dipped in 24% sucrose and placed into the mouth 2 min prior to heel lance Control: Containment in SnuggleUp device (N = 122) NB: all infants were contained in SnuggleUp device			s after heel lance in sucrose group (pacifier dipped in 24% sucrose - estimated at 0.02 g) , (mean 7.87, SD 3.35), compared to control group (mean 9.80, SD 3.55) (F(24.09), P < 0.0001). Statistically significant reduction in PIPP scores in pacifier and water group (mean 8.44, SD 3.55) compared to control group (mean 9.80, SD 3.55) (F(9.00), P = 0.003). Trend towards lower PIPP scores with sucrose and pacifier group compared to water and pacifier group (F (3.62), P < 0.05)
Stevens 2005	66 preterm infants, 26 to 30 weeks, postnatal age 72 h	Heel lance	Standard care-positioning and swaddling (N = 21) Standard care-positioning and swaddling and 0.1 mL sterile water via syringe into the mouth immediately followed by a pacifier 2 min prior to painful procedure (N = 23) Standard care-positioning and swaddling and 0.1 mL 24% sucrose via syringe	PIPP at day 7, 14, 21 and 28 at routine heel lance	Not reported	Significant main effect of group (P = 0.03) with differences occurring between the sucrose + pacifier group and standard care group (t (60) = -2.54; P = 0.01). Mean PIPP scores were generally higher in the standard care group No significant main effect of time Adverse effects: no

Table 1. Trials assessing pain during heel lances (*Continued*)

			into the mouth immediately followed by a pacifier 2 min prior to painful procedure (N = 22) These interventions were given every time there was a painful procedure during the first 28 days of life			group differences for adverse events, clinical outcomes or neurobiological risk status
Storm 2002	48 preterm, median GA of 32 weeks, median postnatal age of 14 days	Heel lance	2 mL of 15% sucrose, N = 12 1 mL of 25% sucrose, N =12 Milk via NG tube N = 12 Milk via NG tube + 25% sucrose, N = 12 All infants were given water prior to a second heel lance	Differences in crying time for pre-heel lance to heel lance procedure Changes in HR from pre-heel lance to heel lance procedure Difference in skin conductance from pre-heel lance to heel lance procedure	Not reported	Significantly less crying in infants receiving 1 mL of 25% sucrose (P < 0.05) and food (milk) + 1 mL of 25% sucrose (P < 0.05) No significant differences between groups in changes in HR from pre-heel lance to heel lance procedure (P value not reported) No statistically significant smaller increase in skin conductance variables compared to their water control session (P value not reported)
Unceta-Barranechea 2008	150 term infants	Heel lance	Facilitated tucking NNS + water NNS + 2 mL 24% sucrose	Mean crying time between groups Modified NFCS	Mean, SD	Statistically significant differences in crying time between control group and 2 intervention groups (P < 0.001). No significant difference

Table 1. Trials assessing pain during heel lances (*Continued*)

						between sucking with placebo and sucking with sucrose groups (P = 0.735) Statistically significant differences in pain score between control group and 2 intervention groups (P < 0.001). No significant difference between sucking with placebo and sucking with sucrose groups (P = 0.105)
Yilmaz 2011	120 infants GA 37 to 42 weeks Control group (N = 30): mean GA (SD) = 39.67 (0.80) Mother's milk group (N = 30): mean GA (SD) = 39.10 (1.03) Sucrose group (N = 30): mean GA (SD) = 39.10 (0.71) Pacifier group (N = 30): mean GA (SD) = 39.20 (0.93)	Heel lance	Control group: newborns were in their mothers' lap; no interventions were made before the painful procedure Mother's milk group: 2 mL mother's milk 2 min before the procedure by using a syringe with the needle removed and avoiding contact of the syringe with the mouth and lips Sucrose group: 2 mL sucrose of 20% by using a syringe 2 min before the procedure Pacifier group: given a pacifier	NIPS score, HR, respiratory rate, crying time	Mean, SD	No differences in HR and O_2 saturation between groups After the procedure, the mean crying time of the sucrose group was shorter than those of the other groups. Comparing the crying times of the control and experimental groups according to the procedure time showed no statistically significant differences between the values for before and during the procedure (F = 1.50, P > 0.05); (F = 2.43, P > 0.05) Before the procedure, the lowest

Table 1. Trials assessing pain during heel lances (*Continued*)

						NIPS mean was in the sucrose group and the highest NIPS mean was in the pacifier group. During the procedure, no statistically significant differences were found between the groups for NIPS means (P > 0.05). After the procedure, the sucrose group showed the lowest response to pain, while the mother's milk group had the highest response. Comparing the NIPS means of the control and experimental groups according to the procedure times, statistically significant differences were found between the groups for values obtained before and after the procedure (F = 3.49, P < 0.05); (F = 6.71, P < 0.05)

bpm: beats per minute; DAN: Douleur Aigue du Nouveau-ne; GA: gestational age; HR: heart rate; IQR: interquartile range; NFCS: Neonatal Facial Coding System; NG: nasogastric; NIPS: Neonatal Infant Pain Scale; NNS: non-nutritive sucking; PIPP: Premature Infant Pain Profile; RSF: Ross Special Formula; SD: standard deviation; SEM: standard error of the mean; SpO_2: oxygen saturation; $TcpO_2$: transcutaneous oxygen pressure.

