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

Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A

Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A.
Sucrose for analgesia in newborn infants undergoing painful procedures.
Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD001069.
DOI: 10.1002/14651858.CD001069.pub5.

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[Intervention Review]

Sucrose for analgesia in newborn infants undergoing painful procedures

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Editorial group: Cochrane Neonatal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2017.

Citation: Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database of Systematic Reviews* 2016, Issue 7. Art. No.: CD001069. DOI: 10.1002/14651858.CD001069.pub5.

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, method of administration and safety of sucrose for relieving procedural pain in neonates as assessed by validated composite pain scores, physiological pain indicators (heart rate, respiratory rate, saturation of peripheral oxygen in the blood, transcutaneous oxygen and carbon dioxide (gas exchange measured across the skin - $TcpO_2$, $TcpCO_2$), **n**ear **i**nfra**r**ed **s**pectroscopy (NIRS), **e**lectro**e**ncephalo**g**ram (EEG), or behavioural pain indicators (cry duration, proportion of time crying, proportion of time facial actions (e.g. grimace) are present), or a combination of these and long-term neurodevelopmental outcomes.

Search methods

We used the standard methods of the Cochrane Neonatal. We performed electronic and manual literature searches in February 2016 for published randomised controlled trials (RCTs) in the Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library*, Issue 1, 2016), MEDLINE (1950 to 2016), EMBASE (1980 to 2016), and CINAHL (1982 to 2016). We did not impose language restrictions.

Selection criteria

RCTs in which term or preterm neonates (postnatal age maximum of 28 days after reaching 40 weeks' postmenstrual age), or both, received sucrose for procedural pain. Control interventions included no treatment, water, glucose, breast milk, breastfeeding, local anaesthetic, pacifier, positioning/containing or acupuncture.

Data collection and analysis

Our main outcome measures were composite pain scores (including a combination of behavioural, physiological and contextual indicators). Secondary outcomes included separate physiological and behavioural pain indicators. We reported a mean difference (MD) or weighted MD (WMD) with 95% confidence intervals (CI) using the fixed-effect model for continuous outcome measures. For categorical data we used risk ratio (RR) and risk difference. We assessed heterogeneity by the I^2 test. We assessed the risk of bias of included trials using the Cochrane 'Risk of bias' tool, and assessed the quality of the evidence using the GRADE system.

Main results

Seventy-four studies enrolling 7049 infants were included. Results from only a few studies could be combined in meta-analyses and for most analyses the GRADE assessments indicated low- or moderate-quality evidence. There was high-quality evidence for the beneficial effect of sucrose (24%) with non-nutritive sucking (pacifier dipped in sucrose) or 0.5 mL of sucrose orally in preterm and term infants: Premature Infant Pain Profile (PIPP) 30 s after heel lance WMD -1.70 (95% CI -2.13 to -1.26; I^2 = 0% (no heterogeneity); 3 studies, n = 278); PIPP 60 s after heel lance WMD -2.14 (95% CI -3.34 to -0.94; I^2 = 0% (no heterogeneity; 2 studies, n = 164). There was high-quality evidence for the use of 2 mL 24% sucrose prior to venipuncture: PIPP during venipuncture WMD -2.79 (95% CI -3.76 to -1.83; I^2 = 0% (no heterogeneity; 2 groups in 1 study, n = 213); and intramuscular injections: PIPP during intramuscular injection WMD -1.05 (95% CI -1.98 to -0.12; I^2 = 0% (2 groups in 1 study, n = 232). Evidence from studies that could not be included in RevMan-analyses supported these findings. Reported adverse effects were minor and similar in the sucrose and control groups. Sucrose is not effective in reducing pain from circumcision. The effectiveness of sucrose for reducing pain/stress from other interventions such as arterial puncture, subcutaneous injection, insertion of nasogastric or orogastric tubes, bladder catherization, eye examinations and echocardiography examinations are inconclusive. Most trials indicated some benefit of sucrose use but that the evidence for other painful procedures is of lower quality as it is based on few studies of small sample sizes. The effects of sucrose on long-term neurodevelopmental outcomes are unknown.

Authors' conclusions

Sucrose is effective for reducing procedural pain from single events such as heel lance, venipuncture and intramuscular injection in both preterm and term infants. No serious side effects or harms have been documented with this intervention. We could not identify an optimal dose due to inconsistency in effective sucrose dosage among studies. Further investigation of repeated administration of sucrose in neonates is needed. There is some moderate-quality evidence that sucrose in combination with other non-pharmacological interventions such as non-nutritive sucking is more effective than sucrose alone, but more research of this and sucrose in combination with 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 (pain relief) in newborn infants undergoing painful procedures

Review question

Cochrane reviewers investigated how well sucrose (table sugar) works as a reliever of pain in newborn babies who are having painful procedures (e.g. an injection, or heel lance, or insertion of a needle to obtain a blood sample (venipuncture), or eye examinations). The babies' pain responses (e.g. crying, grimacing) were assessed by scoring systems for pain used by health care professionals to measure the pain that babies are experiencing. In addition, the reviewers wanted to investigate whether the level of pain relief is related to the dose of sucrose, or the method of delivery (e.g. as a solution squirted into the mouth, or on a pacifier (also called a soother or dummy), and whether there are any safety concerns about using sucrose to relieve pain.

Background

Although there are ways to manage the pain of surgery, medical illness and major procedures, ways of preventing or reducing pain from minor medical procedures (e.g. heel lance and venipuncture) have, until relatively recently, been lacking. Sucrose has been examined for its calming effects in crying newborns and its pain-relieving effects for invasive procedures in full-term and premature newborns.

Study characteristics

We searched the medical literature widely up to February 2016 for studies that investigated the pain-relieving effect of sucrose for minor medical procedures in newborn full-term and premature babies. We included randomised controlled trials only, as these provide the most reliable medical evidence. We identified 74 studies that reported on a total of more than 7000 infants in this Cochrane Review.

Thirty-eight studies included full-term babies only, 31 included premature babies only, and five included both full-term and premature babies. Heel lance was the painful procedure in 38 studies, and venipuncture in nine; the remaining studies investigated a wide variety of other minor painful procedures.

The studies used a variety of delivery methods for the sucrose solution (oral syringe, dropper or sucrose-dipped pacifier), as well as a range of concentrations and volumes of dose. Sucrose treatment was compared with giving the babies a similar volume of water, a pacifier, routine care, breastfeeding, 'facilitated tucking' (holding the infant in a flexed position with arms close to the body and hands placed to promote sucking), laser acupuncture, swaddling, warmth, anaesthetic cream for the skin (EMLA), or a combination of these. The studies used a range of pain assessment scales to measure their results.

Study funding sources

We did not identify any studies that received funding from the industry.

Key results

There was high-quality evidence that sucrose reduces different measures of newborn pain during heel lance, venipuncture and intramuscular injection. However, sucrose does not provide effective pain relief during circumcision. There is conflicting evidence for whether sucrose reduces pain for other minor painful procedures and further research is needed to investigate these more thoroughly.

Twenty-nine studies reported on adverse events (harms of the sucrose and other treatments) and found that the number of minor adverse events (e.g. choking or gagging) was very low, and was similar in the different groups (so not attributable to the sucrose treatment). No major adverse events were reported.

Quality of evidence

Although sucrose has been widely studied as a pain reliever for newborn babies, most studies have included few babies and have used many different measures of pain to assess its effectiveness. We identified high-quality evidence that sucrose reduces pain for heel lance, venipuncture and intramuscular injection. The quality of evidence was low or moderate in favour for the use of sucrose for other painful procedures.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Sucrose (20% to 33%) compared with water for pain associated with heel lance

Patient or population: neonates with heel lance-associated pain

Settings: hospital

Intervention: sucrose (20% to 33%)

Comparison: water

Outcomes	Illustrative comparative risks (mean and range)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Water	Sucrose (20% to 33%)			
PIPP at 30 s after heel lance Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA. A lower score = less pain (Stevens 1996)	The mean for PIPP ranged across control groups from 8.5 to 9.62	The WMD for PIPP in the intervention groups was lower: -1.42 (95% CI -2.86 to 0.01)	105 (2)	⊕⊕⊖⊖ **low**	Bias: there were some concerns about bias in both studies (see RoB tables) Consistency: there was moderate inconsistency between the study point estimates (I^2 = 51 %) Precision: there was low precision in the point estimate with wide 95% CIs) Indirectness: all trials were conducted in the target population (no concern about indirectness)
PIPP at 60 s after heel lance Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants >3 6 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	The mean for PIPP in the control group was 8.59	The mean for PIPP in the intervention groups was lower: -1.80 (95% CI -3.81 to 0.21)	31 (1)	⊕⊕⊖⊖ **low**	Bias: there were concerns about allocation concealment and performance bias in this single study Consistency: N/A as there was only one study Precision: there was lack of precision due to small sample size Indirectness: the study was conducted in the target population

PIPP score during heel lance (1st heel lance) Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	The mean for PIPP in the control group was 7.3	The mean for PIPP in the intervention group was the same as in the control group: 0.00 (95% CI -1.52 to 1.52)	107 (1)	⊕⊕⊕⊖ **moderate**	Bias: there were no concerns about bias in this study Consistency: as there was only one study in this analysis concerns about consistency were N/A Precision: this was a relatively large single study (no lack of precision) Indirectness: the study was conducted in the target population
DAN score at 30 s after heel lance Range of scale 0-10 A lower score = less pain (Carbajal 1997)	The mean DAN score in the control group was 9.5	The mean DAN score in the intervention group was lower: -1.90 (95% CI -8.58 to 4.78)	32 (1)	⊕⊕⊖⊖ **low**	Bias: concerns about blinding of performance and detection bias Consistency: as there was only one study in this analysis concerns about consistency were not N/A Precision: small sample size Indirectness: the study was conducted in the target population
NIPS during heel lance Range of scale 0-7 A lower score = less pain Lawrence 1993	The mean NIPS score in the control group was 3	The mean NIPS score in the intervention group was lower: -2.00 (95% CI -2.42 to -1.58)	56 (1)	⊕⊕⊕⊖ **moderate**	Bias: no concerns about bias Consistency: as there was only one study in this analysis concerns about consistency were N/A Precision: small sample size Indirectness: the study was conducted in the target population (no concern about indirectness)

*The basis for the **assumed risk** was 'The mean PIPP, DAN and NIPS scores across control groups according to the values reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention groups for the PIPP, DAN and NIPS scores with their 95% CI'.
CI: confidence interval; **DAN:** Douleur Aiguë du Nouveau-né Scale; **PIPP:** Premature Infant Pain Profile; **PMA:** postmenstrual age; **N/A:** not applicable; **NIPS:** Neonatal Infant Pain Scale; **WMD:** weighted mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 2.

Sucrose (24%) compared with breastfeeding for heel lance-associated pain

Patient or population: neonates with heel lance-associated pain

Settings: hospital

Intervention: sucrose 24%

Comparison: breastfeeding

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Breastfeeding	Sucrose (24%)			
PIPP - Preterm infants	The mean PIPP score in the breast feeding group was 7 Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	The mean PIPP score in the sucrose group was lower: -1.75 (95% CI -2.22 to -1.28)	47 (1)	⊕⊕⊖⊖ **low**	Bias: there were concerns about performance and detection bias Consistency: as there was only one study in this analysis concerns about consistency were N/A Precision: small sample size Indirectness: the study was conducted in the target population (no concern about indirectness)

*The basis for the **assumed risk** was 'The mean PIPP score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the PIPP score with its 95% CI'.
CI: confidence interval; **PIPP:** Premature Infant Pain Profile; **PMA:** postmenstrual age; **N/A:** not applicable

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 3.

Sucrose (24%) + NNS compared with water + NNS or pacifier dipped in sucrose compared with pacifier dipped in water for heel lance-associated pain

Patient or population: newborns with heel lance-associated pain

Settings: hospital

Intervention: sucrose (24%) + NNS

Comparison: water + NNS

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Water + NNS	Sucrose + NNS			
NFCS Range of scale 0-10 in term infants 0-9 in preterm infants A lower score = less pain Grunau 1987	The mean NFCS score in the water + NNS groups was 2.1	The mean NFCS score in the sucrose + NNS group was lower than in the water + NNS group: -0.60 (95% CI -1.47 to 0.47)	100 (1)	⊕⊕⊖⊖ **low**	Bias: many items scored 'unclear' on the RoB assessment Consistency: as there was only one study in this analysis concerns about consistency were N/A Precision: relatively large sample size (no lack of precision) Indirectness: the study was conducted in the target population (no concern about indirectness)
PIPP 30 s after heel lance (term and preterm infants) Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	The mean PIPP score ranged across control groups from 6.3 to 10.19	The WM PIPP score in the sucrose + NNS group was lower than in the control group: - 1.70 (95% CI -2.13 to -1.26)	278 (3)	⊕⊕⊕⊕ **high**	Bias: there was low risk of bias in all three studies. Consistency: the findings of the three studies were consistent, I^2 = 0% (no heterogeneity). Precision: large sample size (no lack of precision). Indirectness: the studies were conducted in the target population (no concern about indirectness).
PIPP 60 s after heel lance	The mean PIPP score ranged	The WM PIPP score in the sucrose + NNS group was lower than	164 (2)	⊕⊕⊕⊕ **high**	Bias: there was low risk of bias in both studies

Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	across control groups from 10.54 to 11.2	in the control group: - 2.14 (95% CI -3.34 to -0.94)		Consistency: the findings of the two studies were consistent, I^2 = 0% (no heterogeneity) Precision: large sample size (no lack of precision) Indirectness: the studies were conducted in the target population (no concern about indirectness)

*The basis for the **assumed risk** was 'The mean NFCS and PIPP scores across control groups according to the values reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention groups for the NFCS and PIPP scores with their 95% CI'.
CI: confidence interval; RoB: risk of bias; **N/A:** not applicable;**NFCS:** Neonatal Facial Coding System;**NNS:** non-nutritive sucking; **WM:** weighted mean

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 4.

Sucrose (24%) + NNS + NIDCAP compared with breast milk (by breastfeeding) for heel lance-associated pain

Patient or population: neonates with heel lance-associated pain

Settings: hospital

Intervention: sucrose (24%) + NNS + NIDCAP

Comparison: breast milk (by breastfeeding)

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Breast milk (by breastfeeding)	Sucrose (24%) + NNS + NIDCAP			
PIPP score Range of scale 0-21 for infants < 28 weeks PMA	The mean PIPP score in the breast milk (by breast feeding) group was 7	The mean PIPP score in the sucrose (24%) + NNS + NIDCAP group was lower than in the control group:	47 (1)	⊕⊕⊖⊖ **low**	Bias: there was a high risk of performance and detection bias as the interventions could not be blinded

and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)		- 1.75 (95% CI -4.03 to 0.53)			Consistency: as there was only one study in this analysis concern about consistency was N/A Precision: small sample size (lack of precision) Indirectness: the study was conducted in the target population (no concern about indirectness)

*The basis for the **assumed risk** was 'The mean PIPP score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the PIPP score with its 95% CI'.
CI: confidence interval; **PIPP:** Premature Infant Pain Profile; **PMA:** postmenstrual age; **N/A** not applicable; **NIDCAP:** Newborn Individualized Developmental Care and Assessment Program;**NNS:** non-nutritive sucking

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 5.

Sucrose (24%) + NNS + NIDCAP support compared with breast milk (by syringe) for heel lance-associated pain

Patient or population: neonates with heel lance-associated pain

Settings: hospital

Intervention: sucrose (24%) + NNS + NIDCAP support

Comparison: breast milk (by syringe)

Outcomes	**Illustrative comparative risks* (95% CI)**		**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**			
	Breast milk (by syringe)	**Sucrose (24%) + NNS + NIDCAP support**			
PIPP score	The mean PIPP score in the breast	The mean PIPP score in the sucrose (24%) + NNS + NIDCAP support group was low-	47 (1)	⊕⊕⊖⊖ **low**	Bias: there was a high risk of performance and detection bias as the interventions could not be blinded

Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	milk (by syringe) group was 5.38	er than in the control group: -0.13 (95% CI -2.41 to 2.15)		Consistency: as there was only one study in this analysis concern about consistency was N/A Precision: small sample size (lack of precision) Indirectness: the study was conducted in the target population (no concern about indirectness)

*The basis for the **assumed risk** was 'The mean PIPP score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the PIPP score with its 95% CI'.
CI: confidence interval; **PIPP:** Premature Infant Pain Profile; **PMA:** postmenstrual age; **N/A** not applicable; **NIDCAP:** Newborn Individualized Developmental Care and Assessment Program;**NNS:** non-nutritive sucking

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 6.

Sucrose (24%) compared with laser acupuncture for pain associated with heel lance

Patient or population: neonates with pain associated with heel lance

Settings: hospital

Intervention: sucrose (24%)

Comparison: laser acupuncture

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Laser acupuncture	Sucrose (24%)			
NIPS score Range of scale 0-7	The mean NIPS score was 4.52 in	The mean NIPS score in the sucrose group was lower than in the laser	42 (1)	⊕⊕⊖⊖ **low**	Bias: There was high risk of selection bias and performance bias in this study

A lower score = less pain Lawrence 1993	the laser acupuncture group	group: -0.86 (95% CI -1.43 to -0.29)			Outcome assessments were made from video tapes (low risk of bias) Consistency: As there was only one study in this analysis concern about consistency was N/A Precision: small sample size (lack of precision) Indirectness: the study was conducted in the target population (no concern about indirectness)

*The basis for the **assumed risk** was 'The mean NIPS score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the NIPS score with its 95% CI'.
CI: confidence interval; **N/A:** not applicable; **NIPS:** Neonatal Infant Pain Scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 7.

Sucrose (24%) compared with sucrose (24%) + NNS for pain associated with heel lance

Patient or population: neonates with pain associated with heel lance

Settings: hospital

Intervention: sucrose (24%)

Comparison: sucrose (24%) + NNS

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Sucrose (24%) + NNS	Sucrose (24%)			
Revised NFCS Range of scale	The mean NFCS score in the sucrose (24%) + NNS group was 0.02	The mean NFCS score in the sucrose (24%) only group was higher than in the sucrose (24%) + NNS	343 (1)	⊕⊕⊕⊖ **moderate**	Bias: there was a risk of performance and detection bias in this study as the coder could have distinguished the different groups

0-10 in term infants 0-9 in preterm infants A lower score = less pain Grunau 1987		group: 0.43 (95% CI 0.23 to 0.63)		Consistency: as this was a single study a rating of consistency was N/A Precision: this study had a very large sample size with a narrow 95% CI (no concerns about precision) Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean NFCS score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the NFCS score with its 95% CI'.
CI: confidence interval; **N/A:** not applicable; **NFCS:** Neonatal Facial Coding System; **NNS:** non-nutritive sucking.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 8.

Sucrose (24%) compared with sucrose (24%) + swaddling for pain associated with heel lance

Patient or population: neonates with pain associated with heel lance

Settings: hospital

Intervention: sucrose (24%)

Comparison: sucrose (24%) + swaddling

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Sucrose (24%) + swaddling	Sucrose (24%)			
Revised NFCS Range of scale 0-10 in term infants	The mean NFCS score in the sucrose (24%) + swaddling group was 0.05	The mean NFCS score in the sucrose (24%) group was higher than in the sucrose (24%) + swaddling	343 (1)	⊕⊕⊕⊖ **moderate**	Bias: there was a risk of performance and detection bias in this study as the coder could have distinguished the different groups

0-9 in preterm infants A lower score = less pain Grunau 1987		group: 0.40 (95% CI 0.19 to 0.61)			Consistency: as this was a single study a rating of consistency was N/A Precision: this study had a very large sample size with a narrow 95% CI (no concerns about precision) Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean NFCS score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the NFCS score with its 95% CI'.
CI: confidence interval; **N/A:** not applicable; **NFCS:** Neonatal Facial Coding System

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 9.

Sucrose (24%) compared with sucrose (24%) + NNS + swaddling for pain associated with heel lance

Patient or population: neonates with pain associated with heel lance

Settings: hospital

Intervention: sucrose (24%)

Comparison: sucrose (24%) + NNS + swaddling

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Sucrose (24%) + NNS + swaddling	Sucrose (24%)			
Revised NFCS Range of scale 0-10 in term infants	The mean NFCS score in the sucrose (24%) + NNS + swaddling group was 0.02	The mean NFCS score in the sucrose (24%) group was higher than in the sucrose (24%) + NNS + swad-	337 (1)	⊕⊕⊕⊖ **moderate**	Bias: there was a risk of performance and detection bias in this study as the coder could have distinguished the different groups

0-9 in preterm infants A lower score = less pain Grunau 1987		dling group: 0.43 (95% CI 0.23 to 0.63)		Consistency: as this was a single study a rating of consistency was N/A Precision: this study had a very large sample size with a narrow 95% CI (no concerns about precision) Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean NFCS score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the NFCS score with its 95% CI'.
CI: confidence interval; **N/A:** not applicable; **NFCS:** Neonatal Facial Coding System; **NNS:** non-nutritive sucking

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 10.

Sucrose (20%) compared with facilitated tucking for pain associated with repeated heel lances

Patient or population: neonates with pain associated with repeated heel lances

Settings: hospital

Intervention: sucrose (20%)

Comparison: facilitated tucking

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Facilitated tucking	Sucrose (20%)			
Total Bernese Pain Scale for Neonates (BPSN) during heel lance	The mean Total Bernese Pain Scale in the control group was 9.75	The mean Total Bernese Pain Scale was lower in the in the intervention	48 (1)	⊕⊕⊕⊖ **moderate**	Bias: there was some risk of bias in this study as the intervention was not blinded

Range: The BPSN contains 9 items; 3 physiologic (HR, RR, oxygen saturation) and 6 behavioural (grimacing, body movements, crying, skin colour, sleeping patterns, consolation) items. Each item is scored on a 3 point scale (0-3) points. **Higher scores for the behavioural items and greater changes in the physiological items indicate increased pain, whereas a total score of ≤ 11 is considered nonpainful.** Cignacco 2004		group: MD -2.27 (95% CI -4.66 to 0.12)			Consistency: as this was a single study consistency was N/A Precision: this was a small study and the CI was wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness
Total Bernese Pain Scale for Neonates during recovery from heel lance **Range: See comments above.** Cignacco 2004	The mean Total Bernese Pain Scalein the control group was 5.18	The mean Total Bernese Pain Scale was lower in the intervention group: MD -0.31 (95% CI -1.72 to 1.10)	48 (1)	⊕⊕⊕⊖ **moderate**	Bias: There was some risk of bias in this study as the intervention was not blinded. Consistency: As this was a single study consistency was N/A. Precision: This was a small study and the CI was wide around the point estimate. Directness: The study was conducted in the target population - no concerns about indirectness.