Table 2. Trials assessing pain during venipunctures

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Abad 1996	28 preterm, 29 to 36 weeks' GA, infants, postnatal age 1 to 26 days	Venipuncture	2 mL of 12% sucrose via syringe (N = 8) 2 mL of 24% sucrose via syringe (N = 8) 2 mL of spring water via syringe (N = 12) 2 min prior to venipuncture	Time crying for 3 min after venipuncture HR: pre solution, post solution, 5 min after venipuncture Mean SpO_2 and respiratory rate pre solution, post solution, 5 min after venipuncture	Median, IQR Mean, SEM Mean, SD	Significant group effect noted, (F(2, 25) = 4.26; P = 0.0256) for cry duration 3 min after venipuncture. Cry duration was significantly reduced in 2 mL of 24% (0.48 g) sucrose group (19.1 sec) compared to 2 mL of 12% (0.24 g) sucrose (63.1 sec) and water (72.9 sec) groups (P < 0.05) Significant group effect for HR, F (2, 25) = 6.37, P = 0.006. Overall time effect, F(2, 50) = 14.15, P < 0.001. No significant interaction between treatment group and time. Post hoc Tukey test showed that group receiving 2 mL of 12% sucrose (0.24 g) had lower HR compared to the 2 mL of 24% sucrose group (0.48 g) or water group at all 3 time points (pre solution, P = 0.

Table 2. Trials assessing pain during venipunctures (*Continued*)

						048; post solution, P = 0.010; 5 min after, P = 0.007) No significant differences noted between groups over time for SpO_2 and respiratory rates (no P values reported)
Acharya 2004	39 preterm neonates, mean 30.5 weeks' GA, mean postnatal age 27.2 days	Venipuncture	2 mL of 25% (0.5 g) sucrose administered by syringe into front of infant's mouth over 2 min, 4 min prior to venipuncture	Duration of first cry (beginning to end of first cry); total duration of crying (onset of first cry to cessation of all crying) Mean change in HR from pre-procedure, procedure and post-procedure phase of venipuncture Mean SpO_2 (%) at pre-procedure, procedure and post-procedure NFCS changes across 3 phases of venipuncture	Mean (SD)	Mean duration of first cry lower in infants who received sucrose (18.6 s (24.4)) compared to infants who received water (52.3 s (56)) (estimated treatment effect = 33.7, P < 0.001). Mean total duration of crying was significantly lower in infants who received sucrose (31.9 s (41.9)) compared to infants who received water (72.5 s (66.7)) (estimated treatment effect = 40.6, P < 0.001) Mean change in HR from pre-procedure to procedure was lower in the infants receiving sucrose compared to water

Table 2. Trials assessing pain during venipunctures (*Continued*)

						(estimated treatment effect = 7.5, P = 0.003). Mean change in HR from pre-procedure to post-procedure was lower in the infants who received sucrose compared to water (estimated treatment effect = 4.16, P = 0.036) No significant differences between groups with respect to changes in SpO_2 from pre-procedure to procedure phase (P = 0.17) Changes in mean NFCS scores were significantly lower in the sucrose group compared to water group from pre-procedure to procedure phase (estimated treatment effect = 1.08, P = 0.013) and between the pre-pro- cedure and post-procedure phase (estimated treatment effect = 2. 39, P < 0.001)
Alsaedi 2009	36 preterm infants, median (range): GA 32 (27 to 46) , mean (SD) GA 32.4 (2.0) - 2 dif-	Venipuncture	Babies randomly allocated to 6 different regimens (0.5 mL sterile water with paci-	HR, SpO_2, PIPP, respi- ratory rate, blood pressure, glucose check	Range, mean	PIPP score: significantly different between treatment groups P = 0.0005, over

Table 2. Trials assessing pain during venipunctures (*Continued*)

	ferent mean GA reported in the article		fier, 0.5 mL sterile water without pacifier, 0.5 mL sucrose 24% with pacifier, 0.5 mL sucrose 24% without pacifier, pacifier alone and control group) during a stay in intensive care of up to 15 days			time P < 0.0005 24% sucrose + pacifier resulted in lowest pain scores (P < 0.05) No difference in respiratory rate (P = 0.193) , no difference in blood pressure (P = 0.246); no difference in glucose check (P = 0. 227)
Basnet 2010	50 term infants between 12 h to 8 days of life; 59.92 h of life non-sucrose, 68. 76 h of life sucrose group	Venipuncture	No treatment (N = 25) Treatment group: did not report method of administration (i.e. pacifier/ syringe; N = 25)	Duration of cry, DAN scale	Percentage for duration of cry, IQR for DAN scale	13 (52%) infants in sucrose group did not cry compared to 4 (16%) in no treatment group, P = 0.001, mean duration of cry was not significant between groups (P = 0.65) HR increased during procedure (P = 0.008) followed by decrease post procedure (P = 0. 001) in control group; no significant changes in sucrose group (P = 0.39). Decrease in SpO_2 in control group (P = 0. 001) during procedure; no significant changes in sucrose group (P = 0.03) Significantly lower DAN scores in

Table 2. Trials assessing pain during venipunctures (*Continued*)

						the 30% sucrose group (score of 3 (1.5 to 5.5) compared to the control group (score of 7 (5 to 9.5) (P = 0.0001)
Biran 2011	76 preterm infants, mean GA (S group): 32.6 (2.33) weeks, mean GA (S + E group): 32.3 (2.01) weeks	Venipuncture	S group: 0.5 mL of 30% sucrose solution orally and placebo cream (N = 37) S + E group: 30% sucrose solution orally + EMLA on the skin (N = 39)	DAN scale, PIPP	Median, IQR	Mean (SD) DAN pain scores for the S group and the SE group were 7.7 (2.1) and 6.4 (2.5), respectively, during venipuncture and 7.1 (2.8) and 5.7 (3.3) during the post-injection period Significant time effect (P = 0.047) and treatment effect (P = 0.018) effect in favour of S + EMLA group; no significant differences using PIPP
Carbajal 1999	150 term newborn infants, 3 or 4 days old	Venipuncture	No treatment (N = 25) 2 mL of sterile water via syringe over 30 s (N = 25) 2 mL of 30% glucose via syringe (N = 25) 2 mL of 30% sucrose (N = 25) Pacifier alone (N = 25) 2 min prior to venipuncture 2 mL of 30% sucrose via syringe followed by sucking a pacifier (N = 25)	DAN scale	Median, IQR	Median pain scores with IQRs during venipuncture were: no treatment 7 (5 to 10); sterile water group 7 (6 to 10); 30% glucose group 5 (3 to 7); 2 mL of 30% sucrose (0.6 g) group 5 (2 to 8); pacifier alone group 2 (1 to 4); 2 mL of 30% (0.6 g) sucrose with pacifier group 1