*The basis for the **assumed risk** was 'The mean Total Bernese Pain Scale for Neonates score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the mean Total Bernese Pain Scale for Neonates score with its 95% CI'.
CI: confidence interval; **MD** mean difference;**N/A** not applicable

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 11.

Sucrose (20%) compared with facilitated tucking and sucrose (20%) for pain associated with repeated heel lances

Patient or population: neonates with pain associated with repeated heel lances

Settings: hospital

Intervention: sucrose (20%)

Comparison: facilitated tucking and sucrose (20%)

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Facilitated tucking and sucrose (20%)	Sucrose (20%)			
Total Bernese Pain Scale for Neonates during heel lance (preterm infants) Range: The BPSN contains 9 items; 3 physiologic (HR, RR, oxygen saturation) and 6 behavioural (grimacing, body movements, crying, skin colour, sleeping patterns, consolation) items. Each item is scored on a 3 point scale (0-3) points. Higher scores for the behavioural items and greater changes in the physiological items indicate increased pain, whereas a total score of ≤ 11 is considered non-painful. A lower score = less pain Cignacco 2004	The mean Total Bernese Pain Scale for Neonates in the control group was 7.53	The mean Total Bernese Pain Scale for Neonates in the intervention group was lower than in the control group: MD -0.05 (95% CI -2.16 to 2.06)	47 (1)	⊕⊕⊕⊖ **moderate**	Bias: there was some risk of bias in this study as the intervention was not blinded Consistency: as this was a single study consistency was N/A Precision: this was a small study and the CI was wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness
Total Bernese Pain Scale for Neonates during recovery (preterm infants) Range: See information above. A lower score = less pain Cignacco 2004	The mean Total Bernese Pain Scale for Neonates in the control group was 4.23	The mean Total Bernese Pain Scale for Neonates in the intervention groups was higher than in the control group: MD 0.64 (95% CI -0.73 to 2.01)	47 (1)	⊕⊕⊕⊖ **moderate**	Bias: there was some risk of bias in this study as the intervention was not blinded Consistency: as this was a single study consistency was N/A Precision: this was a small study and the CI was wide around the point estimate

	Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean Total Bernese Pain Scale for Neonates score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the mean Total Bernese Pain Scale for Neonates score with its 95% CI'.
CI: confidence interval; **MD** mean difference;**N/A** not applicable

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 12.

Sucrose (12%) compared with water for pain associated with venipuncture

Patient or population: neonates with pain associated with venipuncture

Settings: hospital

Intervention: sucrose (12%)

Comparison: water

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Water	Sucrose (12%)			
NIPS score in term and preterm infants Range of scale 0-7 A lower score = less pain Lawrence 1993	The mean NIPS score was 3.8 in the water group	The mean NIPS score in the sucrose group was lower than in the water group: 0.90 (95% CI -1.81 to 0.01)	111 (1)	⊕⊕⊕⊖ **moderate**	Bias: it is uncertain if outcome assessors were blinded Consistency: as this was a single study a rating of consistency was N/A Precision: this study had a relatively large sample size with a narrow 95% CI (no concerns about precision)

Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean NIPS score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the NIPS score with its 95% CI'.
CI: confidence interval; **N/A:** not applicable; **NIPS:** Neonatal Infant Pain Scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 13.

Sucrose (24% to 30%) compared with control (sterile water or no treatment) for pain associated with venipuncture

Patient or population: neonates with pain associated with venipuncture

Settings: hospital

Intervention: sucrose (24% to 30%)

Comparison: sterile water or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Sterile water or no treatment	Sucrose (24% to 30%)			
PIPP score during venipuncture Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain	The mean PIPP score ranged across control groups from 8.9 to 9.2	The WM PIPP score in the intervention group was lower than in the control group: 2.79 (95% CI-3.76 to -1.83)	213 (2 groups in 1 study)	⊕⊕⊕⊕ **high**	Bias: low risk of bias Consistency: this study reported on two groups of infants; one group was born to non-diabetic mothers and the other group to diabetic mothers. There was no heterogeneity for the results of the two groups I^2 = 0% Precision: this study (with the two groups combined) had a large sample size with a narrow 95% CI (no concerns about precision)

(Stevens 1996; Stevens 2014a)		Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean PIPP score in the control groups according to the values reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention groups for the PIPP score with its 95% CI'.
CI: confidence interval; **PIPP:** Premature Infant Pain Profile; **PMA:** postmenstrual age; **N/A:** not applicable; **WM** weighted mean

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 14.

Sucrose (24% to 30%) compared with sucrose (24% to 30%) + EMLA/liposomal lidocaine cream on the skin for pain associated with venipuncture

Patient or population: neonates with pain associated with venipuncture

Settings: hospital

Intervention: sucrose (24% to 30%)

Comparison: sucrose (24% to 30%) + EMLA/liposomal lidocaine cream on the skin

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Sucrose (24% to 30%) + EMLA/liposomal lidocaine cream on the skin	Sucrose (24% to 30%)			
PIPP score Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain	The mean PIPP score was 7.2 in the control group	The mean PIPP score in the intervention group was higher than in the control group: 1.30 (95% CI -0.12 to 2.72)	76 (1)	⊕⊕⊕⊖ **moderate**	Bias: low risk of bias Consistency: as this was the only study consistency was N/A Precision: this was a relatively small study and the CIs were wide around the point estimate

(Stevens 1996; Stevens 2014a)					Directness: the study was conducted in the target population - no concerns about indirectness
PIPP score during post-injection period Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	The mean PIPP score was 7.1 in the control group	The mean PIPP in the intervention group was higher than in the control group: 0.60 (95% CI -0.73 to 1.93)	76 (1)	⊕⊕⊕⊖ **moderate**	Bias: low risk of bias Consistency: as this was the only study consistency was N/A Precision: this was a relatively small study and the CIs were wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness
DAN score during venipuncture (preterm infants) Range of scale 0-10 A lower score = less pain (Carbajal 1997)	The mean DAN score was 6.4 in the control group	The mean DAN score in the intervention group was higher than in the control group: 1.30 (95% CI 0.26 to 2.34)	76 (1)	⊕⊕⊕⊖ **moderate**	Bias: low risk of bias Consistency: as this was the only study consistency was N/A Precision: this was a relatively small study and the CIs were wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness
DAN score during the post-injection period Range of scale 0-10 A lower score = less pain (Carbajal 1997)	The mean DAN score in the control group was 5.7	The mean DAN score in the intervention groups was higher than in the control group: 1.40 (95% CI 0.03 to 2.77)	76 (1)	⊕⊕⊕⊖ **moderate**	Bias: low risk of bias Consistency: as this was the only study consistency was N/A Precision: this was a relatively small study and the CIs were wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean PIPP scores and the DAN scores in the control groups according to the values reported in the Assumed risk column. The **corresponding risk** was the means in the intervention groups for the PIPP scores and the DAN scores with their 95% CI'.
CI: confidence interval; **DAN:** Douleur Aiguë du Nouveau-né Scale; **PIPP:** Premature Infant Pain Profile; **PMA:** postmenstrual age; **N/A:** not applicable

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 15.

Sucrose (20% to 25%) compared with water or no intervention for pain associated with intramuscular injection

Patient or population: neonates with pain associated with intramuscular injection

Settings: hospital

Intervention: sucrose (20% to 25%)

Comparison: water or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Water or no intervention	Sucrose (20% to 25%)			
NIPS during 1-2 minutes after IM injection Range of scale 0-7 A lower score = less pain Lawrence 1993	The mean NIPS score in the control group was 5.2	The mean NIPS score in the intervention group was lower than in the control group: -2.30 (95% CI -2.93 to -1.67)	60 (1)	⊕⊕⊖⊖ **low**	Bias: concerns about bias for random sequence generation, allocation concealment and lack of blinding for performance and detection Consistency: as this was the only study consistency was N/A Precision: this was a relatively small study and the CIs were wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness
PIPP during IM injection (term infants) - Infants of non-diabetic and diabetic mothers Range of scale 0-21 for infants < 28 weeks PMA and	The mean PIPP score ranged across control groups from 7.2 to 8.5	The WM PIPP score in the intervention groups was lower than in the control group: -1.05 (95% CI -1.98 to -0.12)	232 (2 groups in 1 study)	⊕⊕⊕⊕ **high**	Bias: no concerns about bias Consistency: there was high consistency between the two groups in this study. I^2 = 0% Precision: this was a large study and the CIs were narrow around the point estimates

0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)					Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean NIPP score and the PIPP scores in the control groups according to the values reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention groups for the NIPP score and the PIPP scores with their 95% CI'.
CI: confidence interval; **IM:** intramuscular; **PIPP:** Premature Infant Pain Profile; **PMA:** postmenstrual age; **N/A:** not applicable; **WM:** weighted mean

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 16.

Sucrose (25%) compared with glucose (25%) for pain associated with intramuscular injection

Patient or population: neonates with pain associated with intramuscular injection

Settings: hospital

Intervention:sucrose (25%)

Comparison: glucose (25%)

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Glucose (25%)	Sucrose (25%)			
NIPS during 1-2 minutes after immunization Range of scale 0-7 A lower score = less pain	The mean NIPS score was 3 in the control group	The mean NIPS score in the intervention group was lower than the mean score in the control group: - 0.10 (95% CI -0.89 to 0.69)	60 (1)	⊕⊕⊖⊖ **low**	Bias: concerns about bias for random sequence generation, allocation concealment and lack of blinding for performance and detection Consistency: no concerns as this was the only study

Lawrence 1993					Precision: this was a relatively small study and the CIs were wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean NIPS score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the NIPS score with its 95% CI'.
CI: confidence interval; **N/A:** not applicable; NIPS: Neonatal Infant Pain Scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 17.

Sucrose (24%) compared with sterile water for pain associated with bladder catheterization

Patient or population: neonates with pain associated with bladder catheterization

Settings: hospital

Intervention: sucrose (24%)

Comparison: sterile water

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Sterile water	Sucrose (24%)			
Change in DAN score Range of scale 0-10 A lower score = less pain (Carbajal 1997)	The mean change in DAN score in the control group was 5.29	The mean change in DAN score was lower in the intervention group than in the control group: - 2.43 (95% CI -4.50 to -0.36)	33 (1)	⊕⊕⊕⊖ **moderate**	Bias: There was a low risk of bias in this study Consistency: as this was a single study concerns about consistency were N/A Precision: this was a small study and the CI was wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean Change in DAN score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the NIPS score with its 95% CI'.
CI: confidence interval;**DAN:** Douleur Aiguë du Nouveau-né Scale; **N/A:** not applicable

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 18.

Sucrose (24%) compared with distilled water for pain associated with orogastric tube insertion

Patient or population: neonates with pain associated with orogastric tube insertion

Settings: hospital

Intervention: sucrose (24%)

Comparison: distilled water

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Distilled water	Sucrose (24%)			
PIPP score intra procedure Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	The mean PIPP score was 7.9 in the control group	The mean PIPP score in the intervention group was lower than in the control group: -0.30 (95% CI -1.33 to 0.73)	105 (1)	⊕⊕⊕⊕ **high**	Bias: there was a low risk of bias in this study. The protocol for the study was available to us and there were no deviations Consistency: as this was a single study concerns about consistency were N/A Precision: this was a moderately sized study and the CI was narrow around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness

PIPP score 30 seconds post procedure Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	The mean PIPP score was 5.6 in the control group	The mean PIPP score in the intervention group was lower than in the control group -1.30 (95% CI -2.31 to -0.29)	105 (1)	⊕⊕⊕⊕ **high**	Bias: there was a low risk of bias in this study. The protocol for the study was available to us and there were no deviations Consistency: as this was a single study concerns about consistency were N/A Precision: this was a moderately sized study and the CI was narrow around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness
PIPP score 1 min post procedure Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	The mean PIPP score was 4.6 in the control group	The mean PIPP score in the intervention group was lower than in the control group: -0.50 (95% CI -1.40 to 0.40)	105 (1)	⊕⊕⊕⊕ **high**	Bias: there was a low risk of bias in this study. The protocol for the study was available to us and there were no deviations Consistency: as this was a single study concerns about consistency were N/A Precision: this was a moderately sized study and the CI was narrow around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean PIPP scores in the control group according to the values reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention groups for the PIPP scores with their 95% CI'.
CI: confidence interval; **N/A:** not applicable; **PIPP:** Premature Infant Pain Profile; **PMA:** postmenstrual age

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 19.

Sucrose (24%) by syringe + swaddled +pacifier compared with water by syringe + swaddled + pacifier for pain/distress associated with retinopathy of prematurity (ROP) examination

Patient or population: neonates with pain/distress associated with ROP examination

Settings: hospital

Intervention: sucrose (24%) by syringe + swaddled + pacifier

Comparison: water by syringe + swaddled + soother

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Water by syringe + swaddled + pacifier	Sucrose (24%) by syringe + swaddled +pacifier			
PIPP during exam Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	The mean PIPP score was 14 in the control group.	The mean PIPP score in the intervention group was neither lower nor higher than in the control group: 0.00 (95% CI -2.08 to 2.08	32 (1)	⊕⊕⊖⊖ **low**	Bias: the authors did not describe how the random sequence was generated, nor did they describe how allocation concealment was achieved Consistency: as this was the only study concerns about consistency were N/A Precision: this was a small study and the CI were wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean PIPP score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the PIPP scores with its 95% CI'.
CI: confidence interval; **N/A** not applicable; **PIPP:** Premature Infant Pain Profile; **PMA:** postmenstrual age; **ROP:** retinopathy of prematurity examination

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 20.

Sucrose (24% to 33%) (sucrose or sucrose + NNS) compared with water (or water + NNS) for pain/distress associated with retinopathy of prematurity (ROP) examination

Patient or population: neonates

Settings: hospital

Intervention: sucrose (24% to 33%) (sucrose or sucrose + NNS)

Comparison: water (or water + NNS)

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Water (or water + NNS)	Sucrose (24% to 33%) (or sucrose + NNS)			
PIPP score during eye examination Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	The mean PIPP score ranged across control groups from 11.4 to 16.4	The WM PIPP score in the intervention groups was lower than in the control group: -2.15 (95% CI -2.86 to -1.43)	134 (3)	⊕⊕⊕⊖ **moderate**	Bias: there were some concerns about risk of bias in these studies for random sequence generation and allocation concealment Consistency: the findings were consistent with each other; I^2 = 46% (low heterogeneity) Precision: this was a moderately sized meta-analysis and the CI was narrow around the typical point estimate Directness: the studies were conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean PIPP score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the PIPP scores with its 95% CI'.
CI: confidence interval; **N/A:** not applicable; **NNS:** non-nutritive sucking; **PIPP:** Premature Infant Pain Profile; **PMA:** postmenstrual age; **ROP:** retinopathy of prematurity examination; **WM:** weighted mean

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 21.

Sucrose (24%) compared with EMLA for pain associated with circumcision

Patient or population: neonates undergoing circumcision

Settings: hospital

Intervention: sucrose (24%)

Comparison: EMLA

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	EMLA	Sucrose (24%)			
N-PASS score during circumcision Range of scale 0-13 A lower score = less pain (Hummel 2010)	The mean N-PASS score in the control group was 5.8	The mean N-PASS score in the intervention group was higher: MD 2.40 (95% CI 1.85 to 2.95)	60 (1)	⊕⊕⊖⊖ **low**	Bias: there were concerns about risk of bias in this study for random sequence generation (unclear risk) and high risk of performance and detection bias Consistency: as this was the only study concerns about consistency were N/A Precision: this was a small study and the CI was wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness
N-PASS score after 5 min Range of scale 0-13 A lower score = less pain (Hummel 2010)	The mean N-PASS score in the control group was 3.1	The mean N-PASS score in the intervention group was higher: MD 1.40 (95% CI 0.74 to 2.06)	60 (1)	⊕⊕⊖⊖ **low**	Bias: there were concerns about risk of bias in this study for random sequence generation (unclear risk) and high risk of performance and detection bias Consistency: as this was the only study concerns about consistency were N/A Precision: this was a small study and the CI was wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean N-PASS score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the N-PASS score with its 95% CI'.
CI: confidence interval; **EMLA:** eutectic mixture of local anaesthetic; **MD** mean difference; **N/A** not applicable; **N-PASS:** Neonatal Pain Agitation and Sedation Scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 22.

Sucrose (24%) compared with EMLA + sucrose (24%) for pain associated with circumcision

Patient or population: neonates undergoing circumcision

Settings: hospital

Intervention: sucrose (24%)

Comparison: EMLA + sucrose (24%)

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	EMLA + sucrose (24%)	Sucrose (24%)			
N-PASS score during circumcision Range 0-13 A lower score = less pain (Hummel 2010)	The mean N-PASS score in the control group was 5.2	The mean N-PASS score in the intervention group was higher: MD 3.00 (95% CI 2.42 to 3.58)	60 (1)	⊕⊕⊖⊖ **low**	Bias: there were concerns about risk of bias in this study for random sequence generation (unclear risk) and high risk of performance and detection bias Consistency: as this was the only study concerns about consistency were N/A Precision: this was a small study and the CI was wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness
N-PASS score after 5 min Range 0-13 A lower score = less pain (Hummel 2010)	The mean N-PASS score in the control group was 3.3	The mean N-PASS score in the intervention group was higher: MD 1.20 (95% CI 0.49 to 1.91)	60 (1)	⊕⊕⊖⊖ **low**	Bias: there were concerns about risk of bias in this study for random sequence generation (unclear risk) and high risk of performance and detection bias Consistency: as this was the only study concerns about consistency were N/A Precision: this was a small study and the CI was wide around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean N-PASS score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the N-PASS score with its 95% CI'.
CI: confidence interval; **EMLA:** eutectic mixture of local anaesthetic; **MD** mean difference; **N/A** not applicable; **N-PASS:** Neonatal Pain Agitation and Sedation Scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 23.

Sucrose (24%) compared with for water stress associated with echocardiography

Patient or population: neonates undergoing echocardiography

Settings: hospital

Intervention: sucrose (24%)

Comparison: water

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	No intervention	Sucrose (24%)			
PIPP	The mean PIPP score was 7.4 in the control group Range of scale 0-21 for infants < 28 weeks PMA and 0-18 for infants > 36 weeks PMA A lower score = less pain (Stevens 1996; Stevens 2014a)	The mean PIPP score in the intervention group was lower than in the control group: - 2.15 (95% CI -3.30 to -1.00)	104 (1)	⊕⊕⊖⊖ **low**	Bias: there were concerns about allocation concealment bias and performance blinding in this study Consistency: as this was a single study concerns about consistency were N/A Precision: this was a moderately sized study and the CI was narrow around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean PIPP score in the control group according to the value reported in the Assumed risk column. The **corresponding risk** was the mean in the intervention group for the PIPP scores with its 95% CI'.
CI: confidence interval; **N/A:** not applicable; **PIPP:** Premature Infant Pain Profile; **PMA:** postmenstrual age

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 24.

Sucrose (24%) compared with water for potentially painful procedures for a period of seven days

Patient or population: neonates with pain associated with potentially painful procedures for 7 days

Settings: hospital

Intervention: sucrose (24%)

Comparison: water

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Water	Sucrose (24%)			
Motor development and vigor (MDV) domain of the NAPI tool Normative mean and SD at 36 weeks PMA 63 (14.5) Higher scores are associated with more mature behaviour (Snider 2005)	The mean MDV score at 40 weeks PMA was 76.48 in the control group	The mean MDV score at 40 weeks PMA in the intervention group was lower than in the control group: -1.83 (95% CI -8.59 to 4.93)	93 (1)	⊕⊕⊕⊕ **high**	Bias: there were no concerns about bias in this study Consistency: as this was a single study concerns about consistency were N/A Precision: this was a moderately sized study and the CI was narrow around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness

Alertness and orientation (AO) domain of the NAPI tool Normative mean and SD at 36 weeks PMA 54 (19.4) Higher scores are associated with more mature behaviour (Snider 2005)	The mean AO score at 40 weeks PMA was 67.77 in the control group	The mean AO score at 40 weeks PMA in the intervention group was higher than in the control group: 3.09 (95% CI -6.49 to 12.67)	93 (1)	⊕⊕⊕⊕ **high**	Bias: there were no concerns about bias in this study Consistency: as this was a single study concerns about consistency was N/A Precision: this was a moderately sized study and the CI was narrow around the point estimate Directness: the study was conducted in the target population - no concerns about indirectness

*The basis for the **assumed risk** was 'The mean MDV and the mean AO scores in the control group according to the values reported in the Assumed risk column. The **corresponding risk** was the means in the intervention groups for the MDV and AO scores with their 95% CI'.
AO: 'alertness and orientation' **CI:** confidence interval; **MDV:** 'motor development and vigor'; **N/A:** not applicable; **PMA** post menstrual age; **SD:** standard deviation

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Infants hospitalized in the Neonatal Intensive Care Unit (NICU) undergo frequent painful tissue-breaking procedures for diagnostic and therapeutic purposes. Epidemiological research from audits in NICUs in high-income countries estimates that neonates undergo an average of four to 16 painful exposures per day (Carbajal 2008; Johnston 2011; Lago 2013; Roofthooft 2014; Stevens 2011). Similarly, estimates of procedural pain in infants in low- and middle-income countries - including those in South America (Linhares 2011), Asia (Chen 2012; Jeong 2014), and Africa (Kyololo 2014) - are equally high.

Treatment for prevention or relief of procedural pain for neonates in the NICU varies widely in practice and is generally less than optimal (Carbajal 2008; Johnston 2011). An audit of 3508 tissue-damaging procedures performed on 582 infants across a one week period in 14 Canadian NICUs indicated that only about 50% were accompanied by any form of pharmacologic, behavioural or physical pain-relieving intervention (Johnston 2011). Although clinical practice guidelines outlining strategies to relieve pain from surgery, medical illness, and major procedures exist (Lee 2014), their quality is inconsistent.

Untreated pain in neonates, and particularly preterm infants, during a critical time in brain development, has the potential to result in significant immediate and long-term consequences (Grunau 2013; Walker 2013). These consequences include: (a) changes in somatosensory processing and altered sensitivity to future painful stimuli; (b) impaired neuro-anatomical development; and, (c) behavioural, emotional and learning disabilities (Bartocci 2006; Brummelte 2012; Grunau 2013; Holsti 2005; Slater 2006; Tu 2007; Vinall 2014a; Vinall 2014b Walker 2013; Zwicker 2013).

Description of the intervention

Administration of oral sucrose with or without non-nutritive sucking (NNS) (e.g. pacifiers) and other sweet solutions (e.g. glucose) prior to and during painful procedures have been the most frequently studied interventions for relief of procedural pain in neonates (Bueno 2013; Stevens 2013). Analgesic effects persist up to approximately one year of age, although the robustness of the effect may decline in older infants compared to neonates (Harrison 2013).