Table 2. Trials assessing pain during venipunctures (*Continued*)

						(1 to 2). All groups had significantly lower pain scores compared to sterile water group: 30% glucose (P = 0.005), 2 mL of 30% (0.6 g) sucrose (P = 0.01) , pacifier (P < 0. 0001), 2 mL of 30% (0.6 g) sucrose with pacifier (P < 0.0001) . Pacifier alone group had significantly lower pain scores than infants receiving 30% glucose (P = 0.0001) or 2 mL of 30% (0. 6 g) sucrose (P = 0.001). Trend towards lower pain scores for infants receiving 2 mL of 30% (0.16 g) sucrose with pacifier compared to pacifier alone (P < 0.06)
Gaspardo 2008	33 preterm infants. Median (range) GA of intervention group 30 (25 to 33). Median (range) GA of control group 31 (27 to 33)	Pain assessed at venipuncture phases (baseline, antisepsis, puncture, dressing, recovery). Sucrose administered before every minor painful procedure (venipuncture, arterial puncture, heel-lance, intravenous cannulation, endo-	0.5 mL/kg of sterile water 2 min prior to procedure 0.5 mL/kg 25% sucrose 2 min prior to procedure Volume of solution was adjusted for current body weight	Incidence of cry HR NFCS score ABS score	Percentage Percentage with rate > 160 bpm Percentage attaining score ≥ 3 Percentage attaining score ≥ 4	Cry on the second day there was a significant difference between the sucrose and control groups in the antisepsis phase (P = 0.04) and puncture phases (P = 0.009) in favour of the sucrose group. On day 3, there was

Table 2. Trials assessing pain during venipunctures (*Continued*)

		tracheal tube introduction, endotracheal tube suctioning, gavage insertion for feeding, removal of electrode leads and tape)				a significant difference between groups in the dressing phase (P = 0.04) in favour of the sucrose group. On day 4, significant differences existed between groups at the puncture phase (P = 0.03) in favour of the sucrose group No significant differences in HR were observed NFCS: significant difference was seen between sucrose and control groups on day 2 at the puncture phase (P = 0.05) favouring the sucrose group. Significant difference was also observed on day 3 at the antisepsis phase (P = 0.02) in favour of the sucrose group. No significant differences were observed on day 4, but a trend favouring the sucrose group was noted in the puncture (P = 0. 08) and dressing (P = 0.09) phases

Table 2. Trials assessing pain during venipunctures *(Continued)*

						ABS: significant difference between sucrose and control groups on day 2 at the puncture phase (P = 0.05) favouring the sucrose group. Significant difference observed on day 3 at the antisepsis phase (P = 0.02) in favour of sucrose group. At the dressing phase, the trend favoured the sucrose groups, but this result was not significant (P = 0.09). No significant differences were observed on day 4, but a trend favouring the sucrose group was noted in the puncture (P = 0.08) and dressing (P = 0.09) phases
Montoya 2009	111 neonates (55 in treatment group and 56 in control group)	Venipuncture	5 min before venipuncture: 1 mL of 12% sucrose (treatment group) or distilled water (control group)	Overall NIPS score	Means	NIPS scores significantly lower for infants who received sucrose (2.9 (SD 2.3)) versus water (3.8 (SD 2.6)) (t = -2.063, P = 0.041)
Taddio 2011	330 infants, mean GA (SD) 39.5 (1.2), liposomal lidocaine group (N = 110), mean GA (SD) 39.6 (1),	Venipuncture	Liposomal lidocaine group: 1 g of liposomal lidocaine 4% cream to the dorsum of the hand, oc-	Facial grimacing, cry duration (seconds), Observer-rated pain using a VAS (0 to 10 cm), HR(bpm), SpO_2	Mean, 95% CI	The mean facial grimacing score differed among the randomised groups (P < 0.001). Post-hoc analyses demon-

Table 2. Trials assessing pain during venipunctures (*Continued*)

	sucrose group (N = 110), mean GA (SD) 39.6 (1.3), sucrose liposomal lidocaine group (N = 110) , mean GA (SD) 39.6 (1.3)		cluded by a dressing (Tegaderm) for 30 to 40 min Sucrose group: 2 mL of 24% sucrose solution, administered by mouth using a syringe over 1 to 2 min Sucrose liposomal lidocaine group: both sucrose and liposomal lidocaine Placebos were used for liposomal lidocaine and sucrose (i.e. double-dummy design), so that all infants received a topically administered cream (liposomal lidocaine or placebo cream) and oral solution (sucrose or placebo water) Non-randomised group of healthy neonates undergoing venipuncture were administered water	(%)		strated a significantly lower score for the sucrose group compared with liposomal lidocaine (mean difference 27; 95% CI -36 to -19; P < 0. 001) and for the sucrose plus liposomal lidocaine group compared with the liposomal lidocaine group (mean difference 23; 95% CI 31 to 14; P < 0.001). No evidence of different between the sucrose and sucrose plus liposomal lidocaine groups Cry duration differed among groups (P < 0. 001). Infants in the sucrose and sucrose plus liposomal lidocaine groups cried less than infants in the liposomal lidocaine group (mean difference: 38 s; 95% CI -52 to -25; P < 0.001; and mean difference: 39 s; 95% CI - 52 to - 25; P < 0.001, respectively).

Table 2. Trials assessing pain during venipunctures (*Continued*)

						There was no evidence of a difference in cry duration between the sucrose and sucrose plus liposomal lidocaine group (mean difference: 0 s; 95% CI -13 to -14; P = 0.95) No difference in VAS, HR or SpO_2 When compared with the non-randomised placebo-control group, the liposomal lidocaine group had significantly lower facial grimacing (mean difference 17; 95% CI -27 to -7; P < 0.001) and VAS scores (1.7 cm; 95% CI 2.5 to 0.9; P < 0.001) . HR, SpO_2 and procedure duration were significantly higher in the liposomal lidocaine group compared to the control group. Cry duration and procedure success rate did not different beyond chance No significant adverse events reported

ABS: Activated Behavioural State; bpm: beats per min; CI: confidence interval; DAN: Douleur Aigue du Nouveau-ne; EMLA: eutectic mixture of local anaesthetics; GA: gestational age; HR: heart rate; IQR: interquartile range; NFCS: Neonatal Facial Coding System;

NIPS: Neonatal Infant Pain Scale; PIPP: Premature Infant Pain Profile; SD: standard deviation; SEM: standard error of the mean; SpO_2: oxygen saturation; VAS: visual analogue scale.

Table 3. Trials assessing pain during heel lances and venipunctures

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Ogawa 2005	100 healthy full-term infants Heel lance group GA 40 weeks (range 38-42 weeks) Heel lance + sucrose group GA 39 weeks (range 37 to 41 weeks) Venipuncture group GA 39 weeks (range 37 to 41 weeks) Venipuncture + sucrose group GA 39 weeks (range 37 to 41 weeks)	Heel lance or venipuncture	Heel lance + 0.1 mL of sterile water on infant's tongue via syringe 2 min before procedure (N = 25) Heel lance + 0.1 mL of 50% sucrose on infant's tongue via syringe 2 min before procedure (N = 25) Venipuncture + 0.1 mL of sterile water on infant's tongue via syringe 2 min before procedure (N = 25) Venipuncture + 0.1 mL of 50% sucrose on infant's tongue via syringe 2 min before procedure (N = 25)	Duration of first cry (sec), first crying time/total procedure time (%) and the ration of crying: no crying NFCS score 1 min after oral administration of water/sucrose (1), disinfection of skin before heel lance or venipuncture (2), during skin puncture (3), during blood sampling (4), during compression to stop bleeding (5), during application of plaster (6) and 1 min after application of plaster (7)	Reported medians, range and mean, SD Reported in graph form, median and IQR	Significant reduction in duration of first cry in heel lance group given sucrose compared to heel lance alone ($P < 0.05$) Significantly reduced NFCS scores in sucrose group during heel lance (median 47, IQR 31 to 60) and during compression to stop bleeding (median 32, IQR 8 to 54) compared to the water group (median 58, IQR 54 to 65, median 52, IQR 41 to 61, respectively) ($P < 0.01$) Sucrose did not significantly reduce NFCS scores during or after venipuncture

GA: gestational age; IQR: interquartile range; NFCS: Neonatal Facial Coding System; SD: standard deviation.

Table 4. Trials assessing pain during ROP examinations

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Boyle 2006	40 preterm infants, median GA 29 weeks (24 to 34 weeks) Sterile water group: median GA 27 weeks, median postnatal age 45 days Sucrose group: median GA 29 weeks, median postnatal age 43 days Water and pacifier group: median GA 30 weeks, median postnatal age 41 days Sucrose and pacifier group: median GA 29 weeks, median postnatal age mean 42 days	Eye examination for ROP	1 mL sterile water via a syringe into the mouth (group 1; N = 10) 1 mL sucrose 33% via a syringe into the mouth (group 2; N = 10) 1 mL sterile water via a syringe into the mouth and pacifier (group 3; N = 9) 1 mL sucrose 33% via a syringe into the mouth and pacifier (group 4; N = 11) *all were given 2 min before start of the eye examination*	PIPP during examination of eye	Mean, SD, 95% CI	PIPP scores of Mean (SD)were: 15.3 (1.9), 14.3 (1.6), 12.3 (2.9), and 12.1 (3.4) for groups 1, 2, 3, and 4 Significant differences in PIPP scores between the groups, P = 0.023 Infants in pacifier groups scored significantly lower than groups without pacifiers, P = 0.003 (95% CI -4.23 to -0.96) No significant differences between groups receiving sucrose vs. groups receiving water
Gal 2005	23 neonates, GA 24 to 29 weeks, postnatal age 28 to 93 days	Eye examination for ROP	2 mL of sterile water 2 mL of 24% sucrose (N = 23, cross-over design) Mydriatic eye drops (phenylephrine HCl 1%, cyclopentolate HCl 0.2%) and local anaesthetic eye drops (proparacaine HCl 0.5%; 2 drops) given	Decreased SpO_2 by ≥ 10% pre-examination, at eye speculum insertion and post-examination PIPP scores at 5 and 1 min pre-examination, eye speculum insertion, and 1 and 5 min post-examination	Percentage of population Means, SD reported	No significant difference in SpO_2 between water group and sucrose group PIPP score at the eye examination significantly lower in the group given sucrose (mean 8.3, SD 4.5) compared to the placebo group (mean 10.5, SD