How the intervention might work

Analgesic, calming and stress reducing effects of sucrose were first reported in infant rats (Blass 1989; Ren 1997; Shide 1989). These effects occurred rapidly, persisted for several minutes and were blocked by systemic opioid receptor antagonists. They were age dependent and had differential maturational effects consistent with changes in the endogenous analgesic mechanisms and the development of the gustatory and pain pathways (Anseloni 2002). Researchers contend that sucrose may act at, or be mediated at, the level of the brainstem (Anseloni 2002; Anseloni 2005; Fitzgerald 2015), which has been shown to be a primary relay in the ascending gustatory pathway in animals (Anseloni 2005).

In human infants, the analgesic and calming effects of sweet-tasting solutions are speculated to influence endogenous opioid pathways activated by the sweet taste (Blass 1994). However, the underlying mechanisms for calming and pain may differ. These mechanisms may be additive or synergistic, but most likely depend on normal functioning of central mechanisms. Further research has demonstrated that the effects are associated with the potency of sweet taste (sweeter, more concentrated solutions), rather than volume of solution administered; with sucrose being more analgesic than glucose and fructose, and lactose not demonstrating any analgesic effects (Blass 1994). In a systematic review/meta-analysis of the efficacy of sucrose for procedural pain management in 13 trials and 982 neonates, Stevens 1997a found that the proportion of time crying decreased with 0.24 g to 0.48 g sucrose (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).

Despite advances through research on the potential mechanisms of sucrose analgesia, further research is required to enhance our understanding of the opioid pathways involved in the developing infant, the effectiveness of sucrose when administered with concomitant opioids and/or other pain-relieving interventions, and with repeated use for extended periods of time (Harrison 2012).

Why it is important to do this review

This systematic review is a substantive update of the original 1998 Cochrane Review (Stevens 1998), and the updates completed in 2001, 2004, 2010 and 2013 (Stevens 2001; Stevens 2004; Stevens 2010; Stevens 2013). The most recently updated version in 2013 included 57 studies - with 4730 term and preterm neonates - demonstrated that single doses of sucrose were effective and safe for reducing pain associated with several single painful procedures performed in stable full-term and preterm neonates (Stevens 2013). Tissue-damaging procedures included heel lance, venipuncture, eye examinations, circumcision, subcutaneous injections, bladder catheterization, and nasogastric tube insertion. A meta-analysis of four studies indicated that a range of sucrose doses (from a few drops to 0.5 mL of 24% solution) significantly reduced composite infant pain scores.

Repeated use, or use in extremely preterm and sick infants has rarely been addressed (Harrison 2009). Johnston reported that preterm infants of less than 31 weeks gestational age who were exposed to more than 10 repeated doses of sucrose a day were more prone to poorer attention and motor development in early life (Johnston 2002; Johnston 2007). Other studies have not reported differences between sucrose and non-sucrose groups (Banga 2015; Gaspardo 2008; Stevens 2005b; Taddio 2009a). However, comprehensive studies evaluating repeated dosing of sucrose for all painful procedures during hospitalizations of the neonate have not been undertaken. Concerns regarding the repeated use of sucrose and cumulative volumes administered during painful procedures in the developing brains of preterm infants have been raised (Ranger 2014).

Although 24% or 25% sucrose solutions are the most widely used concentrations for treatment of procedural pain in clinical practice, there is considerable variation in the volumes of sucrose reported to be effective in diminishing pain, and a more than 20-fold variation in doses used in clinical practice (Taddio 2009a). There is currently no clear recommendation regarding the optimal volume of sucrose for analgesia in infants, or for the use of sucrose in the presence of opioid analgesia, despite frequent administration of opioids to infants during their NICU stay (Harrison

2009; Johnston 2011). Ideally the amount of sucrose (mg/kg body weight) administered should be reported. A critical evaluation of guidelines for incorporating sucrose as an intervention for preventing or ameliorating procedural pain in infants indicates that recommendations for practitioners are not clear (Lee 2014). These knowledge gaps and lack of consistent strategies for effective application of knowledge most likely contribute to the current suboptimal or non-standardized utilization of sucrose in NICUs.

OBJECTIVES

To determine the efficacy, effect of dose, method of administration and safety of sucrose for relieving procedural pain in neonates as assessed by validated composite pain scores, physiological pain indicators (heart rate, respiratory rate, saturation of peripheral oxygen in the blood, transcutaneous oxygen and carbon dioxide (gas exchange measured across the skin - $TcpO_2$, $TcpCO_2$), **n**ear **i**nfra**r**ed **s**pectroscopy (NIRS), **e**lectro**e**ncephalo**g**ram (EEG), or behavioural pain indicators (cry duration, proportion of time crying, proportion of time facial actions (e.g. grimace) are present), or a combination of these and long-term neurodevelopmental outcomes.

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. We did not include quasi-randomised trials. We included only published studies and no abstracts were included as we have identified discrepancies in numbers of infants enrolled between abstracts and final publications (Walia 1999) (see Selection of studies). We did not impose language restrictions.

For the 2013 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. The same inclusion criteria were used for this 2016 update.

Types of participants

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

Types of interventions

Interventions included administration of sucrose via oral syringe, dropper or in addition to a pacifier for treatment of procedural pain. For the 2013 update of the review we extended inclusion criteria to all studies that used sucrose as an intervention for any acute painful procedure including heel lance, venipuncture, subcutaneous injection, intramuscular injection, arterial puncture, circumcision, bladder catheterization, insertion of orogastric or nasogastric tube, and eye examination for retinopathy of prematurity (ROP). Control group interventions included breastfeeding, breast milk or milk formula, water (sterile, tap, distilled, spring), local anaesthetics, pacifier, positioning/containing, facilitated tucking, warmth no treatment, and various concentrations of glucose. For this 2016 update we added echocardiography as a stressful intervention and laser acupuncture as a control group intervention.

Types of outcome measures

For this 2016 update we reorganized the outcomes as follows:

Primary outcomes

- Composite pain score: A composite pain score includes indicators of pain from multiple dimensions (e.g. behavioural and physical - e.g.PIPP-R). Multidimensional behavioural pain score: A multidimensional behavioural pain score includes multiple indicators of pain but from one dimension (e.g. NFCS). Validated pain scores in this review included the Premature Infant Pain Profile (PIPP; Stevens 1996), Revised PIPP (PIPP-R; Stevens 2014a), Douleur Aiguë du Nouveau-né Scale (DAN; Carbajal 1997), Neonatal Infant Pain Scale (NIPS; Lawrence 1993), Neonatal Facial Coding System (NFCS; Grunau 1987), Neurobehavioural Assessment of Preterm Infants (NAPI; Snider 2005), Neonatal Pain Agitation and Sedation Scale (N-PASS; Hummel 2010) and the Bernese Pain Scale for Neonates (BPSN; Cignacco 2004). We did not include the results for the COMFORTneo Scale in the 'Summary of findings' tables (van Dijk 2009), as it has not been fully validated. We do report on the results from studies that used that pain scale in the Results section.
- Long-term neurodevelopmental outcomes (assessed by a standardized and validated assessment tool, a child developmental specialist, or both) at 18 to 24 months, or at any later age in childhood.

Secondary outcomes

Individual behavioural pain indicators:

- cry duration;
- proportion of time crying;
- proportion of time facial actions were present;
- facial actions.

Individual physiological pain indicators:

- heart rate;
- respiratory rate;
- oxygen saturation of the blood;
- $TcpO_2$;
- $TcpCO_2$;
- cortisol level;
- NIRS;
- EEG.

Any adverse effects reported.

Search methods for identification of studies

Electronic searches

We used the standard methods of Cochrane Neonatal. We carried out electronic searches for relevant RCTs in MEDLINE (PubMed; 1950 to February 2016), EMBASE (1980 to February 2016), CINAHL (1982 to February 2016) and the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2016). Search terms used in the PubMed search are shown in Appendix 1. Similar search terms were used in the other databases. One author (AO) selected the trials

for inclusion or exclusion and one other author (JY) confirmed the selections.

Searching other resources

We searched bibliographies and personal files (BS, JY AO). We did not include unpublished studies as they have not been peer-reviewed. We obtained additional information from published studies if needed. We have listed identified abstracts under excluded studies. We did not apply any language restrictions. We searched the ISRCTN database (www.isrctn.com), the National Institute of Health Clinical Trials database (clinicaltrials.gov), and the International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) in February 2016. One author (AO) selected the ongoing trials for inclusion and exclusion and another author (JY) confirmed the selections.

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). In the 2013 update and the current 2016 update the types of participants were more clearly defined to include maximum postnatal age of 28 days after reaching 40 weeks' PMA. 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

For this 2016 update three reviewers (AO, SH, AS) extracted data separately using pre designed forms. We compared the data and resolved differences. We had additional data provided by investigators for four studies we had previously included (Allen 1996; Harrison 2003; Johnston 1999; Stevens 1999).

Assessment of risk of bias in included studies

Three reviewers (AO, SH, AS), who were not blinded to trial authors or institutions, assessed the methodological quality of each study independently. Three authors (BS, JY, AO) have published trials that were included in this update of the review. For these trials two authors (SH, AS) did the data abstraction and RoB assessments.

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

1. Random sequence generation (selection bias): for each included study, we categorized the risk of selection bias as:
   a. low risk - adequate (any truly random process, e.g. random number table; computer random number generator);
   b. high risk - inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
   c. unclear risk - no, or unclear, information provided.
2. Allocation concealment (selection bias): for each included study, we categorized the risk of bias regarding allocation concealment as:
   a. low risk - adequate (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
   b. high risk - inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
   c. unclear risk - no, or unclear, information provided.
3. Blinding (performance bias): for each included study, we categorized 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:
   a. low risk - adequate for personnel (a placebo that could not be distinguished from the active drug was used in the control group);
   b. high risk - inadequate, personnel aware of group assignment;
   c. unclear risk - no, or unclear, information provided.
4. Blinding (detection bias): for each included study, we categorized 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 categorized the methods used with regard to detection bias as:
   a. low risk - adequate follow-up was performed with assessors blinded to group assignment;
   b. high risk - inadequate, assessors were aware of group assignment at follow-up ;
   c. unclear risk - no, or unclear, information provided.
5. Incomplete outcome data (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 categorized the methods with respect to the risk of attrition bias as:
   a. low risk - adequate (< 10% missing data);
   b. high risk - inadequate (> 10% missing data);
   c. unclear risk - no, or unclear, information provided.
6. Selective reporting (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:
   a. low risk - adequate (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review had been reported);
   b. high risk - inadequate (where not all the study's prespecified outcomes had been reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; or the study failed to include results of a key outcome that would have been expected to have been reported);
   c. 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:
   a. low risk - no concerns of other bias raised;
   b. high risk - e.g. investigators were aware of results before the end of the study; differences exist between abstracts and final publications of papers concerning the number of participants enrolled;
   c. unclear - concerns raised about potential sources of bias that could not be verified by contacting the authors.

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

Quality of evidence

For this update the quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach in order to assess the quality of the body of evidence relating to the following primary outcomes for each of the comparisons listed under Objectives (Guyatt 2011a; Schünemann 2009):

1. composite pain score
2. long-term neurodevelopmental outcomes (assessed by a standardized and validated assessment tool, a child developmental specialist, or both) at 18 to 24 months, or at any later age in childhood. No study reported on long-term neurodevelopmental outcomes, and therefore this outcome could not be included in the GRADE assessment.

We used the RevMan table editor (RevMan 2014), which is based on GRADEprofiler (GRADEpro 2014), to create 'Summary of findings' tables. We produced a summary of the intervention effect and a measure of quality for each of the main comparisons and outcomes listed above (if reported) using the GRADE approach (Guyatt 2011a). The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. The GRADE approach considers evidence from RCTs as being of high quality, but this quality rating may be downgraded on the basis of any of five areas: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias (Guyatt 2011a). The GRADE approach results in an assessment of the quality of a body of evidence as one of four grades explained below.

1. High quality: we are very confident that the true effect lies close to that of the estimate of the effect. Further research is very unlikely to change our confidence in the estimate of effect.
2. Moderate quality: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Further research is very likely to have and important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. We are very uncertain about the estimate (Schünemann 2013).

The review authors independently assessed the quality of the evidence found for outcomes identified as critical or important for clinical decision making, namely: composite pain score. No study reported on long-term neurodevelopmental outcomes.

When we considered the risk of bias, the presence of inadequate concealment of allocation or randomised assignment, incomplete follow-up or unblinded outcome assessment reduced our confidence in the effect estimates, and we downgraded the quality of evidence accordingly (Guyatt 2011b). We evaluated consistency by comparing the similarity of point estimates, extent of overlap of confidence intervals and statistical criteria, including measurement of heterogeneity (I^2). We downgraded the quality of evidence when inconsistency across study results was present, large and unexplained (i.e. some studies suggested important benefit and others no effect or harm without a clinical explanation) (Guyatt 2011c). We assessed precision according to the 95% confidence interval around the pooled estimation (Guyatt 2011d). If trials had been conducted in populations other than the target population, we would have downgraded the quality of evidence because of indirectness (Guyatt 2011e). Publication bias was not applicable, as only three or fewer studies were included in each analysis. We entered data (i.e. pooled estimates of the effects and corresponding 95% confidence intervals) and made explicit judgments for each of the above aspects assessed in the 'Summary of findings' tables. Because of the large number of comparisons (n = 37) and outcomes under each comparison we elected to include only those comparisons that included outcomes for validated pain scores (BPSN, DAN, NAPI, NFCS, NIPS, N-PASS, PIPP, PIPP-R). All judgements involving the assessment of the study characteristics described above are explained in foot notes or comments in the 'Summary of findings' tables.

Measures of treatment effect

We performed statistical analyses using RevMan 5.3 (RevMan 2014). We analyzed 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) if the RD was statistically significant. We analyzed continuous data using mean difference (MD). We reported the 95% confidence interval (CI) on all estimates. Three authors (AO, SH and AS) used the formulas reported in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 7.7.3.2) to convert 95% confidence intervals to standard deviations (SD) (Higgins 2011; RevMan 2014). Following advice from Dr Michael Bracken (statistician of the Cochrane Neonatal Review Group) we decided not to convert medians and interquartile or full ranges to means and SDs.

Unit of analysis issues

We did not identify any cluster randomised trials and so did not encounter any unit of analysis issues.

Dealing with missing data

Many authors did not report means and SDs for the outcomes. We transformed 95% CIs to SDs using the techniques described under Measures of treatment effect. Many studies reported the results in graph form only, and we could not incorporate the findings in RevMan-analyses.

Assessment of heterogeneity

We report the I^2 statistic for all analyses in which more than one trial was included. We categorized the heterogeneity using the following labels and cut-offs for the results of the I^2 test; less than 25%, no heterogeneity present; 25% to 49%, low heterogeneity; 50% to 74%, moderate heterogeneity; and 75% or more, high heterogeneity. If we detected statistical heterogeneity, we explored the possible causes (e.g. differences in study quality, participants (term or preterm infants), intervention regimens or outcome assessments) using post hoc subgroup analyses.

Assessment of reporting biases

We planned to construct forest plots if there were at least 10 studies included in one meta-analysis that assessed the same outcome in comparable trials of the same intervention in the same population, however, no single meta-analysis fulfilled this criterion.

Data synthesis

We used the statistical package RevMan 5.3 provided by Cochrane (RevMan 2014). For meta-analyses, we reported a weighted mean difference (WMD) with 95% CI using a fixed-effect model for continuous outcome measures if at least two studies were included in the analysis, otherwise we reported the mean difference (MD). For categorical outcomes we reported the typical (if at least two trials were included) risk ratio (RR), risk difference (RD), and, if the RD was statistically significant, we planned to report the NNTB or NNTH. All values were reported with their 95% CIs.

Subgroup analysis and investigation of heterogeneity

We did not make separate subgroup comparisons for different painful/stressful procedures (heel lance, venipuncture, arterial puncture, subcutaneous injections, pain associated with IM injections (hepatitis B immunization and injection of vitamin K), bladder catheterization, insertion of nasogastric or orogastric tubes, ROP eye examination, circumcision, and echocardiography exam) or for multiple procedures.

Sensitivity analysis

Under each comparison for the outcomes we report the results in the term and the preterm populations separately and combined these whenever data were available.

RESULTS

Description of studies

Two authors (AO, JY) identified an additional 20 studies for inclusion in this current 2016 update through the searches of the literature (Abbasoglu 2015; Al Qahtani 2014; Asmerom 2013; Banga 2015; Cignacco 2012; Dilli 2014; Gray 2012; Gray 2015; Leng 2013; Leng 2015; Liaw 2011; Liaw 2013; Marin Gabriel 2013; Milazzo 2011; Pandey 2013; Potana 2015; Simonse 2012; Suhrabi 2014; Thakkar 2016; Tutag Lehr 2015). The flow chart for the literature searches is shown in Figure 1. In this current update the authors excluded the study by Scaramuzzo 2013 as it was a quasi-randomised controlled trial. In addition two studies were classified as awaiting classification due to a need for translation (Moradi 2012b; Moradi 2012a). One newly identified study was excluded after translation as the infants were older (mean 8.5 months) than the accepted age for inclusion in this review (28 days) (Aziznejad 2013). We excluded the study by Fernandez 2003, which was added at the 2013 update, as it assessed the effects of heel stroke.

Figure 1. Study flow diagram: review update

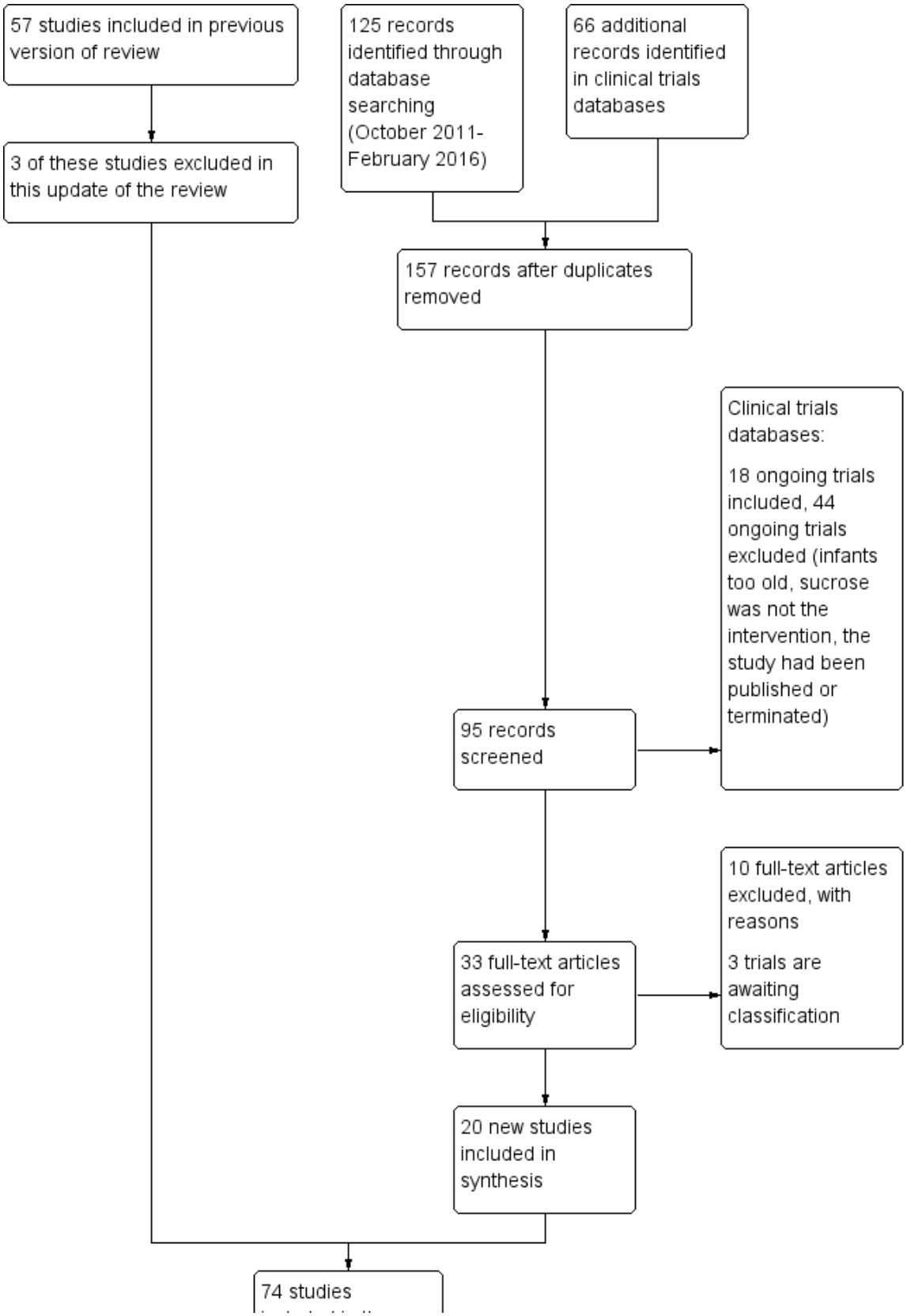
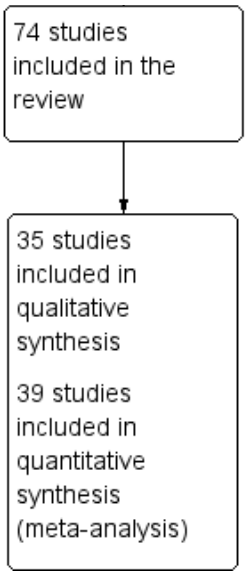


Figure 1. (Continued)



The authors excluded one study that had been included at the previous 2013 update as they reclassified it as a quasi-randomised trial (Ozdogan 2010), and excluded another that had previously been awaiting classification, as the word 'random' did not appear anywhere in the text (Akman 2002). The authors identified several papers as secondary publications to studies, and these are now listed under their primary study references, namely: the 2004 paper published by Boyer and co-workers is now listed under Johnston 2002; the Angeles 2015 paper is now listed under Asmerom 2013; and the Yin 2015 paper is now listed under Liaw 2013. The study by Singh 2001 is still awaiting classification as we have not been able to obtain a reprint.

The authors identified a total of 18 ongoing studies for this 2016 update of the review, details are about these are provided in Characteristics of ongoing studies (Campbell-Yeo 2013; ISRCTN59514984; ISRCTN73259137; NCT02344368; Montanholi 2012; NCT01742520; NCT01190995; NCT01438008; NCT01552993; NCT01800318; NCT01894659; NCT01931020; NCT02133716; Passariello 2014; Philip 2012; Roue 2013; Shah 2015; Stevens 2014).

For the 2013 and 2016 updates of this review, the inclusion criteria were expanded to include any painful/stressful procedure (rather than heel lance and venipuncture only), and included studies that assessed the efficacy of repeated doses of sucrose.