Table 4. Trials assessing pain during ROP examinations (*Continued*)

			to both groups prior to examination			4.0), P = 0.01); however, this effect was not sustained at 1 and 5 min post-examination
Grabska 2005	32 preterm infants, mean GA 28 weeks, mean postnatal age 50.8 days	Eye examination for ROP	Sterile water delivered either directly into the mouth or via a nipple 2 min prior to eye examination (N = 16) 24% oral sucrose was delivered either directly into the mouth via a nipple 2 min prior to eye examination (N = 16) Doses were adjusted by weight: < 1 kg = 0.5 cm^3 (0.12 g); 1 to 1.5 kg = 1.0 cm^3 (0.24 g); 1.5 to 2 kg = 1.5 cm^3 (0.36 g); > 2 kg = 2.0 cm^3 (0.48 g) All infants were swaddled and offered a pacifier All infants received tropicamide 0.5% and phenylephrine 2.5% eye drops approximately 30 min before examination. Topical tetracaine was instilled into the eyes just prior to the examination	% of the eye examination the infant spent crying Mean HR, at baseline, post-eye drop instillation, post-study drug, during eye examination and post-eye examination* RR and SpO_2 at baseline, post-eye drop instillation, post-study drug, during eye examination and post-eye examination* PIPP at baseline, during eye examination, post-eye examination* *measures were taken at 1-min intervals and were means for each study period - study period times (in min) were not defined	Mean, SD	No significant difference in crying time between the sucrose and water groups Significant increases in HR, in both groups from baseline (P < 0.01) No differences between the sucrose and placebo groups in HR at any time point Significant reduction in SpO_2 in infants receiving sucrose after the study drug (mean 95%, SD 4%) compared to the water group (mean 97%, SD 3%) Significant reduction in SpO_2 in infants receiving sucrose during the eye examination (mean 93%, SD 5%; P < 0.05) compared to the water group (mean 96%, SD 3%; P < 0.05) No significant

Table 4. Trials assessing pain during ROP examinations (*Continued*)

						difference in RR and SpO_2 at 2 min post-examination. No significant differences in PIPP scores between the sucrose and placebo groups before, during and after eye examinations
Mitchell 2004	30 preterm infants Water group: mean GA 27.3 weeks, mean postnatal age 8.2 weeks Sucrose group: mean GA 26.5 weeks, mean postnatal age 8.5 weeks	Eye examination for ROP	Pacifier and 3 doses of 0.1 mL sterile water via syringe into the mouth (N = 15) Pacifier and 3 doses of 0.1 mL 24% sucrose via syringe into the mouth (N = 15) *1st dose given 1.5 min before local anaesthetic eye drops, 2nd dose right at placement of the eye speculum, 3rd dose 120 s after 2nd drop* All infants received proparacaine hydrochloride 0.5% eye drops and were swaddled before the eye examination	PIPP at baseline, at eye drop instillation, at examination of left eye and at 30, 60, 90 and 120 s after the examination	Mean, SEM	Statistically significant differences in mean PIPP scores were found between sucrose group (mean 8.8, SEM 0.7) and the water group (mean 11.4, SEM 0.6) during the eye examination (P = 0.0077). However, this was not sustained after the eye examination
Rush 2005	30 preterm infants < 32 weeks' GA or weighing < 1500 g Control group:	Eye examination for ROP	Prior to examination: instillation of 0.5% proparacaine and 1% tropicamide, then 15	Total crying time out of 5 min starting at the onset of the ROP examination	Reported means and SEM Not reported SpO_2 means and SEM reported	No significant differences in crying time between treatment and con-

Table 4. Trials assessing pain during ROP examinations (*Continued*)

	mean GA 28.88 weeks (range 25 to 31 weeks) Treatment group: mean GA of 29.57 weeks (range 26 to 32 weeks)		min later eye drop instillation of 0.5% tropicamide, 2.5% phenylephrine and 0.5% tropicamide Control group: no swaddling, no pacifier and no holding (N = 16) Treatment group: swaddled in warm blanket 15 min prior to examination; given pacifier soaked in 24% sucrose solution and held by nurse until 15 min after examination (N = 14)	HR 30 min before eye drop instillation and 5 min before ROP examination, during examination, 5 min after examination SpO_2 and RR at 30 min before eye drop instillation and 5 min before the ROP examination, SpO_2 and RR at ROP (3 measurements) and SpO_2 and RR 5 min after ROP examination	RR not reported	trol groups There was no significant difference in HR between groups. No significant differences between treatment group and the control group for SpO_2 and respiratory rate at any point
O'Sullivan 2010	40 preterm infants corrected age: mean = 33.0 ± 1.1 weeks	Eye examination for ROP	Treatment group: 0.2 mL of sucrose with pacifier soaked in 24% sucrose solution (N = 20) Water group: 0.2 mL of sterile water by mouth (N = 20)	N-PASS, HR and SpO_2 at baseline, # of bradycardia and desaturation, adverse events	Median, range	Significantly lower N-PASS score at speculum insertion in sucrose compared to control group (6.5 vs. 5.0; P = 0.02); during procedure (9.5 vs. 7.5; P = 0.03). No differences between treatment group and the control group for number of bradycardia or oxygen desaturation

CI: confidence interval; GA: gestational age; HR: heart rate; N-PASS: Neonatal Pain, Agitation and Sedation Scale; PIPP: Premature Infant Pain Profile; ROP: retinopathy of prematurity; RR: respiratory rate; SD: standard deviation; SEM: standard error of the mean; SpO_2: oxygen saturation.

Table 5. Trials assessing pain during subcutaneous injections

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Allen 1996	285 term infants Various age groups based on required immunisations. Age groups were: 2 weeks, 2 months, 4 months, 6 months, 15 months and 18 months Only data for neonates at 2 weeks of age are included in this review	Subcutaneous injection	2 mL 12% sucrose 2 mL sterile water No treatment	Cry duration (during and after procedure)	Mean, SD % time crying	The overall P value for % time crying was significant (F = 5.92, P < 0.005). Pairwise comparisons of the % time spent crying of sucrose and water groups versus the no treatment group show significant differences (P < 0.01 for both comparisons) This was the only age group in which significant differences were observed between sucrose, water and no treatment groups
Mucignat 2004	33 preterm neonates, mean (SD) GA at birth 30 weeks (6 days), GA at injection 32 weeks (6 days)	Subcutaneous injections	Non-nutritive pacifier sucking (41 injections) 0.2 to 0.5 mL of 30% sucrose with pacifier (86 injections) local application of EMLA with pacifier (71 injections) 0.2 to 0.5 mL of sucrose with EMLA and pacifier (67 injections)	Duration of cry from needle introduction until to 2 min after its removal HR before injection, during injection and after injection SpO_2 before injection, during injections and after injection DAN and NFCS scores during injection	Mean, SD	Crying time was significantly lower in the sucrose + EMLA + pacifier group (P = 0.0002). The mean (SD) crying time in each group was as follows: 3.93 s (2.97) in the pacifier only group, 2.81 s (4.81) in the EMLA + pacifier group, 2.32 s (7.51) in the sucrose + pacifier group and 0.89 s (2.66) in

Table 5. Trials assessing pain during subcutaneous injections (*Continued*)

						the sucrose with EMLA + pacifier group There were no significant differences in HR between the 4 groups The only significant difference in SpO_2 between groups occurred during injection, which was lower in the NNS group (P = 0.02) Significant reduction in DAN and NFCS scores in EMLA + NNS, sucrose + NNS, and sucrose + EMLA + pacifier groups compared to NNS alone

DAN: Douler Aigue Du Nouveau-ne; EMLA: eutectic mixture of local anaesthetics; GA: gestational age; HR: heart rate; NFCS: Neonatal Facial Coding System; NNS: non-nutritive sucking; SD: standard deviation.

Table 6. Trials assessing pain during nasogastric intubations

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
McCullough 2008	20 infants, mean (SD) GA 30.7 weeks (2.3)	NG tube insertion	0.5 - 2 mL of sterile water 2 min prior to procedure 0.5 - 2 mL 24% sucrose 2 min prior to procedure Volume of solution was adjusted	Incidence of cry Baseline HR and change in HR from baseline during NG tube insertion Baseline SpO_2 and change in SpO_2 from baseline during NG tube insertion NFCS	% Mean, SD Median	There was a non-significant trend (P = 0.069) for fewer sucrose-treated infants to cry during NG tube insertion (8/26), compared with the placebo group (14/25) Infants in the su-

Table 6. Trials assessing pain during nasogastric intubations (*Continued*)

			for current body weight > 2 kg = 2 mL 1.5 to 2 kg = 1.5 mL < 1.5 kg = 0.5 mL	during NG tube insertion and after insertion		crose group had higher mean pretreatment baseline HR than placebo group but showed no change in HR during NG tube insertion (mean change -0.7 bpm). The HR of the placebo group increased during NG tube insertion (mean change +11). This difference approached statistical significance (P = 0.055) No significant changes in mean SpO_2 occurred in either groups Sucrose group had a significant lower median NFCS score during NG tube insertion compared with the water group (1 (range 0 to 4) vs. 3 (range 0 to 4), median difference 1 (95% CI 0 to 2); P = 0.004) After NG tube insertion, the NFCS scores fell to a median of 0 in both groups

Table 6. Trials assessing pain during nasogastric intubations (*Continued*)

						To see if NFCS is specific for pain, authors analysed the 4 components on their own. Nasolabial folds showed a significant inhibition in the sucrose group (present in 4/26 (15%) compared with 12/25 (48%) in the placebo group; P = 0.012)
Kristoffersen 2011	24 preterm infants. 28 to 32 weeks GA, crossover designs	NG tube insertion	6 interventions: pacifier, no pacifier, combined, with no fluid, 0.2 mL sterile water, or 0.2 mL 30% sucrose	PIPP scores	Median, range	Median PIPP score during the procedure was 9 and decreased gradually towards 4 after 5 min. The lowest PIPP score in pacifier with oral sucrose combination compared to no treatment (P < 0.001). Highest pain score in sterile water group

bpm: beats per minute; GA: gestational age; HR: heart rate; NFCS: Neonatal Facial Coding Score; NG: nasogastric; PIPP: Premature Infant Pain Profile; SD: standard deviation; SpO_2: oxygen saturation.

Table 7. Trials assessing pain during circumcision

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Herschel 1998	120 healthy male newborns, ≥ 38 weeks	Circumcision	Control group - no treatment (N = 40) DPNB: 0.8 mL of 1% lidocaine without	HR at baseline, restraint, skin preparation for procedure, lateral clamping, lysis of adhesions,	Mean, SD, mean differences and 95% CI	Mean change in HR from baseline through all follow-up times were significantly

Table 7. Trials assessing pain during circumcision (*Continued*)

			epinephrine injected into dorsolateral penile root 3 min before procedure (N = 40) Pacifier dipped in 50% sucrose with a gauze pad moistened with sucrose inside the nipple 2 min before procedure (N = 39)	dorsal clamping, dorsal cut, retraction, application of Gomco bell and clamp, tightening of clamp, excision of foreskin, removal of clamp, removal of bell, placement of dressing and overall change in HR from baseline SpO_2 at baseline and throughout procedure; change from baseline during the circumcision procedure		different between groups (P < 0. 001) Mean (95% CIs) HR differences: control vs. DPNB: 27.1 bpm (17.6 to 36. 6), control vs. sucrose: 9.7 bpm (0. 1 to 19.3) and sucrose vs. DPNB: 17.4 bpm (7.8 to 27.0) Sucrose had statistically significant effect compared to the no treatment controls (P < 0.001) Significant differences between groups in changes in SpO_2 from baseline to circumcision (P < 0.001) Mean (95% CI) SpO_2 differences between the 3 groups from baseline: -2.5 (-15.8 to 3.12) for the control group, -0. 8 (-4.3 to 5.5) for the DPNB group, 0.7 (-6.8 to 12. 5) for the sucrose group Dif- ferences between both the DPNB and sucrose groups compared to control were