No studies assessing long-term neurodevelopmental outcomes were identified in the 2013 update nor in this current 2016 update.

Included studies

A total of 74 studies (enrolling 7049 infants) are included in this systematic review. Thirty-eight of these studies focused on term infants (Abbasoglu 2015; Allen 1996; Al Qahtani 2014; Altun-Köroğlu 2010; Basnet 2010; Blass 1997; Blass 1999; Carbajal 1999; Codipietro 2008; Gormally 2001; Gray 2012; Gray 2015; Greenberg 2002; Guala 2001; Haouari 1995; Herschel 1998; Isik 2000a; Kaufman 2002; Leng 2013; Leng 2015; Liaw 2011; Marin Gabriel 2013; Mathai 2006; Ogawa 2005; Örs 1999; Overgaard 1999; Ramenghi 1996b; Rogers 2006; Rushforth 1993; Slater 2010; Stang 1997; Suhrabi 2014; Taddio 2008; Taddio 2011; Thakkar 2016; Tutag Lehr 2015; Unceta-Barranechea 2008; Yilmaz 2010), while 31 included preterm infants only (Abad 1996; Acharya 2004; Asmerom 2013; Biran 2011; Boyle 2006; Bucher 1995; Cignacco 2012; Dilli 2014; Elserafy 2009; Gal 2005; Gaspardo 2008; Grabska 2005; Harrison 2003; Johnston 1997; Johnston 1999; Johnston 2002; Kristoffersen 2011; McCullough 2008; Milazzo 2011; Mitchell 2004; Mucignat 2004; O'Sullivan 2010; Okan 2007; Pandey 2013; Ramenghi 1996a; Ramenghi 1999; Rush 2005; Simonse 2012; Stevens 1999; Stevens 2005a; Storm 2002), and five included both preterm and term infants (Banga 2015; Gibbins 2002; Liaw 2013; Montoya 2009; Potana 2015). Details of each study are outlined in the Characteristics of included studies table.

The studies were conducted in 22 different countries; USA (17), Canada (9), UK (9), Turkey (7), India (5), France (3), Spain (3). In China, Italy, Norway, Saudi Arabia, Switzerland, and Taiwan two studies were conducted in each country and one study was conducted in each of Australia, Brasil, Colombia, Denmark, Iran, Ireland, Japan, Nepal, and the Netherlands.

Each included study is described in the Additional tables, which are organized according to the type of painful procedure to which the infants were exposed. As stated in the methods section for this update, three authors (AO, SH, AS) transcribed 95% CIs to SDs whenever possible. If authors reported data in such a way that we could not include the results in RevMan-analyses, we reported the findings according to the authors in the Additional tables. The results of 35 studies could not be included in RevMan-analyses (Abad 1996; Acharya 2004; Allen 1996; Altun-Köroğlu 2010; Blass 1997; Blass 1999; Bucher 1995; Carbajal 1999; Codipietro 2008; Elserafy 2009; Gal 2005; Gaspardo 2008; Gormally 2001; Gray 2012; Johnston 1997; Johnston 2002; Kaufman 2002; Kristoffersen 2011; Leng 2013; Liaw 2013; Marin Gabriel 2013; McCullough 2008; Mucignat 2004; O'Sullivan 2010; Okan 2007; Örs 1999; Overgaard 1999; Ramenghi 1996a; Ramenghi 1996b; Ramenghi 1999; Rushforth 1993; Stevens 2005a; Storm 2002; Thakkar 2016; Yilmaz 2010).The results of those studies are summarized after the analyses for each comparison.

Painful procedures

Heel lance was the most predominant painful procedure, and was studied in 38 trials (Abbasoglu 2015; Altun-Köroğlu 2010; Asmerom 2013; Blass 1997; Blass 1999; Bucher 1995; Cignacco 2012; Codipietro 2008; Gibbins 2002; Gormally 2001; Greenberg 2002; Guala 2001; Haouari 1995; Harrison 2003; Isik 2000a; Johnston 1997; Johnston 1999; Leng 2013; Leng 2015; Liaw 2013; Marin Gabriel 2013; Mathai 2006; Okan 2007; Overgaard 1999; Ramenghi 1996a; Ramenghi 1996b; Ramenghi 1999; Rushforth 1993; Simonse 2012; Slater 2010; Stevens 1999; Stevens 2005a; Storm 2002; Thakkar 2016; Tutag Lehr 2015; Unceta-Barranechea 2008; Yilmaz 2010; Örs 1999) (Table 1). In nine studies, infants were observed during venipuncture (Abad 1996; Acharya 2004; Basnet 2010; Biran 2011; Carbajal 1999; Elserafy 2009; Gaspardo 2008; Montoya 2009; Taddio 2011) (Table 2). One study assessed both heel lance and venipuncture (Ogawa 2005) (Table 3), while another assessed arterial puncture (Milazzo 2011) (Table 4). In two studies, infants were assessed during subcutaneous injections (Allen 1996; Mucignat 2004) (Table 5), and in four studies during intramuscular injection (immunization for hepatitis B) (Gray 2012; Gray 2015; Liaw 2011; Suhrabi 2014) (Table 6). One study assessed infants during bladder catheterization (Rogers 2006) (Table 7), and three studies assessed infants during nasogastric or orogastric tube insertion (Kristoffersen 2011; McCullough 2008; Pandey 2013) (Table 8). Seven studies assessed infants undergoing an examination for ROP (Boyle 2006; Dilli 2014; Gal 2005; Grabska 2005; Mitchell 2004; O'Sullivan 2010; Rush 2005) (Table 9), while four studies involved circumcision (Al Qahtani 2014; Herschel 1998; Kaufman 2002; Stang 1997) (Table 10). Three studies assessed multiple painful procedures (Banga 2015; Johnston 2002; Taddio 2008) (Table 11). One trial assessed stress during echocardiography (Potana 2015) (Table 12).

Twenty-nine studies evaluated adverse effects.

Risk of bias in included studies

The studies we included enrolled between 15 and 671 infants. Forty-eight studies (65%) enrolled < 100 infants. The largest study enrolled 671 term infants, who were randomised to four groups (Leng 2015); sucrose, sucrose + non-nutritive sucking (NNS), sucrose + swaddling, and sucrose + NNS + swaddling. The second largest study enrolled 560 infants (Leng 2013), but we could not include data for sucrose versus sterile water for increase in heart rate and decrease in oxygen saturation at three minutes after heel lance in RevMan-analyses, as they were reported as means and full ranges.

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), as did the concentrations of sucrose and the volume used. Outcomes were reported inconsistently; as means with SDs, standard errors (SE) or 95% CIs, or medians with ranges and often in graphic form without reporting of numerical data.

The risk of bias is reported in the 'Risk of bias' graph (Figure 2) and the 'Risk of bias' summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

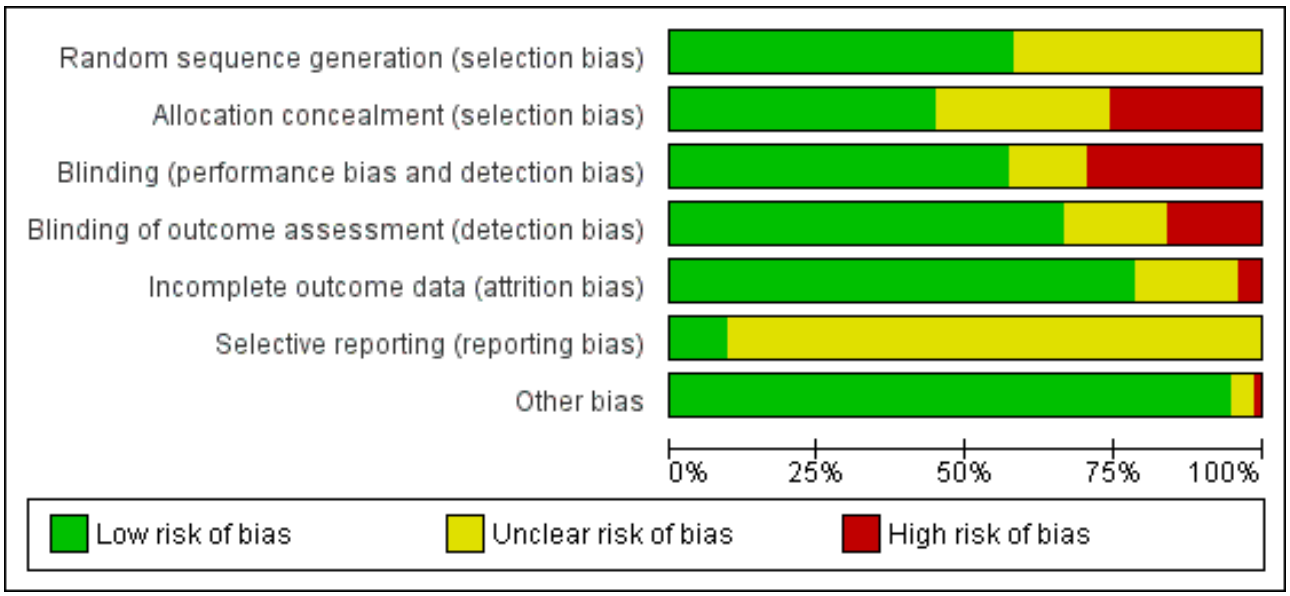


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

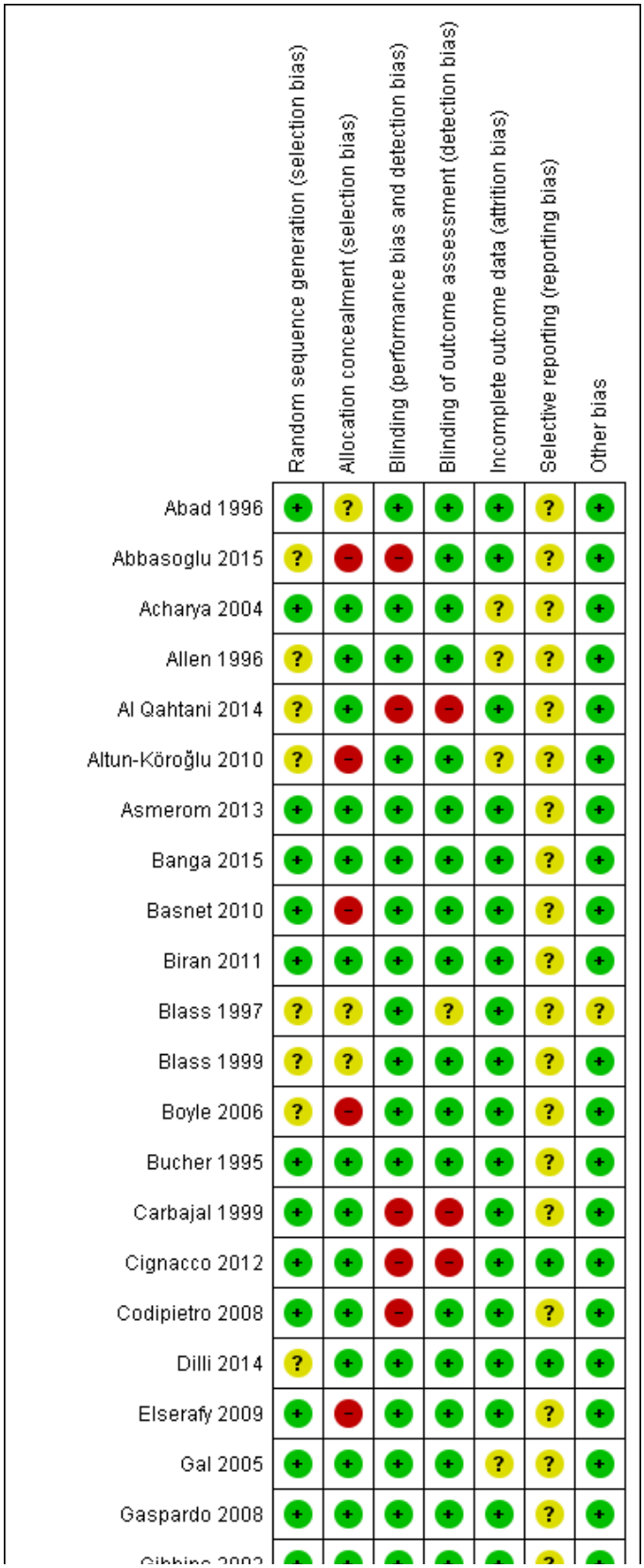


Figure 3. (Continued)

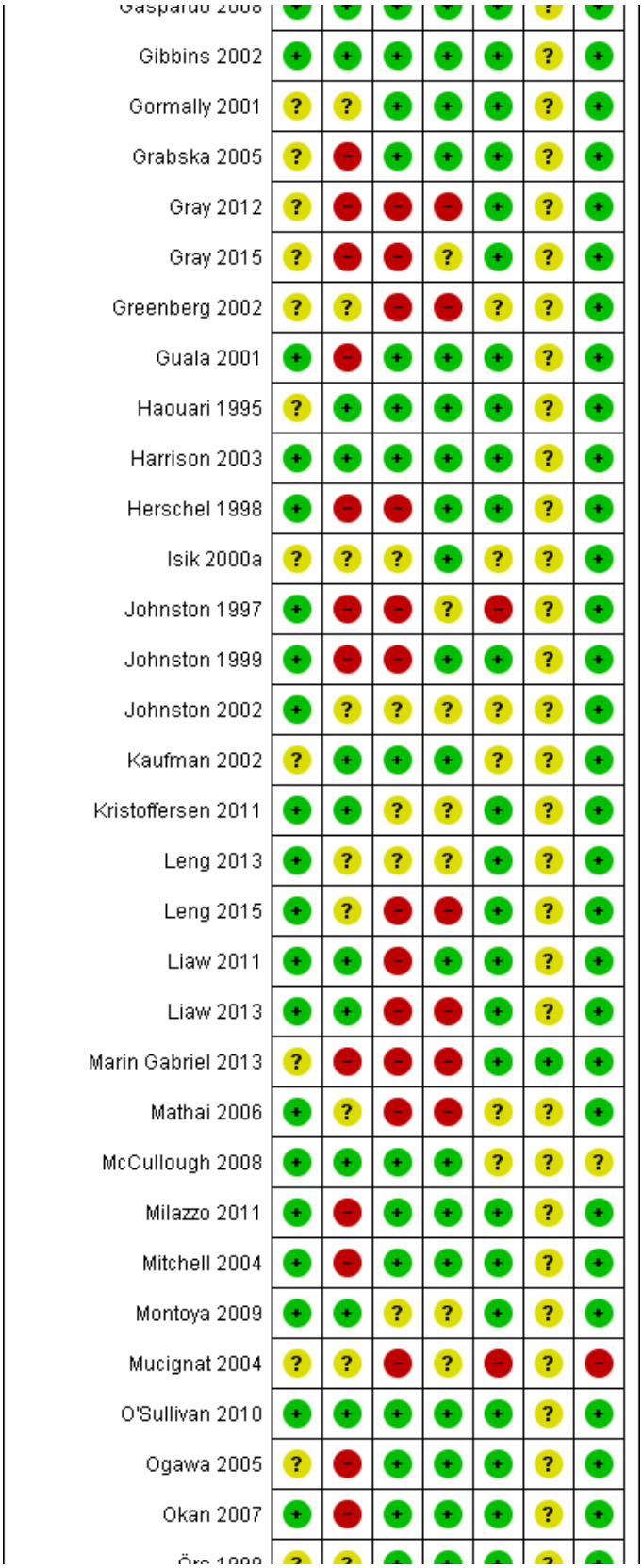
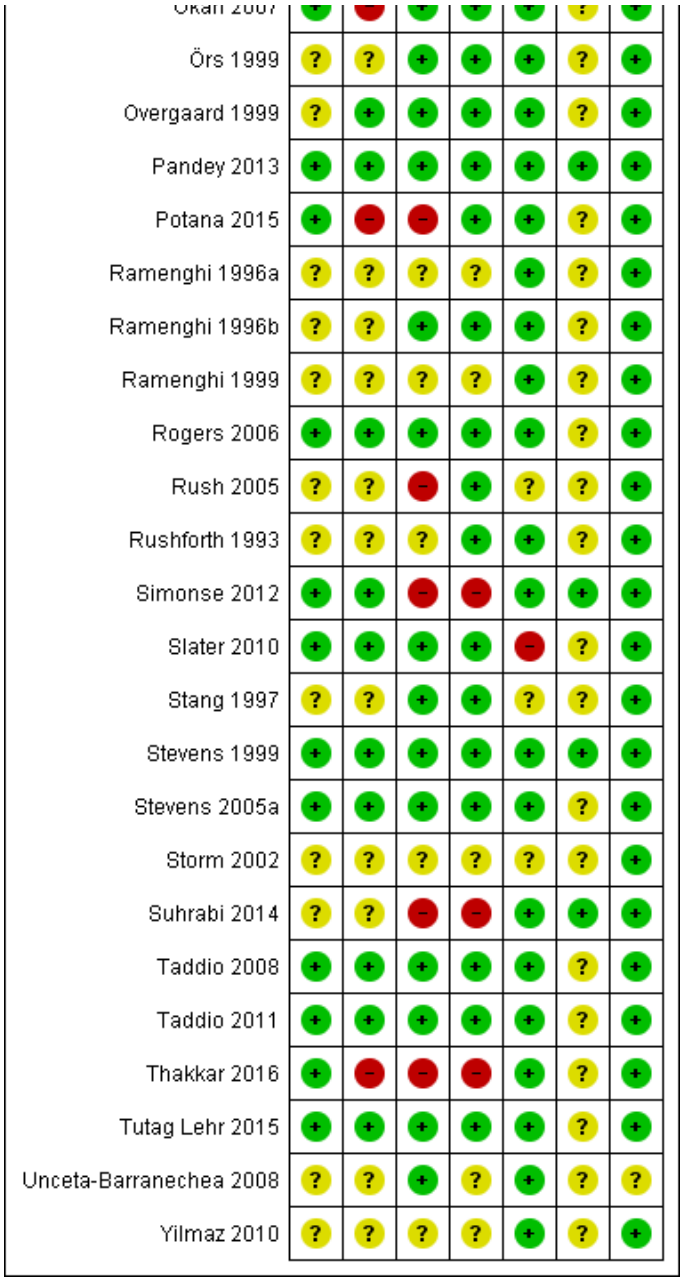


Figure 3. (Continued)



Allocation

Forty-three studies (58%) reported an adequately generated allocation sequence, however, in the remaining 31 studies (42%) it was unclear how the random sequence was generated. In 33 studies (45%) the allocation was adequately concealed. There was a high risk of bias for allocation concealment in 19 studies (26%), and an unclear risk of bias in 22 studies (30%).

Blinding

There was a low risk of performance bias in 42 studies (57%) and a high risk in 22 studies (30%). There was an unclear risk of bias in the remaining 10 studies (14%).

There was a low risk of detection bias in 49 studies (66%), a high risk in 12 studies (16%), and an unclear risk in the remaining 13 studies (18%).

Incomplete outcome data

There was a low risk of attrition bias in 58 studies (78%), a high risk in three studies (4%), and an unclear risk in the remaining 13 studies (18%).

Selective reporting

The protocols for eight studies (11%) were available to us, these had a low risk of reporting bias. The risk of reporting bias was unclear for the remaining 66 studies (89%).

Other potential sources of bias

Other potential bias was detected in one study (1%) in which there was unequal distribution of allocated and received treatments amongst injected infants (Mucignat 2004): NNS = 41, eutectic mixture of local anaesthetic (EMLA; a topical mixture of lidocaine (2.5%) and prilocaine (2.5%) cream) = 71, sucrose = 86, EMLA + sucrose = 67. The risk of bias was unclear in three studies (4%), and we did not detect other bias in the remaining 70 studies (95%).

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**; **Summary of findings 3**; **Summary of findings 4**; **Summary of findings 5**; **Summary of findings 6**; **Summary of findings 7**; **Summary of findings 8**; **Summary of findings 9**; **Summary of findings 10**; **Summary of findings 11**; **Summary of findings 12**; **Summary of findings 13**; **Summary of findings 14**; **Summary of findings 15**; **Summary of findings 16**; **Summary of findings 17**; **Summary of findings 18**; **Summary of findings 19**; **Summary of findings 20**; **Summary of findings 21**; **Summary of findings 22**; **Summary of findings 23**; **Summary of findings 24**

Tests for heterogeneity were not applicable when data from only one study were included in an analysis. For all included pain measures a lower score indicates lower level of pain.

Effectiveness of sucrose for heel lance

Sucrose (12% to 12.5 %) versus water/routine care (Comparison 1)

Secondary outcomes

Total crying time (s) (Outcome 1.1)

One study reported on 42 term infants (Greenberg 2002). There was a significantly shorter duration of total crying time (s) in the sucrose group compared with the water group; MD -48.09 (95% CI - 93.04 to -3.14; Analysis 1.1).

Percentage (%) change in heart rate 1 minute after heel lance (Outcome 1.2)

One study reported on 30 term infants (Haouari 1995). There was no significant difference in percentage change (%) in heart rate one minute after heel lance between the sucrose group and the water group; MD 6.40 (95% CI -13.69 to 26.49; Analysis 1.2).

Sucrose (20% to 33%) versus water (Comparison 2)

Primary outcomes

PIPP at 30 s after heel lance (Outcome 2.1)

One study reported on 44 term infants (Slater 2010), and another study reported on 61 preterm infants (Johnston 1999). For the combined group of term and preterm infants there was no significant difference in the PIPP scores between the sucrose and the water groups; MD -1.42 (95% CI -2.86 to 0.01); I^2 = 51 % (moderate: Analysis 2.1). For term infants the PIPP score was significantly lower in the sucrose group; MD -2.70 (95% CI -4.96 to -0.44), but in the preterm infants group there was no significant difference in the PIPP scores between the sucrose and the water groups; MD -0.56 (95% CI -2.42 to 1.30).

PIPP at 60 s after heel lance (Outcome 2.2)

One study reported on 31 preterm infants (Johnston 1999). There was no significant difference in the PIPP scores in the sucrose group compared with the water group; MD -1.80 (95% CI -3.81 to 0.21; Analysis 2.2).

PIPP during (first) heel lance (Outcome 2.3)

One study reported on 107 newborns of diabetic mothers (Taddio 2008). There was no significant difference in the PIPP scores in the sucrose group compared with the water group; MD 0.00 (95% CI -1.52 to 1.52; Analysis 2.3).

DAN score at 30 s after heel lance (Outcome 2.4)

One study reported on 32 term infants (Mathai 2006). There was no significant difference in the DAN score 30 s after heel lance in the sucrose group compared with the water group; MD -1.90 (95% CI -8.58 to 4.78; Analysis 2.4).

NIPS during heel lance (Outcome 2.5)

One study reported on 56 term infants (Tutag Lehr 2015). The NIPS score during heel lance was significantly lower in the sucrose group compared with the water group; MD -2.00 (95% CI -2.42 to -1.58; Analysis 2.5).