Table 7. Trials assessing pain during circumcision (*Continued*)

						significant (P < 0.05) Control vs. sucrose: -3.3 (-5.0 to -1.6) was statistically significant (P < 0.001)
Kaufman 2002	57 term infants, mean age at time of procedure 30 to 43 h	Circumcision	Gomco method and pacifier dipped in water (N = 14) Gomco method and pacifier dipped in 24% sucrose (N = 14) Mogen method and pacifier dipped in water (N = 15) Mogen method and pacifier dipped in 24% sucrose (N = 14) All infants had EMLA cream applied 1 to 3 h before procedure	Time spent crying during procedure Time spent grimacing Procedure stages: 1) Table - restraint 2) Restraint - forceps 3) Forceps - excision 4) Excision - unrestraint 5) Unrestraint - end	Median and means, graphically Not reported	Cumulative mean time crying for forceps to unrestraint interval in the Gomco-sucrose group was 56 s (median = 53 s) compared to 86 s (median = 78 s) in the Gomco-water group (P = 0.0001). Crying time in Mogen-sucrose and Mogen-water groups were not significantly different Overall, mean crying time significantly decreased in infants treated with sucrose compared to infants treated with water (P = 0.0001) Significantly less time spent grimacing in the Gomco-sucrose group compared to the Gomco-water group (P = 0.0001) No significant differences between Mogen-sucrose and the Mo-

Table 7. Trials assessing pain during circumcision (*Continued*)

						gen-water groups Overall, mean time grimacing was significantly reduced in infants treated with sucrose compared to infants treated with water (P = 0.0001)
Stang 1997	80 healthy term newborn male infants, mean GA 39.5 weeks	Circumcision	DPNB (0.8 mL lidocaine and 0.2 mL saline) plus pacifier dipped in water and using new padded restraint chair DPNB with buffer (0.8 mL of lidocaine and 0.2 mL of sodium bicarbonate) and pacifier dipped in water DPNB (0. 8 mL lidocaine and 0.2 mL saline) and pacifier dipped in 24% sucrose Control: DPNB (0.8 mL lidocaine and 0.2 mL saline) and pacifier dipped in water	Plasma cortisol level 30 min after beginning circumcision	Mean, SD	Plasma cortisol levels not significantly different between groups

CI: confidence interval; DPNB: dorsal penile nerve block; EMLA: eutectic mixture of local anaesthetics; GA: gestational age; HR: heart rate; SD: standard deviation.

Table 8. Trials assessing pain during bladder catheterisation

Study	Participants	Procedures	Intervention	Outcomes	Metrics used	Results
Rogers 2006	80 infants ≤ 90 days of age requiring bladder catheterisation	Bladder catheterisation	2 mL of sterile water via syringe 2 min before procedure (N = 40)	% of subjects crying at maximal insertion Change in DAN	%	Youngest subgroup of infants (1 to 30 days) showed smaller changes

Table 8. Trials assessing pain during bladder catheterisation (*Continued*)

	Subgroup analysis performed: infants 1 to 30, 31 to 60 and 61 to 90 days of age		2 mL of 24% sucrose via syringe 2 min before procedure (N = 40)	scores		in DAN score compared to water group (2.86 vs. 5.29; P = 0.035) Subgroup analysis of infants (1 to 30 days) receiving sucrose were significantly less likely to cry during maximal catheter insertion compared to water group (28.6% vs. 78.6%; P = 0.008)

DAN: Douler Aigue Du Nouveau-ne.

Table 9. Trials assessing pain during multiple procedures

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Boyer 2004	103 infants, GA < 31 weeks (57 infants included in this analysis)	All painful procedures during the 1st week of life	Before every painful procedure, up to 3 doses of: 0.1 mL of 24% sucrose (N = 27) 0.1 mL of sterile water (N = 30)	Salivary cortisol levels at baseline, 30 min after painful procedure at days 1,3, 5,7	Mean, SD	No significant differences between groups for mean cortisol levels at baseline or post painful procedures
Johnston 2002	103 infants Sucrose: 51 infants, mean GA 28.18 (1.72) Water (control): 52 infants, mean GA 28.05 (2.06)	Every time the infant was to undergo an invasive (e.g. heel lance, intravenous cannulation, arterial puncture, injection) or non-invasive but presumably uncomfortable procedure (e.g., endotracheal tube suctioning, tape/lead re-	Sucrose group: 0.1 mL of 24% sucrose were drawn up into sterile syringes and placed in the unit medicine refrigerator Water group: 0.1 mL of water were drawn up into sterile syringes and placed in the unit medicine refrigerator	Neurobehavioural development assessed by the subscales of alertness and orientation and motor development and vigour of theNAPI, SNAP and NBRS	Beta, CI (multiple regression)	No group differences or factors associated with SNAP over each day, with day 7 being of interest because it was calculated on the final 24 h of the intervention and would be most reflective of cumulative physiological effects of the intervention (sucrose 3.72 (3.