Secondary outcomes

Duration of first cry (s) (Outcome 2.6)

One study reported on 32 term infants (Mathai 2006), and another reported on 110 preterm infants (Harrison 2003). When the two groups of infants (term and preterm) were combined (n = 142) there was no significant difference in duration of first cry (s) in the sucrose group compared with the water group; MD -8.63 (-19.88 to 2.61); I^2 = 46.0% (low heterogeneity; Analysis 2.6). In the study performed in term infants (n = 32) there was no significant difference in the crying time (s) between the sucrose group compared with the water group; MD -5.00 (95% CI -17.40 to 7.40). In preterm infants (n =110) there was no significant difference between the duration of first cry (s) between the sucrose and the water groups; MD -25.41 (95% CI -52.06 to 1.24).

Total crying time (s) (Outcome 2.7)

Two studies reported on a total of 88 term infants (Isik 2000a; Mathai 2006). There was a significantly shorter total crying time (s) in the sucrose group than the water group; MD -22.11 (95% CI -32.52 to -11.70; Analysis 2.7). There was moderate heterogeneity for this outcome; I^2 = 59%.

Heart rate (beats/minute) during heel lance (Outcome 2.8)

Two studies reported on 96 term infants (Guala 2001; Tutag Lehr 2015). There was no significant difference in the heart rate (beats/minute) during heel lance; MD -0.81 (95% CI -8.57 to 6.94; Analysis 2.8). There was no heterogeneity for this outcome; I^2 = 0%.

Percentage change in heart rate 1 minute after heel lance (Outcome 2.9)

Two studies reported on 86 term infants (Haouari 1995; Isik 2000a). There was no significant difference in percentage change in heart rate one minute after heel lance in the sucrose group compared with the water group; WMD 0.90 (95% CI -5.81 to 7.61; Analysis 2.9). There was high heterogeneity for this outcome; I^2 = 86%. The

high heterogeneity could be explained by the very different results for the two studies; the Haouari 1995 study showed a significant increase in percentage change in heart rate; MD 9.90 (95% CI 0.41 to 19.39), whereas the Isik 2000a study showed a non-significant decrease; MD -8.10 (95% CI -17.59 to 1.39).

Respiratory rate (breaths/minute) during heel lance (Outcome 2.10)

One study reported on 56 term infants (Tutag Lehr 2015). There was no significant difference in the respiratory rate (breaths/minute) between the sucrose and the water groups during heel lance; MD -1.00 (95% CI -7.64 to 5.64; Analysis 2.10).

Oxygen saturation (%) during heel lance (Outcome 2.11)

One study reported on 56 term infants (Tutag Lehr 2015). There was no significant difference in the oxygen saturation (%) between the sucrose and the water groups during heel lance; MD -5.00 (95% CI -12.79 to 2.79; Analysis 2.11).

Skin blood flow during heel lance - Perfusion Units (PU) (Outcome 2.12)

One study reported on 56 term infants (Tutag Lehr 2015). There was no significant difference in skin blood flow (PU) during heel lance between the sucrose and the water groups; MD -32.00 (95% CI -68.87 to 4.87; Analysis 2.12).

Nociceptive-specific brain activity (mean weight) (Outcome 2.13)

One study reported on 44 term infants (Slater 2010). There was no significant difference in the nociceptive-specific brain activity (mean weight by EEG) between the sucrose and the water groups; MD 0.02 (95% CI -0.05 to 0.09; Analysis 2.13).

Sucrose (50%) versus water (Comparison 3)

Secondary outcomes

Duration of first cry (s) (Outcome 3.1)

Two studies reported on 80 term infants (Haouari 1995; Ogawa 2005). There was a significantly shorter duration of first cry (s) in the sucrose group compared with the water group; MD -63.20 (95% CI -79.20 to -47.19; Analysis 3.1); I^2 = 0% (none).

Percent change in heart rate 1 minute after heel lance (Outcome 3.2)

One study reported on 30 term infants (Haouari 1995). There was no significant difference in percent change in heart rate one minute after heel lance in the sucrose group compared with the water group; MD 2.60 (95% CI -11.43 to 16.63; Analysis 3.2).

Sucrose (24% to 25%) versus breastfeeding (Comparison 4)

Primary outcomes

PIPP (Outcome 4.1)

One study reported on 47 preterm infants (Simonse 2012). There was a significantly lower PIPP score in the sucrose group than in the breastfeeding group; MD -1.75 (95% CI -2.22 to -1.28; Analysis 4.1).

Comfort score (Outcome 4.2)

One study reported on 47 preterm infants (Simonse 2012). The Comfort score was significantly lower in the sucrose group than in the breastfeeding group; MD -2.60 (95% CI -3.06 to -2.14; Analysis 4.2).

Sucrose (24%) + NNS versus water + NNS, or pacifier dipped in sucrose versus pacifier dipped in water (Comparison 5)

Primary outcomes

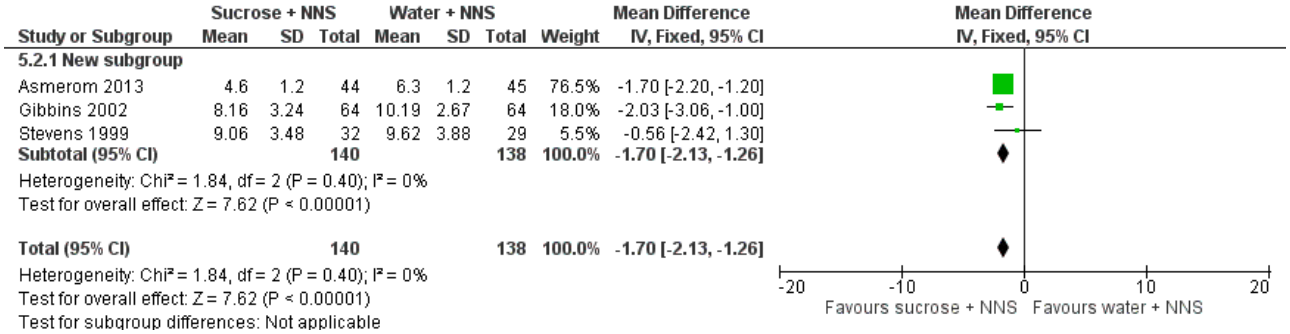
NFCS (Outcome 5.1)

One study reported on 100 term infants (Unceta-Barranechea 2008). There was no significant difference in the NFCS score in the sucrose + NNS group compared to the water + NNS group; MD -0.60 (95% CI -1.47 to 0.27; Analysis 5.1).

PIPP 30 s after heel lance (term and preterm infants) (Outcome 5.2)

One study reported on 128 term and preterm infants (mean PMA 33.7 weeks for the entire group) (Gibbins 2002). There was a significantly reduced PIPP in the sucrose + NNS group compared to the water + NNS group; MD -2.03 (95% CI -3.06 to -1.00). Another study reported on 61 preterm infants, who received either a pacifier dipped in sucrose or a pacifier dipped in water (Stevens 1999). There were no significant differences in the PIPP score between the sucrose and water groups; MD -0.56 (95% CI -2.42 to 1.30). A third study, Asmerom 2013, reported on 89 preterm infants who received sucrose (24%) + NNS or sterile water + NNS. There was a significantly reduced PIPP in the sucrose + NNS group compared to the water + NNS group; MD -1.70 (95% CI -2.20 to -1.20). When the three studies were combined (n = 278) there was a significantly lower PIPP score at 30 s after heel lance in the sucrose group than the water group; WMD -1.70 (95% CI -2.13 to -1.26; Analysis 5.2; Figure 4); I^2 = 0 % (no heterogeneity).

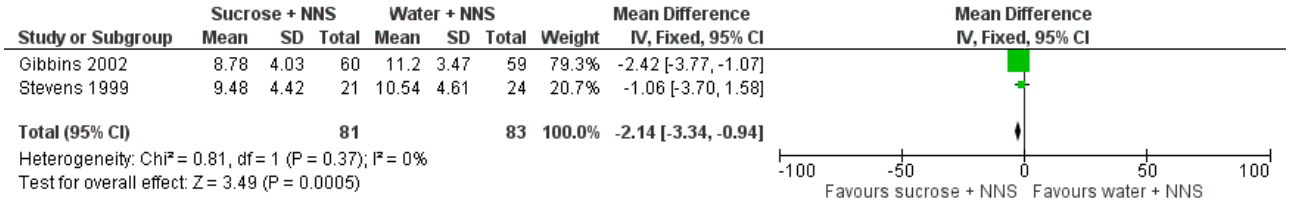
Figure 4. Forest plot of comparison: 6 Heel lance: Sucrose (24%) + NNS vs. water + NNS, outcome: 6.2 PIPP 30 s after heel lance (term and preterm infants).



PIPP 60 s after heel lance (term and preterm infants) (Outcome 5.3)

One study reported on 119 term and preterm infants (Gibbins 2002). There was a significantly reduced PIPP score in the sucrose + NNS group compared to the water + NNS group; MD -2.42 (95% CI -3.77 to -1.07). Another study reported on 45 preterm infants, who received either pacifier dipped in sucrose or pacifier dipped in water (Stevens 1999). There were no significant differences in the PIPP score between the sucrose and water groups; MD -1.06 (95% CI -3.70 to 1.58). When the two studies were combined there was a significantly lower PIPP score in the sucrose group compared with the water group; WMD -2.14 (95% CI -3.34 to -0.94; Analysis 5.3; Figure 5); I^2 = 0% (no heterogeneity).

Figure 5. Forest plot of comparison: 6 Heel lance: Sucrose (24%) + NNS vs. water + NNS, outcome: 6.3 PIPP 60 s after heel lance.



Secondary outcomes

Crying time (s) (Outcome 5.4)

One study reported on 100 term infants and compared sucrose + NNS with water + NNS (Unceta-Barranechea 2008). Another study reported on 42 term infants and compared a sucrose-coated pacifier with a water-moistened pacifier (Greenberg 2002). When the two studies were combined there was no significant difference in the crying time (s) in the sucrose + NNS group compared to the water + NNS group; MD -1.41 s (95% CI -9.87 to 7.04; Analysis 5.4); I^2 = 83% (high).

Sucrose (20%) versus human milk (Comparison 6)

Secondary outcomes

Crying time (s) (Outcome 6.1)

One study reported on 35 term infants (Mathai 2006). There was no significant difference in crying time in the sucrose group compared with the human milk group; MD -8.00 s (95% CI -21.07 to 5.07; Analysis 6.1).

Sucrose (24%) + NNS + Newborn Individualized Developmental Care and Assessment Program (NIDCAP) support versus breast milk via breastfeeding (Comparison 7)

Primary outcomes

PIPP score (Outcome 7.1)

One study reported on 47 preterm infants (Simonse 2012). There was no significant difference in the PIPP score in the sucrose + NNS + NIDCAP support group compared with the breast milk by breastfeeding group; MD -1.75 (95% CI -4.03 to 0.53; Analysis 7.1).

COMFORTneo score (Outcome 7.2)

One study reported on 47 preterm infants (Simonse 2012). The COMFORTneo score was significantly lower in the sucrose + NNS + NIDCAP support group than in the breast milk via breastfeeding group; MD -2.60 (95% CI -4.84 to -0.36; Analysis 7.2).

Sucrose (24%) + NNS + Newborn Individualized Developmental Care and Assessment Program (NIDCAP) support versus breast milk via syringe (Comparison 8)

PIPP score (Outcome 8.1)

One study reported on 47 preterm infants (Simonse 2012). There was no significant difference in the PIPP score in the sucrose + NNS + NIDCAP support group compared with the breast milk via syringe group; MD -0.13 (95% CI -2.41 to 2.15; Analysis 8.1).

COMFORTneo score (Outcome 8.2)

One study reported on 47 preterm infants (Simonse 2012). The COMFORTneo score was not significantly different in the sucrose + NNS + NIDCAP support group compared with the breast milk by syringe group; MD -0.50 (95% CI -2.74 to 1.74; Analysis 8.2).

Repeated heel lances: sucrose (20%) versus facilitated tucking (Comparison 9)

Primary outcomes

Total Bernese Pain Scale for Neonates during heel lance (Outcome 9.1)

One study reported on 48 infants (Cignacco 2012). There was no significant difference in the total Bernese Pain Scale for Neonates during heel lancing between the sucrose and the facilitated tucking groups; MD -2.27 (95% CI -4.66 to 0.12; Analysis 9.1).

Total Bernes Pain Scale for Neonates during recovery (Outcome 9.2)

One study reported on 48 infants (Cignacco 2012). There was no significant difference in the total Bernese Pain Scale for Neonates during recovery between the sucrose and the facilitated tucking groups; MD -0.31 (95% CI -1.72 to 1.10; Analysis 9.2).

Repeated heel lances: sucrose (20%) versus facilitated tucking + sucrose (20%) (Comparison 10)

Primary outcomes

Total Bernese Pain Scale for Neonates during heel lance (Outcome 10.1)

One study reported on 47 infants (Cignacco 2012). There was no significant difference in the total Bernese Pain Scale for Neonates during heel lance between the sucrose and the facilitated tucking groups; MD -0.05 (95% CI -2.16 to 2.06; Analysis 10.1).

Total Bernese Pain Scale for Neonates during recovery (Outcome 10.2)

One study reported on 47 infants (Cignacco 2012). There was no significant difference in the total Bernese Pain Scale for Neonates during recovery between the sucrose and the facilitated tucking groups; MD 0.64 (95% CI -0.73 to 2.01; Analysis 10.2).

Sucrose (30% to 33%) versus glucose (30% to 33%) (Comparison 11)

Secondary outcomes

Heart rate (beats/minute) during heel lance (Outcome 11.1)

One study reported on 40 term infants (Guala 2001). There was no significant difference n the heart rate (beats/minute) during heel lance in the sucrose group compared with the glucose group; MD 6.20 (95% CI -6.19 to 18.59; Analysis 11.1).

Crying time (s) (Outcome 11.2)

One study reported on 56 term infants (Isik 2000a). There was a significantly shorter crying time (s) in the sucrose group compared with the glucose group; MD -34.89 (95% CI -61.67 to -8.11; Analysis 11.2).

Percentage change in heart rate one minute after heel lance (Outcome 11.3)

One study reported on 56 term infants (Isik 2000a). there was no significant difference in the percentage change in heart rate (%) one minute after heel lance between the sucrose group and the glucose group; MD -6.58 (95% CI -14.85 to 1.69; Analysis 11.3).

Sucrose (50%) versus glucose (50%) (Comparison 12)

Secondary outcomes

Heart rate (beats/minute) during heel lance (Outcome 12.1)

One study reported on 40 infants (Guala 2001). The heart rate (beats/minute) during heel lance was significantly higher in the sucrose group compared with the glucose group; MD 16.30 (95% CI 1.93 to 30.67; Analysis 12.1).

Sucrose (24%) versus laser acupuncture (Comparison 13)

Primary outcomes

NIPS score (Outcome 13.1)

One study reported on 42 term infants (Abbasoglu 2015). The NIPS score was significantly lower in the sucrose group compared with the laser acupuncture group during heel lance; MD -0.86 (95% CI -1.43 to -0.29; Analysis 13.1).

Secondary outcomes

Crying time (s) (Outcome 13.2)

One study reported on 42 term infants (Abbasoglu 2015). The crying time (s) was significantly lower in the sucrose group than in the laser acupuncture group during heel lance; MD -51.29 (95% CI -73.11 to -29.47; Analysis 13.2).

Sucrose (24%) versus sucrose (24%) + NNS (Comparison 14)

Primary outcomes

Revised NFCS (Outcome 14.1)

One study reported on 343 term infants (Leng 2015). The revised NFCS score was significantly higher in the sucrose group than in the sucrose + NNS group; MD 0.43 (95% CI 0.23 to 0.63; Analysis 14.1).

Secondary outcomes

Increase in heart rate (%) (Outcome 14.2)

One study reported on 343 term infants (Leng 2015). There was a significantly higher increase (%) in the heart rate in the sucrose group compared with the sucrose + NNS group; MD 2.29 (95% CI 0.44 to 4.14; Analysis 14.2).

Decrease in oxygen saturation of blood (%) (Outcome 14.3)

One study reported on 343 term infants (Leng 2015). There was a significantly larger decrease (%) in the oxygen saturation of blood in the sucrose group compared with the sucrose + NNS group; MD 0.48 (95% CI 0.10 to 0.86; Analysis 14.3).

Sucrose (24%) versus sucrose (24%) + swaddling (Comparison 15)

Primary outcomes

Revised NFCS (Outcome 15.1)

One study reported on 343 term infants (Leng 2015). The revised NFCS score was significantly higher in the sucrose group compared with the sucrose + swaddling group; MD 0.40 (95% CI 0.19 to 0.61; Analysis 15.1).

Secondary outcomes

Increase in heart rate (%) (Outcome 15.2)

One study reported on 343 term infants (Leng 2015). There was no significant difference in the increase (%) in the heart rate in the sucrose group compared with the sucrose + swaddling group; MD 0.57 (95% CI -1.43 to 2.57; Analysis 15.2).

Decrease in oxygen saturation of blood (%) (Outcome 15.3)

One study reported on 343 term infants (Leng 2015). There was no significant difference in the decrease (%) in the oxygen saturation of blood in the sucrose group compared with the sucrose + swaddling group; MD 0.30 (95% CI -0.07 to 0.67; Analysis 15.3).

Sucrose (24%) versus sucrose (24%) + NNS + swaddling (Comparison 16)

Primary outcomes

Revised NFCS (Outcome 16.1)

One study reported on 337 term infants (Leng 2015). The revised NFCS score was significantly higher in the sucrose group compared with the sucrose + NNS + swaddling group; MD 0.43 (95% CI 0.23 to 0.63; Analysis 16.1).

Secondary outcomes

Increase in heart rate (%) (Outcome 16.2)

One study reported on 343 term infants (Leng 2015). There was a significantly larger increase (%) in the heart rate in the sucrose

group compared with the sucrose + NNS + swaddling group; MD 3.25 (95% CI 1.43 to 5.07; Analysis 16.2).

Decrease in oxygen saturation (%) (Outcome 16.3)

One study reported on 343 term infants (Leng 2015). There was a significantly larger decrease (%) in the oxygen saturation of blood in the sucrose group compared with the sucrose + NNS + swaddling group; MD 0.79 (95% CI 0.44 to 1.44; Analysis 16.3).

Data from 21 studies could not be included in analyses in RevMan (Altun-Köroğlu 2010; Blass 1997; Blass 1999; Bucher 1995; Codipietro 2008; Gormally 2001; Johnston 1997; Leng 2013; Liaw 2013; Marin Gabriel 2013 ; Okan 2007; Örs 1999; Overgaard 1999; Ramenghi 1996a; Ramenghi 1996b; Ramenghi 1999; Rushforth 1993; Stevens 2005a; Storm 2002; Thakkar 2016; Yilmaz 2010); for details see Table 1, though a brief summary is provided below.

In the Altun-Köroğlu 2010 study there were no statistically significant differences observed between the hind milk group and the sucrose group for all measures. In Blass 1997 there was significantly less crying time during blood collection in the sucrose group than in the water group, and, in the later Blass 1999 study, sucrose diminished cry duration compared to water. In Bucher 1995 cry duration was significantly reduced by sucrose compared to water. In Codipietro 2008 the duration of first cry was shorter in the breastfeeding group than the sucrose group, as were the PIPP scores (two minutes after heel lance). Gormally 2001 reported a significant effect of holding on pain concatenation scores for facial activity, with no difference between infants who received sucrose and those who did not. Johnston 1997 found a significant decrease in percentage facial action in the sucrose alone group and the sucrose plus rocking group compared to the water group. In the large study, Leng 2013, the average pain score three minutes after the procedure was significantly lower in the sucrose groups compared to the glucose groups. Liaw 2013 found that infants receiving NNS + oral sucrose + tucking or NNS + oral sucrose experienced more quiet sleep occurrences than those receiving routine care. Marin Gabriel 2013 reported a significantly lower percentage of crying with both the breast fed + skin-to-skin contact group and also the sucrose + skin-to-skin contact group compared with the skin-to-skin contact group. In Okan 2007 the sucrose and glucose groups showed a shorter time for the duration of first cry and total crying time than the water group. In Overgaard 1999 the NIPS scores one minute after heel lance and one minute after blood sampling were statistically significantly lower in the sucrose group than the water group. Ramenghi 1996a noted lower mean pain scores in the group receiving sucrose at one and two minutes after heel lance compared to the water group. In Ramenghi 1996b the pain scores were significantly lower in the sucrose (25% and 50%) groups and the Calpol group compared to the water group. In the third study by the Ramenghi group (Ramenghi 1999), which was a cross-over study (sucrose and water were given by nasogastric tube or intraorally, but the infant received either sucrose or water both times), significant reductions in behavioural scores were noted in the sucrose group compared with the water group. It is notable that infants in the 25% sucrose group displayed a significant reduction in behavioural score (P value 0.001) when sucrose was given intraorally compared to via a nasogastric tube. Rushforth 1993 used a low concentration of sucrose (7.5%) and found no difference in median percentage crying time between the sucrose group and the group that received water. In Stevens 2005a 66 infants were randomised to (1) standard of care (positioning + swaddling), (2) standard of care, sterile water via syringe and pacifier or (3) standard of care, 24% sucrose via syringe and pacifier two minutes prior to painful interventions during the first 28 days of life. PIPP scores were recorded at day 7, 14, 21, and 28 at routine heel lance. There was a significant main effect of group (P = 0.03) with differences occurring between the sucrose + pacifier group and standard care group at pain assessment at 60 s (P value 0.01). Mean PIPP scores were generally higher in the standard care group. Storm 2002 reported significantly less crying in infants in the groups that received sucrose (25%) or sucrose (25%) + milk compared to the groups that received a lower concentration of sucrose (15%) or milk. Thakkar 2016 reported lower median PIPP scores in the sucrose + NNS group compared to the sucrose only, NNS only, or no intervention groups. Yilmaz 2010 reported that the mean crying time in the sucrose group was lower than in the groups where the infant was sitting on the mother's lap, received mother's milk by syringe, or was given a pacifier. Örs 1999 noted that there was a significant decrease in crying time for the sucrose group compared to the human milk or sterile water groups, and recovery time from crying was shorter in the sucrose group, as was the percentage change in heart rate after heel lance.

Effectiveness of sucrose for venipuncture

Sucrose (12%) versus water (Comparison 17)

Primary outcomes

NIPS scores in term and preterm infants (Outcome 17.1)

One study reported on 111 preterm and term infants (Montoya 2009). There was no significant difference in the NIPS score between the sucrose and the water groups; MD -0.90 (95% CI -1.81 to 0.01; Analysis 17.1).

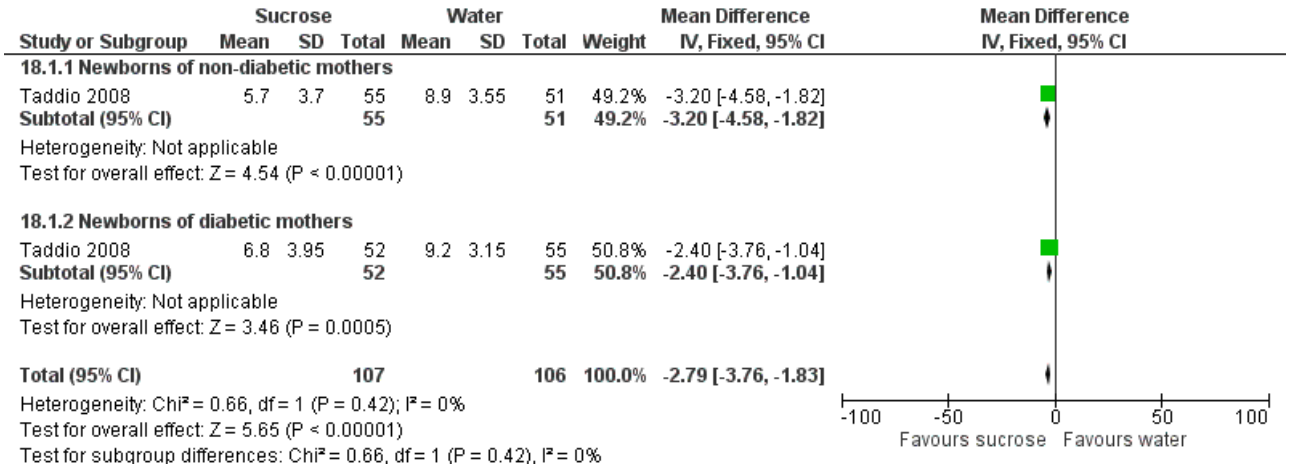
Sucrose (24% to 30%) versus control (sterile water or no treatment) (Comparison 18)

Primary outcomes

PIPP score during venipuncture (Outcome 18.1)

One study reported on 213 term infants (106 born to non-diabetic mothers and 107 to diabetic mothers) (Taddio 2008). For the two groups of infants combined there was a significant reduction in the PIPP score in the sucrose group compared with the sterile water group; WMD -2.79 (95% CI -3.76 to -1.83; Analysis 18.1; Figure 6); I^2 = 0 % (no heterogeneity). In the 106 infants born to non-diabetic mothers there was a significant reduction in the PIPP score in the sucrose group compared with the water group; MD -3.20 (95% CI -4.58 to -1.82). In the 107 infants born to diabetic mothers there was a significant reduction in the PIPP score in the sucrose group compared with the water group; MD -2.40 (95% CI -3.76 to -1.04).

Figure 6. Forest plot of comparison: 18 Venipuncture: sucrose (24% to 30%) versus control (sterile water or no treatment), outcome: 18.1 PIPP score during venipuncture.



Secondary outcomes

Duration of cry (s) in term infants (Outcome 18.2)

One study reported on 50 term infants (Basnet 2010). There was no significant difference between the sucrose and water groups in the duration of cry (s); MD -16.50 (95% CI -71.41 to 38.41; Analysis 18.2).

Sucrose (50%) versus water (Comparison 19)

Secondary outcomes

Duration of first cry (s) in term infants (Outcome 19.1)

One study reported on 50 term infants (Ogawa 2005). There was no significant difference in the duration of first cry (s) between the sucrose and the water group; MD -14.00 (95% CI -51.79 to 23.79; Analysis 19.1).

Sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/ liposomal lidocaine cream on the skin (Comparison 20)

Primary outcomes

PIPP score in preterm infants during venipuncture (Outcome 20.1)

One study reported on 76 preterm infants (Biran 2011). There was no significant difference in the PIPP score between the sucrose and the sucrose + EMLA/liposomal lidocaine group; MD 1.30 (95% CI -0.12 to 2.72; Analysis 20.1).

PIPP score in preterm infants during recovery period (Outcome 20.2)

One study reported on 76 preterm infants (Biran 2011). There was no significant difference in the PIPP score during the recovery period between the sucrose and the sucrose + EMLA/liposomal lidocaine group; MD 0.60 (95% CI -0.73 to 1.93; Analysis 20.2).

DAN score during venipuncture in preterm infants (Outcome 20.3)

One study reported on 76 preterm infants (Biran 2011). The DAN score during venipuncture was significantly higher in the sucrose group compared with the sucrose + EMLA/liposomal lidocaine group; MD 1.30 (95% CI 0.26 to 2.34; Analysis 20.3).

DAN score in preterm infants during recovery period (Outcome 20.4)

One study reported on 76 preterm infants (Biran 2011). The DAN score during the recovery period was significantly higher in the sucrose group compared with the sucrose + EMLA/liposomal lidocaine group; MD 1.40 (95% CI 0.03 to 2.77; Analysis 20.4).

Facial grimacing score in term infants (Outcome 20.5)

One study reported on 213 term infants (Taddio 2011). There was no significant difference between the sucrose group and the sucrose + EMLA/liposomal lidocaine group for the facial grimacing score; MD -5.00 (95% CI -13.48 to 3.48; Analysis 20.5).

Observer-rated pain visual analogue scale (VAS) (cm) (Outcome 20.6)

One study reported on 213 term infants (Taddio 2011). There was no significant difference between the sucrose group and the sucrose + EMLA/liposomal lidocaine group for observer rated pain (VAS) (cm); MD -0.70 (95% CI -1.55 to 0.15; Analysis 20.6).

Secondary outcomes

Mean crying time (s) during all procedures (Outcome 20.7)

One study reported on 213 term infants (Taddio 2011), and another study reported on 76 preterm infants (Biran 2011). For the two studies combined (n = 289) there was no significant difference between the sucrose group and the sucrose + EMLA/liposomal lidocaine group for mean crying time (s); MD 1.83 (95% CI -10.42 to 14.09; Analysis 20.7); I^2 = 0% (no heterogeneity). In term infants (n = 213) there was no significant difference between the sucrose group and the sucrose + EMLA/liposomal lidocaine group for mean crying time (s); MD 0.00 (95% CI -13.79 to 13.79) (Taddio 2011). In preterm infants (n = 76) there was no significant difference between the sucrose group and the sucrose + EMLA/liposomal lidocaine group for mean crying time; 8.69 (95% CI -17.97 to 35.35) (Biran 2011).

Heart rate (beats/minute) in term infants (Outcome 20.8)

One study reported on 213 term infants (Taddio 2011). The heart rate (beats/minute) was significantly higher in the sucrose group than the sucrose + EMLA/liposomal lidocaine group; MD 5.00 (95% CI 0.39 to 9.61; Analysis 20.8).

Oxygen saturation (%) in term infants (Outcome 20.9) Analysis 20.9

One study reported on 213 term infants (Taddio 2011). There was no significant difference between the sucrose group and the sucrose +

EMLA/liposomal lidocaine group for oxygen saturation (%); MD 0.20 (95% CI -0.33 to 0.73; Analysis 20.9).

Sucrose (24%) versus liposomal lidocaine (Comparison 21)

Primary outcomes

Facial grimacing score (Outcome 21.1)

One study reported on 216 term infants (Taddio 2011). There was a significantly lower facial grimacing score in the sucrose group compared to the liposomal lidocaine group; MD -28.00 (95% CI -36.48 to -19.52; Analysis 21.1).

Observer-rated pain (VAS) (cm) (Outcome 21.2)

One study reported on 216 term infants (Taddio 2011). There was no significant difference in the observer-rated pain (VAS) (cm) in the sucrose group compared to the liposomal lidocaine group; MD -0.40 (95% CI -1.25 to 0.45; Analysis 21.2).

Cry duration (sec) (Outcome 21.3)

One study reported on 216 term infants (Taddio 2011). There was a significantly shorter cry duration (s) in the sucrose group compared to the liposomal lidocaine group; MD -39.00 (95% CI -52.43 to -25.57; Analysis 21.3).

Heart rate (beats/minute) (Outcome 21.4)

One study reported on 216 term infants (Taddio 2011). There was no significant difference in the heart rate (beats/minute) in the sucrose group compared to the liposomal lidocaine group; MD 3.00 (95% CI -1.95 to 7.95; Analysis 21.4).

Oxygen saturation (%) (Outcome 21.5) Analysis 21.5

One study reported on 216 term infants (Taddio 2011). There was no significant difference in the percentage oxygen (%) saturation in the sucrose group compared to the liposomal lidocaine group; MD 0.50 (95% CI -0.03 to 1.03; Analysis 21.5).

Results from five studies could not be included in RevMan-analyses, but are described in a narrative here. Abad 1996 reported shorter cry duration three minutes after venipuncture in the sucrose (24%) group compared to the sucrose (12%) group and the water group. In Acharya 2004 the duration of first cry was shorter in infants who received sucrose, as was total duration of crying. Mean change in heart rate from pre procedure to procedure and post procedure was lower in the infants who received sucrose. Changes in mean NFCS scores were significantly lower in the sucrose group than in the water group from pre procedure to the procedure phase and the post procedure phase. Carbajal 1999 reported lower DAN scores in the groups that received glucose, sucrose, pacifier, or sucrose + pacifier compared to water. There was a trend towards lower pain scores for infants receiving sucrose with a pacifier compared to a pacifier alone. In the Elserafy 2009 cross-over study every infant received each of six different regimens during a maximum stay of 15 days. Sucrose + pacifier resulted in the lowest pain (PIPP) scores. The sucrose groups had significantly lower crying times compared to the other groups. Gaspardo 2008 (listed under additional table Table 11) studied different phases of venipuncture on different days. All significant results favoured the sucrose group. On day 2 the percentage of neonates crying showed a significant difference between the sucrose and control groups in the antisepsis phase and puncture phases. On day 3, there was a significant difference between groups in the percentage of neonates crying in the dressing phase. On day 4, significant differences existed between groups at the puncture phase. A significant difference in the NFCS ≥ 3 was seen between sucrose and control groups on day 2 at the puncture phase, and on day 3 a significant difference was observed at the antisepsis phase. There was a significant difference in the percentage of neonates with active behavioural state (ABS) score ≥ 4 between sucrose and control groups on day 2 at the puncture phase, and on day 4 at the antisepsis phase.

Effectiveness of sucrose for arterial puncture

Sucrose (24%) versus no intervention in preterm infants (Comparison 22)

Secondary outcomes

Heart rate (beats/minute) after needle insertion (Outcome 22.1)

One study reported on 47 preterm infants (Milazzo 2011). There was no significant difference in the heart rate (beats/minute) between the sucrose group and the no intervention group after needle insertion; MD -1.90 (95% CI -11.73 to 7.93; Analysis 22.1).

Heart rate (beats/minute) one minute after procedure completed (Outcome 22.2)

One study reported on 47 preterm infants (Milazzo 2011). There was no significant difference in the heart rate (beats/minute) between the sucrose group and the no intervention group one minute after procedure completion; MD -2.40 (95% CI -10.56 to 5.76; Analysis 22.2).

Oxygen saturation in blood (%) after needle insertion (Outcome 22.3)

One study reported on 47 preterm infants (Milazzo 2011). There was no significant difference in the oxygen saturation after needle insertion between the sucrose group and the no intervention group; MD -1.00 (95% CI -4.65 to 2.65; Analysis 22.3).

Oxygen saturation in blood (%) one minute after procedure (Outcome 22.4)

One study reported on 47 preterm infants (Milazzo 2011). There was no significant difference in the oxygen saturation (%) one minute after the procedure between the sucrose group and the no intervention group; MD -2.90 (95% CI -5.95 to 0.15; Analysis 22.4).

Milazzo 2011 was the only study identified for arterial puncture.

Effectiveness of sucrose for subcutaneous injection

Two reports studied the effects of sucrose for subcutaneous injection (Allen 1996, Mucignat 2004). Neither of the studies reported the results in a way that permitted the use of data in RevMan-analyses. For details see Table 5.

In the Allen 1996 study two-week old infants who received either sterile water or sucrose solution cried significantly less than infants who received no intervention ($P < 0.005$). Mucignat 2004 found significant reductions in DAN and NFCS scores in the EMLA + NNS, sucrose + NNS, and sucrose + EMLA + pacifier groups.

Effectiveness of sucrose for pain associated with intramuscular injection (immunization or vitamin K) (term infants)

Sucrose (25%) versus water or no intervention (Comparison 23)

Primary outcomes

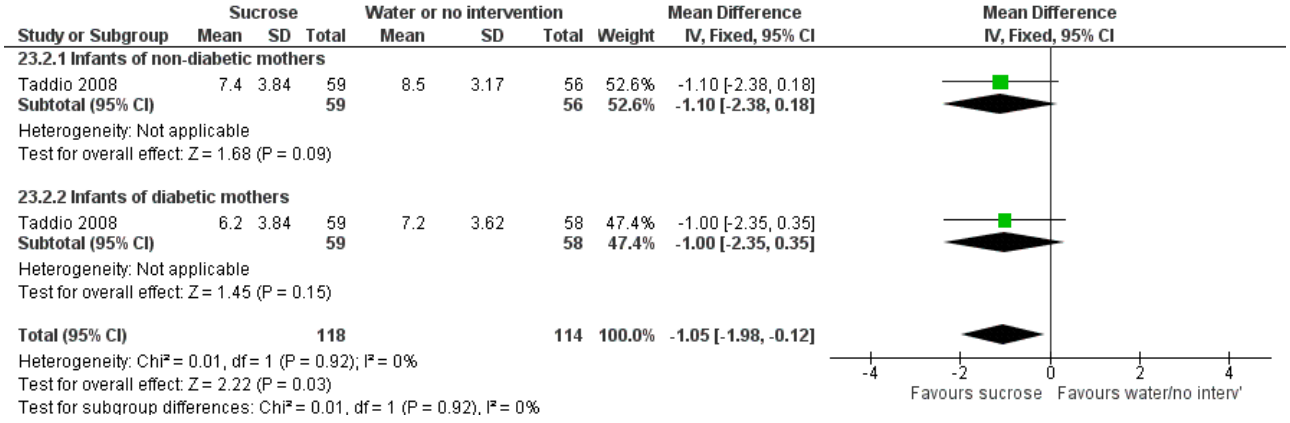
NIPS during one to two minutes after immunization (term infants) (Outcome 23.1)

One study reported on 60 term infants (Suhrabi 2014). There was a significant reduction in the NIPS score between one and two minutes after immunization in term infants in the sucrose group compared to the no intervention group; MD -2.30 (95% CI -2.93 to -1.67; Analysis 23.1).

PIPP during intramuscular injection (term infants) (Outcome 23.2)

One study reported on 232 term infants (115 infants were born to non-diabetic mothers and 117 were born to diabetic mothers) (Taddio 2008). The combined group (n = 232) showed a significantly lower PIPP score in the sucrose group compared with the water group; WMD -1.05 (95% CI -1.98 to -0.12; Analysis 23.2; Figure 7); I^2 = 0% (no heterogeneity). Among the infants born to non-diabetic mothers (n = 115) there was no significant difference between the group that received sucrose and the group that received water; MD -1.10 (95% CI -2.38 to 0.18). Among the infants born to diabetic mothers there was no significant difference between the group that received sucrose and the group that received water; MD -1.00 (95% CI -2.35 to 0.35).

Figure 7. Forest plot of comparison: 23 Intramuscular injection (term infants): Sucrose (20-25%) vs. water or no intervention, outcome: 23.2 PIPP during IM injection (term infants).



Secondary outcomes

Duration of cry (s) (Outcome 23.3)

One study reported on 110 infants (Liaw 2011). The duration of cry (s) was significantly shorter in the sucrose group than in the no intervention group; MD -163.83 (95% CI -192.58 to -135.08; Analysis 23.3).

Sucrose (25%) versus glucose (25%) (Comparison 24)

Primary outcomes

NIPS during one to two minutes after immunization (term infants) (Outcome 24.1)

One study reported on 60 infants (Suhrabi 2014). There was no significant difference in the NIPS score between one and two minutes after immunization in term infants in the sucrose group compared with the glucose group; MD -0.10 (95% CI -0.89 to 0.69; Analysis 24.1).

Sucrose (25%) versus sucrose (25%) + warmth (Comparison 25)

Secondary outcomes

Crying time (s) (Outcome 25.1)

One study reported on 29 term infants (Gray 2015). There was a significantly longer crying time (s) in the sucrose group than the sucrose + warmth group; MD 15.20 (95% CI 11.52 to 18.88; Analysis 25.1).

Grimacing time (s) (Outcome 25.2)

One study reported on 29 term infants (Gray 2015). There was a significantly longer grimacing time (s) in the sucrose group compared with the sucrose + warmth group; MD 16.20 (95% CI 12.35 to 20.05; Analysis 25.2).

One study could not be included in RevMan-analyses Gray 2012. For details see Table 6. This trial reported that warmer infants cried significantly less than infants exposed to sucrose taste or pacifier suckling after vaccination. Heart rate patterns reflected this analgesia. Core temperature did not differ between study groups.

Effectiveness of sucrose for bladder catheterization

Sucrose versus sterile water (Comparison 26)

Primary outcome

Change in DAN score (Outcome 26.1)

One study reported on 33 infants (Rogers 2006). There was significantly less change in the DAN score in the sucrose group than in the water group; MD -2.43 (95% CI -4.50 to -0.36; Analysis 26.1).

Secondary outcomes

Infants crying at maximal catheter insertion (Outcome 26.2)

One study reported on 33 infants (Rogers 2006). The number of infants crying at maximal catheter insertion was significantly lower in the sucrose group than in the sterile water group; RR 0.34 (95%

CI 0.14 to 0.82; Analysis 26.2); RD -0.51 (95% CI -0.81 to -0.22); NNTB = 2 (95% CI 1 to 5).

Rogers 2006 was the only study identified for bladder catheterization.

Effectiveness of sucrose for orogastric or nasogastric tube insertion

Sucrose (25%) versus distilled water (Comparison 27)

Primary outcomes

PIPP score intraprocedure (Outcome 27.1)

One study reported on 105 infants subjected to orogastric tube insertion (Pandey 2013). There was no significant difference in the PIPP score during the procedure; MD -0.30 (95% CI -1.33 to 0.73; Analysis 27.1).

PIPP score at 30 s postprocedure (Outcome 27.2)

One study reported on 105 infants (Pandey 2013). There was a significantly lower PIPP score in the sucrose group than the water group at 30 s postprocedure; MD -1.30 (95% CI -2.31 to -0.29; Analysis 27.2).

PIPP score one minute postprocedure (Outcome 27.3)

One study reported on 105 infants (Pandey 2013). There was no significant difference between groups in the PIPP score one minute postprocedure; MD -0.50 (95% CI -1.40 to 0.40; Analysis 27.3).

Data from two studies that assessed the pain associated with nasogastric tube insertion could not be used in RevMan-analyses (Kristoffersen 2011; McCullough 2008). For details see Table 8.

Kristoffersen 2011 found that a pacifier + 30% sucrose provided the most effective pain reduction (P value < 0.001 versus no treatment). The highest pain score was in sterile water group. McCullough 2008 reported that the sucrose group had a significant lower median NFCS score during NG tube insertion compared with the water group (1 (range 0 to 4) versus 3 (range 0 to 4), median difference 1 (95% CI 0 to 2); P = 0.004).

Effectiveness of sucrose for retinopathy of prematurity (ROP) examination

Sucrose (24%) by syringe + swaddle + pacifier versus water by syringe + swaddle + pacifier (Comparison 28)

Primary outcome

PIPP during the examination (Outcome 28.1)

One study reported on 32 infants (Grabska 2005). There was no significant difference in the PIPP score during the examination between the two groups; MD 0.00 (95% CI -2.08 to 2.08; Analysis 28.1).

Secondary outcomes

Crying time (%) (Outcome 28.2)

One study reported on 32 infants (Grabska 2005). There was no significant reduction in the percentage of crying time (%) between the comparison groups; MD -10.00 s (95% CI -32.91 to 12.91; Analysis 28.2).

Heart rate (beats/minute) (Outcome 28.3)

One study reported on 32 infants (Grabska 2005). There was no significant reduction in the heart rate (beats/minute) between the comparison groups; MD -6.00 (95% CI -19.33 to 7.33; Analysis 28.3).

Mean blood pressure (mmHg) (Outcome 28.4)

One study reported on 32 infants. (Grabska 2005) There was no significant difference in the mean blood pressure (mmHg) between the comparison groups; MD -7.00 (95% CI -18.48 to 4.48; Analysis 28.4).

Respiratory rate (breaths/minute) (Outcome 28.5)

One study reported on 32 infants (Grabska 2005). There was no significant reduction in the respiratory rate (breaths/minute) between the comparison groups; MD 2.00 (95% CI -5.07 to 9.07; Analysis 28.5).

Oxygen saturation (%) (Outcome 28.6)

One study reported on 32 infants (Grabska 2005). There was a significant difference in the percentage oxygen saturation (%) between the comparison groups with a lower oxygen saturation in the sucrose group; MD -3.00 (95% CI -5.86 to -0.14; Analysis 28.6) favouring the water group.

Sucrose (24%) + swaddled + held versus lying in the crib (Comparison 29)

Secondary outcomes

Total crying time (s) (Outcome 29.1)

One study reported on 30 infants (Rush 2005). There was no significant reduction in the total crying time (s) between the two groups; MD -33.90 (95% CI -76.22 to 8.42; Analysis 29.1).

Oxygen saturation (%) during examination (Outcome 29.2)

One study reported on 30 infants (Rush 2005). There was no significant difference in the oxygen saturation (%) between the two groups; MD -1.71% (95% CI -5.85 to 2.43; Analysis 29.2).