Table 9. Trials assessing pain during multiple procedures (*Continued*)

		moval, gavage insertion for feeding)				33), water 4.10 (3.18); F(1,101) 0.093, P = 0.761). On the basis of analysis of covariance with PCA at birth and number of invasive procedures as covariates, there were no group differences on any of the secondary outcomes of NBRS scores at 2 weeks; postnatal age (sucrose 1.42 (1.32), water 1.68 (1.58); F(1,101) 0.640, P = 0.426) or at discharge (sucrose 2.29 (2.68), water 2.31 (2.47); F(1,100) = 0.002, P = 0.965)
Taddio 2008	240 newborn infants born to non-diabetic and diabetic mothers, GA ≥ 36 weeks	3 heel lances, venipuncture and intramuscular vitamin K injection	2 mL of 24% sucrose given to infants of non-diabetic mothers (N = 60) 2 mL of 24% sucrose given to infants of diabetic mothers (N = 60) 2 mL of sterile water given to infants of non-diabetic mothers (N = 60) 2 mL of sterile water given to infants of diabetic mothers (N = 60)	PIPP scores overall, during intramuscular injection, during venipuncture and all 3 heel lances	Mean, SD, 95% CI	Overall PIPP scores significantly lower among newborns given sucrose (mean 6.8, SD 2.9) compared to placebo (mean 8.1, SD 2.5) (mean difference -1.3, 95% CI -2.0 to -0.6; P < 0.001) PIPP scores during intramuscular injection did not differ between the sucrose and placebo group for non-diabetic or dia-

Table 9. Trials assessing pain during multiple procedures (*Continued*)

						betic mothers PIPP scores during venipuncture was significantly lower among infants of non-diabetic mothers who received sucrose compared to placebo (mean score 5.7, 95% CI 4.7 to 6.7 vs. mean score 8.9, 95% CI 7.9 to 9.9; P < 0.001). Similar results were found among infants of diabetic mothers (sucrose: mean score 6.8, 95% CI 5.7 to 7.9 vs. placebo: mean score 9.2, 95% CI 8.4 to 10.1; P < 0.001) During first 3 heel lances, newborns from diabetic mothers receiving sucrose or placebo did not have significantly different PIPP scores

CI: confidence interval; GA: gestational age; NAPI: Neurobehavioral Assessment of the Preterm Infant; NBRS: Neuro-Biological Risk Score; PCA: postconceptional age; PIPP: Premature Infant Pain Profile; SD: standard deviation; SNAP: Score for Neonatal Acute Physiology.

Table 10. Trials assessing pain during multiple procedures during heel stroke

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Fernandez 2003	34 term infants Water group: mean GA 39 weeks (1)	Heel stroke	Water group: 2 mL of water Sucrose group: 2	Crying behaviours, EEG, ECG and facial expressions	Mean, SD	Infants who received water (mean 33%, SD 37) cried more than those who received su-

Table 10. Trials assessing pain during multiple procedures during heel stroke (*Continued*)

	Sucrose group: mean GA 38 weeks (2)		mL of 12% sucrose The pipette containing the liquid was placed towards the front and centre of the mouth, and the solution was then released in small amounts			crose (mean 14%, SD 24) (t [28] = 1.66, P = 0.05) and also grimaced more (mean 39%, SD 35) than the sucrose infants (mean 19%, SD 25) during the heel stroke procedure (t [28] = 1.74, P < 0.05). One-tailed t-tests for HR revealed that the HR for the infants in both the sucrose (t [18] = 3.68, P < 0.01) and water groups (t [6] = 2.49, P < 0.05) increased from the pre-heel stroke phase (mean 144 bpm, SD 13, sucrose; mean 146 bpm, SD 9, water) to the heel stroke phase (mean 153 bpm, SD 10, sucrose; mean 154 bpm, SD 10, water) One-tailed t-tests for HR revealed (Figure 2) that the HR for the infants in the sucrose group decreased from the heel stroke phase (mean 155 bpm, SD 11) to the post-heel stroke phase (mean 143 bpm, SD 13) (t [18] = 4.35, P < 0.001), whereas the HR for the infants in the water group remained elevated from heel stroke phase (mean 154 bpm, SD 11) to post heel stroke (mean 152 bpm, SD 15) (t [6] = 0.43, P > 0.50)

bpm: beats per minute; ECG: electrocardiography; EEG: electroencephalography; GA: gestational age; HR: heart rate; SD: standard deviations.

WHAT'S NEW

Last assessed as up-to-date: 17 February 2012.

Date	Event	Description
17 February 2012	New search has been performed	This updates the review "Sucrose for analgesia in newborn infants undergoing painful procedures" published in *The Cochrane Library*, Issue 3, 2010 (Stevens 2010). Thirteen new studies were added in the current update.
17 February 2012	New citation required but conclusions have not changed	For the purpose of the current updated review, the inclusion criteria were expanded to include all minor painful procedures (rather than heel lance and venipuncture only) The updated review criteria included studies that assessed the efficacy of repeated doses of sucrose

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 2, 1998

Date	Event	Description
3 February 2008	Amended	Converted to new review format.
20 April 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

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Literature search and identification of trials for inclusion

Evaluation of methodological quality of included trials

Abstraction and meta-analysis of data

Verifying and entering data into RevMan

Writing of text of review

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DECLARATIONS OF INTEREST

Four authors (BS, JY, GL, AO) have been involved in trials included in this review.

SOURCES OF SUPPORT

Internal sources

- Faculty of Nursing, University of Toronto, Canada.
- Mount Sinai Hospital, Toronto, Canada.
- The Hospital for Sick Children, Toronto, Canada.

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update of the review, inclusion criteria were extended to all studies that used sucrose as an intervention for any acute painful procedure, including subcutaneous injections, circumcision, bladder catheterisations and eye examinations for ROP, as well as repeated doses of sucrose. Long-term neurodevelopmental outcomes were added for this update.

NOTES

N/A

INDEX TERMS

Medical Subject Headings (MeSH)

*Punctures; Analgesics [*administration & dosage]; Infant, Newborn; Pain [physiopathology; *prevention & control]; Pain Measurement; Randomized Controlled Trials as Topic; Sucrose [*administration & dosage]

MeSH check words

Humans