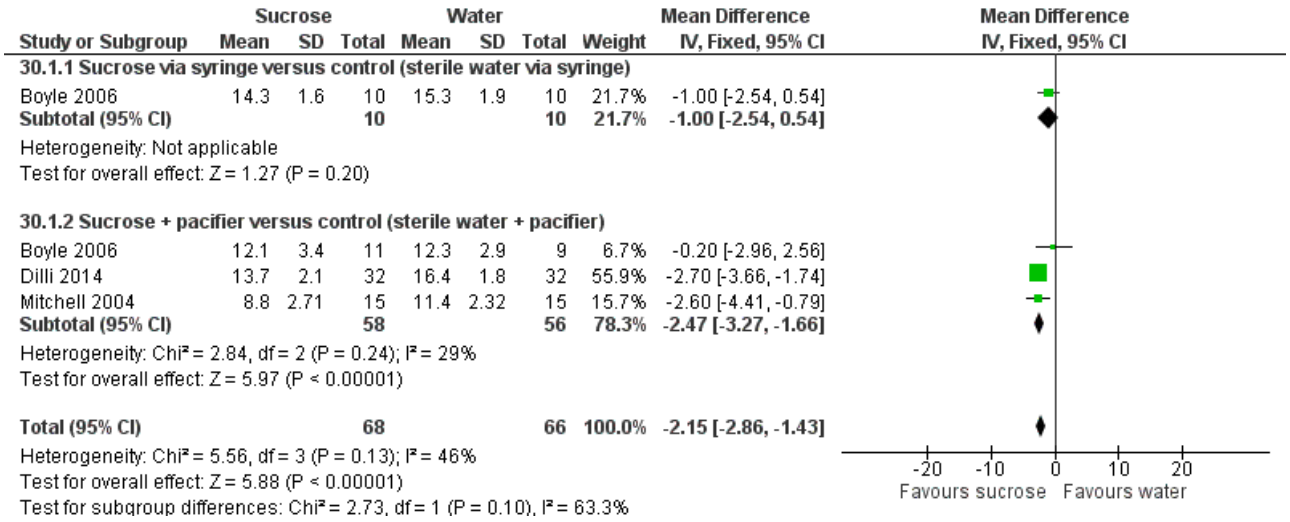
Sucrose (24% to 33%) (sucrose or sucrose + NNS) versus control (water or water + NNS) (Comparison 30)

Primary outcomes

PIPP score during eye examination (Outcome 30.1)

Three studies reported on 134 infants for this outcome (Boyle 2006; Dilli 2014; Mitchell 2004). The Boyle 2006 study contributed to two analyses for this outcome. In the first analysis (n = 20), which compared sucrose 33% versus sterile water via syringe, there was no significant difference between the groups MD -1.00 (95% CI -2.54 to 0.54). There was a significant reduction in the PIPP score in the combined group of sucrose with or without NNS; WMD -2.15 (95% CI -2.86 to -1.43; Analysis 30.1; Figure 8). There was low heterogeneity for this analysis (I^2 = 46%). Sucrose + pacifier was more effective than sterile water + pacifier; WMD -2.47 (95% CI -3.27 to -1.66; I^2 = 29% (low heterogeneity); 3 studies, 114 infants; Analysis 30.1; Figure 8).

Figure 8. Forest plot of comparison: 30 ROP examination: sucrose (24% to 33%) (sucrose or sucrose + NNS) versus control (water or water + NNS), outcome: 30.1 PIPP score during eye examination.



Secondary outcomes

Crying time (s) during eye examination (Outcome 30.2)

One study reported on 64 infants (Dilli 2014). There was a significant reduction in the crying time (s) in the sucrose group + NNS compared to the NNS group; -21.10 (95% CI -33.10 to -9.10; Analysis 30.2).

The results of two studies could not be used in RevMan-analyses (Gal 2005; O'Sullivan 2010). For details see Table 9. Gal 2005 reported that the PIPP scores at the eye examination were significantly lower in the group given sucrose (mean 8.3, SD 4.5) compared to the placebo group (mean 10.5, SD 4.0), P value 0.01); however, this effect was not sustained at one and five minutes post examination. O'Sullivan 2010 found a significantly lower N-PASS score in the sucrose group compared to the control group at speculum insertion (6.5 versus. 5.0; P value 0.002) and during the procedure (9.5 versus 7.5; P value 0.003). There were no significant differences between the sucrose group and the water group for episodes of desaturation, bradycardia, or adverse outcomes.

Effectiveness of sucrose for circumcision

Sucrose (50%) solution on a premature nipple, with a 2 x 2 cm sterile gauze pad inside the nipple moistened by the fluid versus no treatment (Comparison 31)

Secondary outcomes

Change from baseline in heart rate (beats/minute) (Outcome 31.1)

One study reported on 56 infants (Herschel 1998). There was no significant difference in the change from baseline in heart rate (beats/minute) between the sucrose and the no treatment groups; MD -9.70 (95% CI -19.82 to 0.42; Analysis 31.1).

Sucrose (24%) versus eutectic mixture of local anaesthetic (EMLA) (Comparison 32)

Primary outcomes

N-PASS score during circumcision (Outcome 32.1)

One study reported on 60 infants (Al Qahtani 2014). There was a significantly higher N-PASS score (indicating more pain) in the sucrose versus the EMLA group; MD 2.40 (95% CI 1.85 to 2.95; Analysis 32.1).

N-PASS score after 5 minutes (Outcome 32.2)

One study reported on 60 infants (Al Qahtani 2014). There was a significantly higher N-PASS score (indicating more pain) after 5 minutes in the sucrose versus the EMLA group; MD 1.40 (95% CI 0.74 to 2.06; Analysis 32.2).

Secondary outcomes:

Heart rate (beats/minute) during circumcision (Outcome 32.3)

One study reported on 60 infants (Al Qahtani 2014). There was a significantly higher heart rate (beats/minute) in the sucrose group than in the EMLA group; MD 6.00 (95% CI 0.19 to11.81; Analysis 32.3).

Repiratory rate (breaths/minute) during circumcision (Outcome 32.4)

One study reported on 60 infants (Al Qahtani 2014). There was no significant difference in respiratory rate (breaths/minute) between the sucrose group and the EMLA group; MD -1.90 (95% CI -4.00 to 0.20; Analysis 32.4).

Oxygen saturation (%) during circumcision (Outcome 35.5)

One study reported on 60 infants (Al Qahtani 2014). There was a significantly lower oxygen saturation (%) in the sucrose group compared to the EMLA group; MD -2.70 (95% CI -3.70 to -1.70; Analysis 32.5).

Sucrose (24%) versus EMLA + sucrose (24%) (Comparison 33)

Primary outcomes

N-PASS score during circumcision (outcome 33.1)

One study reported on 60 infants (Al Qahtani 2014). There was a significantly higher N-PASS score (indicating more pain) in the sucrose vs the EMLA group; MD 3.00 (95% CI 2.42 to 3.58; Analysis 33.1).

N-PASS score after five minutes (Outcome 33.2)

One study reported on 60 infants (Al Qahtani 2014). There was a significantly higher N-PASS score (indicating more pain) after five minutes in the sucrose group compared to the EMLA group; MD 1.20 (95% CI 0.49 to 1.91; Analysis 33.2).

Secondary outcomes

Heart rate (beats/minute) during circumcision (Outcome 33.3)

One study reported on 60 infants (Al Qahtani 2014). There was a significantly higher heart rate (beats/minute) in the sucrose group compared to the EMLA group; MD 12.00 (95% CI 06.62 to 17.38; Analysis 33.3).

Repiratory rate (breaths/minute) during circumcision (Outcome 33.4) Analysis 33.4

One study reported on 60 infants (Al Qahtani 2014). There was no significant difference in respiratory rate (cycles/minute) between the sucrose group and the EMLA group; MD 0.60 cycles/minute (95% CI -1.77 to 2.97; Analysis 33.4).

Oxygen saturation (%) during circumcision (Outcome 33.5)

One study reported on 60 infants (Al Qahtani 2014). There was a significantly lower percentage of oxygen saturation in the sucrose group compared to the EMLA group; MD -3.40 (95% CI -4.39 to -2.41; Analysis 33.5).

Sucrose (50%) on a premature nipple, with a 2 x 2 cm sterile gauze pad inside the nipple moistened by the fluid versus dorsal penile nerve block (DPNB) (Comparison 34)

Secondary outcomes

Change in heart rate (beats/minute) from baseline (Outcome 34.1)

One study reported on 79 infants (Herschel 1998). There was a significantly greater change in heart (rate beats/minute) in the sucrose group than in the DPNB group (favours the DPNB group); MD 17.40 (95% CI 11.16 to 23.64; Analysis 34.1).

Pacifier dipped in 24% sucrose + DNPB versus pacifier dipped in water + DNPB (Comparison 35)

Primary outcomes

Mean Behavioural Distress Scale scores during circumcision (Outcome 35.1)

One study reported on 40 infants (Stang 1997). There was a significantly lower Behavioural Distress Scale score (indicating less pain) in the sucrose + DPNB group compared with the water + DPNB group; MD -0.67 (-1.08 to -0.26; Analysis 35.1).

Secondary outcomes

Mean plasma cortisol levels n mol/dL (Outcome 35.2)

One study reported on 40 infants (Stang 1997). There was no significant difference in the mean plasma cortisol levels (n mol/dL) in the sucrose + DPNB group compared with the water + DPNB group; MD 68.90 (-53.93 to 191.73; Analysis 35.2).

Data from one study could not be used in RevMan-analyses (Kaufman 2002); for details see Table 10. In this study the overall, mean crying time was significantly decreased in infants treated with sucrose compared to infants treated with water (P value 0.0001). Infants in the Gomco clamp + sucrose group spent significantly less time grimacing (P value 0.0001) compared to the Gomco clamp +water group.

Effectiveness of sucrose for stress during echocardiography

Sucrose (24%) versus no medication/placebo (Comparison 36)

Primary outcomes

PIPP score (Outcome 36.1) Analysis 36.1

One study reported on 104 infants (Potana 2015). The PIPP score in the sucrose group was significantly lower compared with the group that got no intervention or placebo; MD -2.15 (95% CI -3.30 to -1.00; Analysis 36.1).

This was the only study we identified that used sucrose during echocardiography.

Effectiveness of sucrose for potentially painful procedures for seven days after enrolment

Sucrose (24%) versus water (Comparison 37)

Primary outcomes

Motor development and vigor (MDV) domain of the NAPI tool at 40 weeks PMA (Outcome 37.1)

One study reported on 93 infants who had been given sucrose or water for every potentially painful procedure for seven days after enrolment in the study (Banga 2015). There was no significant difference in the MDV domain of the NAPI tool between the sucrose and the water groups; MD -1.83 (95% CI -8.59 to 4.93; Analysis 37.1).

Alertness and orientation (AO) domain of the NAPI tool at 40 weeks PMA (Outcome 37.2)

One study reported on 93 infants who had been given sucrose or water for every potentially painful procedure for seven days after enrolment in the study (Banga 2015). There was no significant difference in the AO domain of the NAPI tool between the sucrose and the water groups; MD 3.09 (95% CI -6.49 to 12.67; Analysis 37.2).

The results from the Taddio 2008 study are included under the heel lance and intramuscular injection sections.

The results of the Gaspardo 2008 and Johnston 2002 studies could not be included in RevMan-analyses. See Table 11 for details. In the Gaspardo 2008 study the neonates were evaluated during blood collection each morning. The assessment was divided into five phases: baseline, antisepsis, puncture, dressing, and recovery. The neonates' facial activity (NFCS), behavioural state, and heart rate were evaluated. The data analysis used cut-off scores for painful and distressed responses. Significantly fewer neonates in

the sucrose group than the control group exhibited facial actions that signalled pain during the puncture phase and the antisepsis phase. Significantly fewer neonates in the sucrose group cried during the antisepsis phase, the puncture phase, and the dressing phase. There was no statistical difference between groups for physiological response. The efficacy of sucrose was maintained for pain relief in preterm neonates with no side effects.

Johnston 2002 reported that on the basis of analysis of covariance with PMA at birth and the number of invasive procedures as covariates, there were no group differences (between sucrose and water) for any of the secondary outcomes of Neuro-Biological Risk Scores (NBRS) at two weeks; postnatal age (P = 0.426) or at discharge (P = 0.965). In the sucrose group only, higher number of doses of sucrose predicted lower scores on motor development and vigor, and alertness and orientation at 36 weeks', lower motor development and vigor at 40 weeks', and higher NBRS at 2 weeks' postnatal age. Higher number of invasive procedures was predictive of higher NBRS both times in the water group.

No significant differences found between the sucrose and water groups for Neurobehavioral Assessment of the Preterm Infant (NAPI).

Effects of sucrose on long-term neurodevelopmental outcomes

We identified no studies that reported on long-term neurodevelopmental outcomes (assessed by a standardized and validated assessment tool, a child developmental specialist, or both) at 18 to 24 months or at any later age in childhood.

Adverse effects

In the previous update (Stevens 2013), 16 studies evaluated adverse effects of sucrose compared to placebo (Ramenghi 1996a; Carbajal 1999; Stevens 1999; Guala 2001; Gibbins 2002; Acharya 2004; Gal 2005; Grabska 2005; Stevens 2005a; Rogers 2006; Codipietro 2008; McCullough 2008; Taddio 2008; O'Sullivan 2010; Biran 2011; Taddio 2011). Six of these studies observed minor side effects in infants (Gibbins 2002; Grabska 2005; Stevens 2005a; McCullough 2008; Taddio 2008; O'Sullivan 2010). Gibbins 2002 described minor adverse effects in six infants, none of which occurred in the sucrose + pacifier group. One neonate who received water with pacifier choked when the water was administered but stabilized within 10 s. Three infants randomised to the sucrose group and two infants randomised to the water + pacifier groups experienced oxygen desaturation when the study intervention (sucrose or water) was administered. Each neonate recovered spontaneously with no medical intervention 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 with regard to adverse effects; the investigators observed brief apnoea or self-limiting bradycardia in some infants, but none required clinical intervention. Stevens 2005a 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 in the sucrose group experienced oxygen desaturation or bradycardia.

In this current 2016 update we included 20 newly identified studies and evaluated adverse effects in 13 of them. Dilli 2014 did not notice any choking episode or vomiting in any of the study infants. Gray 2012 observed no adverse events or side effects from the brief exposure to a heat source or change in the infants' ambient temperature, and did not mention any adverse effects related to sucrose. The Tutag Lehr 2015 study assessed a number of adverse events including gagging, choking, and vomiting and noted that only one infant in the sucrose group experienced a mild episode of 'spitting up'. Thakkar 2016 reported on a total of five episodes of adverse events in all four groups. One neonate each in the sucrose group, the NNS group and the sucrose + NNS group desaturated, while two neonates desaturated in the no intervention group. Leng 2015; Marin Gabriel 2013, Milazzo 2011, Pandey 2013, and Simonse 2012 noted no adverse events in any infant. Potana 2015 reported no episode of hyperglycaemia, necrotizing enterocolitis, or feed intolerance after sucrose administration. Abbasoglu 2015 stated that no child developed any clinically visible changes on the skin, and that no side effects were observed in their comparison of laser acupuncture with oral sucrose. Banga 2015 reported that there was no significant difference in the frequency of adverse effects (fall in heart rate or oxygen saturation) across the two groups (sucrose and water).

Seven newly included studies did not report on adverse effects (Al Qahtani 2014; Asmerom 2013; Cignacco 2012; Leng 2013; Liaw 2013; Suhrabi 2014; Gray 2015). In the current review, it would appear that researchers are being much more vigilant in observing and reporting adverse events. The proportion of minor adverse events remains very low with no major adverse events reported.

DISCUSSION

Summary of main results

Below we report for each painful procedure the results from the 'Summary of findings' tables. In those tables we included only results from the most validated pain assessment scales (DAN, NFCS, NIPS, N-PASS, domains of NAPI, PIPP, PIPP-R and Total Bernese Pain Scale for Neonates) and provide GRADE assessments for the quality of the evidence. In brief paragraphs we summarize the results from outcomes that could be included in analyses in RevMan and provide short comments on the results from studies that could not be included in the RevMan-analyses.

As shown in Figure 1, results from only 39 of the 74 included studies could be included in RevMan-analyses, and the remaining studies are included in narrative qualitative syntheses.

The largest study included in any analysis was Leng 2015, which reported on 342 infants, and the two meta analyses with the largest numbers of participants included 278 infants (3 studies) (Figure 4) and 232 infants (2 groups of infants from one study) (Figure 7).

Heel lance

Heel lance was the most common painful procedure and was included in 38 studies. There was moderate quality evidence that sucrose (20% to 30%) compared with water significantly reduced NIPS scores during heel lance (indicating less pain with sucrose). No significant differences were noted in PIPP scores at 30 s or 60 s after heel lance, or during heel lance. There was no difference in DAN scores 30 s after heel lance (Summary of findings for the main comparison).

Sucrose (24%) was a more effective analgesic than breastfeeding (low quality evidence) (Summary of findings 2).

For sucrose (24%) + NNS compared with water + NNS, or pacifier dipped in sucrose compared with pacifier dipped in water there was high quality evidence that PIPP scores at 30 s (Figure 4) and 60 s (Figure 5) were significantly reduced (indicating less pain) and that the NFCS score was non-significantly reduced (Summary of findings 3).

No significant difference was found between sucrose (24%) + NNS + NIDCAP compared with breast milk (by breastfeeding or by syringe) (low quality evidence) (Summary of findings 4; Summary of findings 5).

There was low quality evidence that sucrose was more effective than laser acupuncture in reducing heel lance-associated pain (Summary of findings 6).

There was moderate quality evidence that sucrose (24%) + NNS or sucrose (24%) + swaddling or sucrose (24%) + NNS + swaddling were more effective than sucrose alone to reduce pain associated with heel lance (Summary of findings 7; Summary of findings 8; Summary of findings 9).

Many studies that could not be included in RevMan-analyses, or reported on outcomes other than validated pain assessment scores supported these findings (see summary in the results section).

Sucrose in concentrations of 20% to 30% reduces composite and multidimensional behavioural pain scores, as well as individual behavioural and physiological pain indicators associated with heel lance. Other pain reducing interventions such as NNS and swaddling in association with sucrose provides further pain relief.

Venipuncture

Venipuncture was the painful intervention in nine studies. In addition one study assessed both heel lance and venipuncture (Ogawa 2005), but results were reported separately for the two interventions and we present the results under the two different headings (heel lance and venipuncture).

There was moderate quality evidence that sucrose (12% to 12.5%) versus water had no significant effect on the NIPS score (Summary of findings 12).

There was high quality evidence that the PIPP score was significantly lower in the sucrose group (24% to 30%) than the sterile water group during venipuncture (Summary of findings 13).

Comparison of sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/liposomal lidocaine cream on the skin showed that the DAN scores during venipuncture and the recovery period were significantly higher (indicating more pain) in the sucrose group (moderate quality evidence). There were no significant differences in the PIPP scores at the same time points (Summary of findings 14).

The studies that could not be included in RevMan-analyses or reported outcomes using other non-validated pain assessment scores supported these findings (see summary in the results section) including lower DAN scores, NFCS scores and shorter durations of crying.

Sucrose (24% to 30%) reduces composite and multidimensional behavioural pain scores and cry variables associated with venipuncture.

Arterial puncture

Arterial puncture was the painful intervention in one trial that reported on 47 infants (Milazzo 2011). There was no significant difference between the groups in the physiological outcomes measured; heart rate (beats/minute) or oxygen saturation after needle insertion, or one minute after the procedure. This one small study might have lacked power to ascertain a true difference.

Currently there is lack of evidence for or against the use of sucrose for arterial puncture.

Effectiveness of sucrose for pain during subcutaneous injections

Subcutaneous injection was studied in two trials (Allen 1996; Mucignat 2004). The results could not be included in RevMan-analyses. Allen 1996 found that sucrose decreased the percentage of time that two-week-old infants spent crying. Mucignat 2004 found that crying time was significantly lower in the sucrose + EMLA + pacifier group. There was a significant reduction in DAN and NFCS scores in the EMLA + NNS, sucrose + NNS, and sucrose + EMLA + pacifier groups compared to NNS alone.

There is not sufficient evidence to judge whether sucrose is beneficial or not for reducing pain associated with subcutaneous injections.

Effectiveness of sucrose for pain associated with intramuscular injection (immunization against hepatitis B or injection of vitamin K)

Intramuscular injection was studied in four trials (Gray 2012; Gray 2015; Liaw 2011; Suhrabi 2014).

There was low quality evidence that sucrose (20% to 25%) versus water or no intervention significantly lowers NIPS scores during the one to two minutes after immunization (Summary of findings 15).

There was high quality evidence that PIPP scores during intramuscular injections were significantly lower (indicating less pain) in the sucrose group than the water group for infants born to both non-diabetic and diabetic mothers (Summary of findings 15).

For sucrose (25%) versus glucose (25%) there was no significant difference in the NIPS score one to two minutes after immunization (low quality evidence) (Summary of findings 16).

Data from one trial could not be entered in RevMan-analyses. Gray 2012 showed that providing warmth during immunization for hepatitis B decreased crying and grimacing as much as sucrose or a pacifier did, and in a similar study, Gray 2015, showed that infants exposed to sucrose + warmth cried significantly less and grimaced less compared to the infants who received sucrose only.

There is some high quality evidence that sucrose reduces pain associated with intramuscular injections. Adding a body warmer to administration of sucrose may provide further pain relief. Further research is recommended for that co-intervention.

Bladder catheterization

The painful intervention of bladder catheterization was reported in one study. There was a significantly smaller change in the DAN score in the sucrose group than the water group, and the number of infants crying at maximal catheter insertion was significantly lower in the sucrose group (moderate quality evidence) (Summary of findings 17).

Further research is required to assess the effectiveness of sucrose to reduce pain during bladder catheterization.

Orogastric or nasogastric tube insertion

Orogastric or nasogastric tube insertion was studied in three trials.

Although the sample size was small, there was high quality evidence from one trial of a significantly lower PIPP score 30 s after the procedure in the sucrose (24%) group than in the water group, but no difference in PIPP score during the procedure or one minute after the procedure (Summary of findings 18).

Two studies of nasogastric tube insertion could not be included in RevMan-analyses (Kristoffersen 2011; McCullough 2008). Kristoffersen 2011 found that pacifier + 30% sucrose provided the most effective pain reduction (P value < 0.001 versus no treatment). The highest pain score was for infants in the sterile water group. McCullough 2008 reported that the sucrose group had a significant lower median NFCS score during NG tube insertion compared with the water group.

Further research is required to assess the effectiveness of sucrose to reduce pain during orogastric or nasogastric tube insertion.

ROP examination

ROP examinations were studied in seven trials.

There was no significant difference in the PIPP score between groups for sucrose (24%) by syringe + swaddled + pacifier compared with water by syringe + swaddled + pacifier (low quality evidence) (Summary of findings 19).

The pooling of three studies revealed a significant reduction in the PIPP score for the sucrose group when sucrose (24% to 33%; sucrose ± NNS) was compared with water (water ± NNS). There was a significant reduction in the crying time in the sucrose + NNS group (moderate quality evidence) (Summary of findings 20) (Figure 8).

There is limited evidence that sucrose may confer some pain relief when combined with other pain reducing interventions. Further research on sucrose in combination with other pain reducing interventions is required.

Circumcision

Circumcision was studied in four trials.

For sucrose (24%) versus EMLA there was a significantly higher N-PASS score (indicating more pain for sucrose) during circumcision and 5 minutes after circumcision. The heart rate (beats/minute) was significantly higher and the oxygen saturation was significantly lower in the sucrose group during circumcision (low quality evidence) (Summary of findings 21).

For sucrose (24%) versus EMLA + sucrose (24%) there were significantly higher N-PASS scores in the sucrose only group during circumcision and five minutes after circumcision (low quality evidence) (Summary of findings 22). During circumcision the heart rate (beats/minute) was significantly higher and the oxygen saturation significantly lower in the sucrose only group.

Secondary outcomes

When a pacifier dipped in 24% sucrose + DPNB was compared with a pacifier dipped in water + DNPB there was a significantly lower behavioural score in the group that received sucrose. There was no significant difference in the mean plasma cortisol levels between the groups.

When sucrose (50%) solution on a premature nipple, with a 2 x 2 cm gauze pad inside the nipple moistened by fluid was compared with DPNB there was an increase (indicating more pain) in heart rate (beats/minute) in the sucrose group.

Based on low quality of evidence the use of sucrose alone is insufficient for pain relief from circumcision.

Echocardiography

The stress/pain associated with echocardiography examination was reported in one low-quality evidence study. The mean PIPP score was significantly lower in the sucrose group compared with the no intervention group (Summary of findings 23).

The use of sucrose during echocardiography deserves further study.

Potentially painful procedures for seven days after study entry

One high-quality evidence study reported on two domains of the NAPI score; motor development and vigor (MDV) and alertness and orientation (AO). The potentially painful procedures included; venipuncture, heel lance, peripheral venous catheterization, orogastric or nasogastric tube insertion, intramuscular injection, suprapubic bladder tap, ROP examination and removal of adhesive tapes.

There were no significant differences in these two domains between the sucrose (24%) and water groups at 40 weeks PMA.

Long-term neurodevelopmental outcomes

Long-term neurodevelopmental outcomes were not assessed in any of the included studies.

Adverse effects

Adverse effects were evaluated in 29 studies and in most no side effects were reported. Minor, rare and untoward events included 'spitting up', oxygen desaturation, bradycardia, choking, and brief apnoea. Most of these occurred in both the sucrose and the control groups and were self-resolved. One study that measured blood glucose levels did not find any significant difference between the sucrose and the water group (Taddio 2008).

Adverse effects following the short term use of sucrose are currently not a concern.

Overall completeness and applicability of evidence

Although sucrose has been studied in 74 trials that included 7049 infants, the large variation in painful procedures, dose of sucrose

(concentration and volume), co-interventions in the comparison groups, assessment tools used and differences in the population (term or preterm infants) resulted in a large number of RevMan-analyses that include one or few trials. There were few infants included for each comparison and each outcome, which weakens our ability to draw firm conclusions. However, if the effectiveness of sucrose for a specific intervention were measured by a variety of instruments, and the results showed a similar reduction, this would strengthen the results and the conclusions.

To date, the best studied use of sucrose is for heel lance, venipuncture and intramuscular injections and for these interventions sucrose appears to offer pain relief.

Sucrose does not seem to relieve the pain associated circumcision adequately and there is no strong indication that further studies are indicated. For pain/stress associate with arterial puncture, subcutaneous injection, bladder catheterization, orogastric or nasogastric tube insertion, ROP examination and echocardiography examination further research is warranted. For these procedures, we would recommend that if trials are done, a rescue dose should be available for infants in obvious distress, where the sucrose alone does not seem to be effective in preventing moderate to severe pain.

Quality of the evidence

The quality of the evidence varied from low to high and for each of the painful interventions and comparisons the quality of the evidence is reported in separate 'Summary of findings' tables (Summary of findings for the main comparison to Summary of findings 24). We excluded quasi-randomised trials and trials reported in abstract form only. We could include only a few studies for most comparisons and outcomes. For most outcomes we included the results of a single study only, and so tests for heterogeneity were not applicable. The main reasons for our inability to include study results in RevMan-analyses were that the results were not presented as means and SDs or were presented in graph form only.

By early February 2016, we had identified 74 RCTs that tested the effectiveness of sucrose in reducing stress or pain associated with common, potentially painful procedures in neonates. These studies reported on 7049 neonates. Most studies had a small sample size: the sample sizes ranged from 15 to 671 infants, and 48 studies reported on fewer than 100 infants.

Potential biases in the review process

We are not aware of any biases in the review process. Two authors (AO, JY) selected the trials from the literature searches and there was complete agreement. One author (AO) abstracted data and filled in pre designed forms for 'Risk of bias' assessments and data abstraction, transformed 95% CIs to SDs and two authors (SH, AS) checked the data abstraction and transformation of data. Any discrepancies were discussed and resolved by consensus. Three authors (BS, JY, AO) are coauthors of some included trials. For these trials two authors (SH, AS) did the data abstraction and RoB assessments. One author (BS) is the developer of the PIPP and PIPP-R measure.

Agreements and disagreements with other studies or reviews

In our previous versions of this review (Stevens 2001; Stevens 2004; Stevens 2010; Stevens 2013), we reported inconsistency in effective sucrose dosage, although we identified studies in which the dose ranged from 0.012 g to 0.12 g. Johnston 1997 and Stevens 1999 identified that very small volumes of 24% sucrose (estimated at 0.01 g to 0.02 g) significantly reduced pain. However, the meta-analyses in Stevens 1997a showed 0.18 g sucrose was ineffective in reducing crying and did not differ from the control solution (water). Doses of 0.24 g or more were more effective; there was some additional benefit of administering 0.48 g to 0.50 g sucrose, but effectiveness did not increase when sucrose doses greater than 0.50 g were administered. In this updated review, a significant reduction in PIPP scores was demonstrated with sucrose doses between 0.012 g to 0.12 g (0.05 mL 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 one- to two-point reduction in the PIPP score. Shah 2004 reported that clinicians and researchers consider a 20% reduction in pain to be the minimal clinically important difference, although other researchers suggest a 10% reduction may suffice (Powell 2001). Lemyre 2006 used a three-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 in infants, given their inability to self-report their pain and the level of improvement that could make significant differences either in treatment strategy or the affective component of pain (i.e. how bad pain makes you feel).

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 1999 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 last about four minutes; therefore, the analgesic effect may wear off if procedures are prolonged. The infant's postnatal age may influence the effectiveness of sucrose (Taddio 2008).

Adverse effects following the short-term use of sucrose are currently not a concern. We reported the possible adverse effects in the Effects of interventions. Adverse effects would be more likely to occur when multiple doses of are used. Stevens 2005a found no significant differences in incidence rates for necrotizing enterocolitis between infants who received repeated doses of sucrose over 28 days of life compared to control groups. Johnston 2002 studied 107 preterm infants of less than 31 weeks' postmenstrual age where 1 mL of 24% sucrose or sterile water was administered 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 (AO), motor development and vigour (MDV) on the NAPI scale at 36 weeks, and lower (MDV) 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. Further analysis revealed that 10 or fewer doses of sucrose over a 24-hour period were unlikely to be related to poorer neurodevelopmental scores (Johnston 2007). Banga 2015 reported that 93 infants randomised to either repeated doses of sucrose or water for painful procedures for seven consecutive days showed no significant differences in MDV or AO scales of the NAPI scale or adverse events. Stevens 2005a reported no statistically significant differences between sucrose + pacifier, water + pacifier, or the standard care group on neurobiological risk status outcomes

Generally, infants in this review were healthy term and preterm neonates and very few were under 27 weeks' PMA 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 in this review between crying 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 alone may not be 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 as an outcome. If the reported outcomes reflect the investigators' concept 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. 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 ventilated infants who often do not cry following painful procedures, any cry characteristic would be an inappropriate outcome. Attempts at cry or a silent cry in ventilated infants may be reasonable to consider. A multivariate approach looking at multiple indicators or a composite pain score may be a more comprehensive approach.

The majority of researchers studied heel lance as the painful procedure. However, they provided little detail about this procedure (e.g. type of lancet used, number of attempts, number of squeezes, duration of the procedure). Therefore, it was impossible to determine if the painful stimuli (or painful procedures) were comparable in intensity, duration or frequency between studies. Similarly, details about other procedures (e.g. subcutaneous injection, ROP examination, bladder catheterization and circumcision) and co-interventions such as skin-to-skin (kangaroo care), breastfeeding or comforting strategies (e.g. containment, bundling, tucking or positioning) that may enhance the effect of sucrose would be desirable. The length of observation and return to baseline parameters (e.g. heart rate) of infants following procedures was not reported frequently.

The delivery of sucrose (by syringe, dropper or dipping pacifier) varied among studies. 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 heart rate and metabolic rate, causes infants to self-soothe and elevates the pain threshold. NNS has not been shown to affect cortisol response, vagal tone or oxygen saturation of blood (DiPietro 1994; Gunnar 1992). The calming effects are not sustained following cessation of the NNS alone. This is in contrast to NNS + sucrose administration, where the effects persist for several minutes beyond the cessation of contact. Results from this 2016 update indicate that the use of sucrose with NNS appears to have 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. Infants who received sucrose or glucose before immunisation had moderately reduced incidence and duration of crying. Pillai Riddell 2015 in a systematic review of non-pharmacological interventions found that the most established evidence for managing procedural pain in preterm and term neonates and older infants was for NNS, swaddling, facilitated tucking, and rocking/holding. Bueno 2013 in a systematic review demonstrate that 20% to 30% glucose reduces pain scores and crying during single heel lances and venipunctures and can be recommended as an alternative to sucrose for procedural pain reduction in healthy term and preterm neonates.

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 and those given sterile water; however, the PIPP scores were significantly lower in the infants given sucrose. The authors suggested that oral sucrose does not affect activity in the neonatal brain or spinal cord and many not be an effective analgesic. The small sample size, moderate attrition rates and methods used to measure and analyse EEG and EMG recordings limit the generalization of these findings.

This evidence has been integrated into evidence-based sucrose consensus protocols and guidelines (Dunbar 2006; Lefrak 2006; Sharek 2006). However, in an evaluation of infant pain guidelines (Lee 2014), recommendations were not sufficient, clear or consistent to guide clinical practice. Furthermore, 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).

We still have significant gaps in our understanding of how pain is processed in the developing brain and optimal assessment and treatment approaches (Fitzgerald 2015). Methodological and pain treatment issues need to be addressed, and new evidence generated in light of the existing evidence. A comprehensive approach to validating various measures to evaluate pain in neonates and a standardized approach to measuring outcomes is critical, especially when evaluating pain-relieving interventions that form the basis for clinical decision making.

There is a need to assess the long-term effects of sucrose administration to neonates. Long-term neurodevelopmental outcomes should be assessed by a standardized 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

We included 74 studies in this review, 38 of which examined pain associated with heel lancing. The results from these studies provide further evidence to support the efficacy of sucrose for reducing pain from single and, to a lesser extent, repeated heel lances. The included studies reported on the use of sucrose for venipuncture, intramuscular injection, arterial puncture, subcutaneous injections, nasogastric or orogastric tube insertion, bladder catheterization, retinopathy of prematurity (ROP) examinations, circumcision, and echocardiography exam in hospitalized neonates. However, except for venipuncture and intramuscular injection for which there was high-quality evidence for the use of sucrose, further studies of these other painful procedures are required due to conflicting evidence on the effect of sucrose in reducing pain. Sucrose reduces procedural pain with minimal to no reported adverse effects. Small doses of 24% sucrose (0.01 g to 0.02 g) are efficacious in preterm infants, while larger doses (0.24 g to 0.50 g) reduce the proportion of time term infants spend crying.There is some moderate-quality evidence that sucrose in combination with other non-pharmacological interventions such as non-nutritive sucking is more effective than sucrose alone.

Implications for research

The optimal dose of sucrose for pain relief in term and preterm infants has not yet been established. Researchers should consider establishing more precise and tailored doses based on the infant (e.g. postmenstrual age, severity of illness) and context in which it is to be used. Optimal sucrose doses could be assessed further using sensitivity/meta-regression techniques. More research is needed to address 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 such as ROP exam and circumcision. Strategies need to be initiated to increase understanding of the underlying mechanisms of pain and sucrose for 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 should be cautious when utilising existing evidence to answer questions on efficacy in other painful procedures that have been minimally addressed to date (e.g. lumbar punctures, peripherally inserted central catheter insertions, endotracheal intubation, chest tube insertions). Strengthened study design and methods with particular attention to the adequacy of sample size, acknowledgment of conceptualisation of pain, use of validated pain measures to determine outcomes, and context are required. Use of sucrose in neonates that are of extremely low birthweight, unstable, ventilated, or a combination of these factors needs to be addressed.

Replication of existing studies of high methodological quality, using a valid pain assessment measure and standard set of validated outcomes would allow for further combination of results in meta-analyses. Researchers should report on means and standard deviations (SD) in addition to medians and ranges, if the data are not normally distributed, to allow for the use of meta-analytic techniques. If researchers choose to present data in graph form, they should include the means and SDs in the text (or additional appendices). Preferably the amount of sucrose administered should be reported in g/kg body weight. Future research should focus on long-term effects of repeated sucrose administration with other behavioural and pharmacological interventions in sick and very-preterm neonates. Results should be presented for individual indicators and any composite pain scores constructed from these indicators. The relationship between pain measures and individual physiological and cognitive indicators of nociceptive brain activity should be explored further.

Additional research is urgently needed regarding the understanding of the neurophysiological basis of pain, as well as addressing the pressing clinical need by 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.

Effective knowledge translation strategies are required to translate research evidence on sucrose into practice effectively (Stevens 2014b). For healthcare providers these strategies could include the use of reminders, interactive education and educational outreach and regular audit and feedback sessions.

ACKNOWLEDGEMENTS

We would like to acknowledge the assistance of:

- Ms Moira Lynch for conducting an extensive updated search of MEDLINE, EMBASE and CENTRAL in April 2001 and Ms Tamsin Adams-Webber for her assistance with our 2004 and 2009 updates;
- Ms Yolanda Brosseau, who conducted the searches in February 2016;
- Dr Celeste Johnston, Dr Aage Knudsen, Dr Sharyn Gibbins and Dr Denise Harrison for providing unpublished data;
- Dr Denise Harrison, Jasmine Lamba, Alison Dickson and Sobia Khan for their assistance with quality assessment and data extraction of the studies for the 2013 review update; Ms. Grace Y Lee, who made major contributions to the 2013 update of the review;
- Mr David Corpman for translating the paper by Leng 2013 from Chinese to English;
- Dr Reza Assadi, Mashhad University of Medical Sciences, Mashhad, Iran, for translating one article from Persian to English (Aziznejad 2013);
- Dr Danilyn Angeles for providing additional analyses for the Asmerom 2013 study;
- Dr Shreshtha Banga provided us with additional information regarding the study Banga 2015.

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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, RCT Painful intervention: venipuncture Study location: Department of Pediatrics, University Hospital, La Laguna, Tenerife, Spain Study period: not stated
Participants	28 (29 to 36 weeks' GA) healthy infants, PNA age 1 to 26 days
Interventions	2 mL 12% sucrose via syringe (n = 8) 2 min prior to venipuncture 2 mL 24% sucrose via syringe (n = 8) 2 min prior to venipuncture 2 mL spring water via syringe (n = 12) 2 min prior to venipuncture
Outcomes	Oxygen saturation, respiratory rate, HR (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 SDs for the 3 physiological outcomes and as medians and IQRs for cry duration (in graph form only). Data were collected at 3 time points; just before the administration of the solution, just after administration of the solution and 5 min after venipuncture Adverse effects were not evaluated Data for oxygen saturation, respiratory rate and HR were reported at 5 min after venipuncture and were not included in meta-analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed in advance using numbers taken from a randomisation table

Abad 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Interventions blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed blinded to interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomised infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Abbasoglu 2015

Methods	RCT Painful intervention: heel lance Study location: Baskent University Hospital, Ankara, Turkey Study period: not stated
Participants	42 term newborns undergoing heel lance between postnatal days 3 and 8 as part of routine neonatal inpatient screening for phenylketonuria and hypothyroidism
Interventions	0.5 mL 24% sucrose solution given orally via syringe 2 min before heel lancing Laser acupuncture – 0.3 J energy applied to the Yintang point using a Laser PREMIO-30 unit for 30 s
Outcomes	NIPS, cry duration (s)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	High risk	Blank envelope containing a card indicated 1 of 2 groups. Not stated whether the envelopes were opaque, sealed and sequentially numbered
Blinding (performance bias and detection bias) All outcomes	High risk	The nurse was blinded to group allocation before the envelope was opened, but not afterwards
Blinding of outcome assessment (detection bias)	Low risk	Assessments were made from video tapes (NIPS and cry duration)

Abbasoglu 2015 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all infants enrolled
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Acharya 2004

Methods	Double-blind, randomized, controlled, cross-over trial Painful intervention: venipuncture Study location: NICU at Leicester Royal Infirmary, UK Study period: not stated.
Participants	39 healthy preterm neonates (mean 30.5 (SD 2.3) weeks' GA), mean PNA 27.2 (SD 24.4) days
Interventions	2 mL 25% (0.5 g) sucrose (n = 39) via syringe over 2 min into infant's mouth before 2 routine venipunctures 2 mL water (n = 39) via syringe over 2 min into infant's mouth before 2 routine venipunctures
Outcomes	Rise in HR, oxygen saturation, duration of first cry, total duration of crying, NFCS at the 3 phases of the venipuncture
Notes	Data were reported using means, SDs over the 3 phases of the venipuncture. Data could not be abstracted for the 2 groups prior to cross-over. 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 by a hospital pharmacist
Allocation concealment (selection bias)	Low risk	Allocation controlled by a hospital pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Interventions blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessments were done blinded to intervention group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Inconsistent number of infants reported in Methods section (n = 39) versus discussion section (n = 28)

Acharya 2004 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Al Qahtani 2014

Methods	RCT Painful intervention: circumcision Study location: Day Care Surgery Department of Maternity and Children Hospital, Dammam City, Kingdom of Saudi Arabia Study period: January 2011 and April 2011
Participants	90 full-term newborn males who underwent circumcision GA of 38 weeks or beyond, 5 min Apgar score of 8 or higher, PNA of 12 h or older and birthweight > 2500 g, and to be free from jaundice, anomalies of the penis, and analgesia or sedation in the previous 48 h
Interventions	2 mL oral sucrose (24% w/v) given through a dropper onto the tongue 2 min before the procedure (n = 30) EMLA cream: applied to the shaft of the penis with an occlusive dressing 1 h before the procedure (n = 30) Combination of EMLA cream + oral sucrose (n = 30): 1 g EMLA cream applied to the shaft of the penis with an occlusive dressing 1 h before the procedure + 2 mL oral sucrose (24% w/v) given through a dropper onto the tongue 2 min before the procedure
Outcomes	N-PASS used to assess the severity of pain and neonatal response to pain, 5 min before, during and 5 min after the circumcision for all newborns. The scale measures both physiologic responses (HR, respiratory rate, blood pressure and oxygen saturation) and behavioural responses (crying irritability, behaviour state, facial expression and extremities tone) to pain
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Low risk	The sample was divided randomly into 3 groups. The envelope was opened to classify the neonate randomly to 1 of the groups in order to carry out the appropriate action
Blinding (performance bias and detection bias) All outcomes	High risk	Staff were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Video imaging of the neonate 5 min before, during and until 10 min after the procedure showed the newborn reaction to pain and recorded the duration of crying. The videotapes were reviewed by an individual who was unaware of the infant's treatment group, however, since the sucrose was applied 2 min be-

Al Qahtani 2014 *(Continued)*

		fore the procedure, it was probably possible to tell from the tapes which babies received sucrose
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data reported for all 90 infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Allen 1996

Methods	RCT Painful intervention: immunization injection Study location: a university hospital ambulatory paediatric clinic, Omaha, USA Study period: not stated
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 12% sucrose (n = 16) 2 mL sterile water (n = 15) No treatment (n = 19)
Outcomes	Mean cry duration and percentage time crying during and 3 min after subcutaneous injection
Notes	Data for percentage time crying were presented in graphical form only

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	Low risk	Low risk for sucrose and water; high risk for no intervention group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	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 the analysis

Allen 1996 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Altun-Köroğlu 2010

Methods	Double-blind placebo-controlled study Painful intervention: heel lance Study location: Marmara University Hospital, Istanbul, Turkey Study period: not stated
Participants	75 full-term infants undergoing heel lance
Interventions	3 mL hind milk (n = 25) 3 mL 12.5% sucrose solution (n = 25) 3 mL distilled water (n = 25)
Outcomes	NFCS, crying time, duration of crying, HR. Results reported as medians and IQRs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	High risk	Sealed envelopes were used, however, there was no information regarding whether envelopes were opaque and sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	The test solution was prepared in a covered syringe
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The researchers were blind to the groups and utilized only the video recordings for scoring
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Sample sizes were not provided in Tables 2 and 3. We assumed the numbers from Table 1. Demographic features of the study groups were correct with 25 infants in each group
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Asmerom 2013

Methods	Randomized, double-blind, controlled trial Painful intervention: heel lance Study location: Loma Linda University Children's Hospital NICU, Loma Linda, California, USA Study period: July 2009 to February 2012
Participants	131 preterm infants ≤ 36.5 weeks' PMA who weighed ≥ 800 g, had a central catheter in place, and required a heel lance
Interventions	Sucrose 24% with a pacifier (n = 44): 2 mL for neonates > 2 kg; 1.5 mL for neonates 1.5 kg-2 kg; and 0.5 mL for neonates < 1.5 kg Placebo with pacifier (n = 45) 42 infants received no heel lance no sucrose or placebo
Outcomes	PIPP after 2 min, plasma hypoxanthine, uric acid, xanthine, allantoin HR, oxygen saturation. We received unpublished data for means and SDs from Dr Angeles
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed by a research pharmacist, who used a permuted block randomization table generated by the study statistician
Allocation concealment (selection bias)	Low risk	The study drug was prepared immediately before the experimental procedure by the research pharmacist and labelled as 'study drug' to ensure blinding
Blinding (performance bias and detection bias) All outcomes	Low risk	Neonates randomized to the sucrose group received a single dose of 24% sucrose in the following volumes: 2 mL for neonates >2 kg, 1.5 mL for neonates 1.5-2 kg, and 0.5 mL for neonates that were <1.5 kg. Neonates randomized to the placebo group received an equal volume of sterile water to the anterior portion of the tongue along with a pacifier
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The neonate's face was videotaped by trained research staff to record facial action at 0 min, during the heel lance and up to 30 s post heel lance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported on all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Banga 2015

Methods	RCT

Banga 2015 *(Continued)*

	Painful intervention: each potentially painful procedure for a period of 7 days after enrolment Study location: a tertiary–level teaching hospital in North India Study period: April 2010 to April 2011
Participants	106 newborns, between completed 32 weeks and 37 weeks PMA were randomized to 2 groups sucrose (n = 53) and water (n = 53). 93 infants were available for analysis (47 in the sucrose group and 46 in the water group)
Interventions	Sterile solution 24% sucrose (0.5 mL in 1mL syringe) for every potentially painful procedure during the first 7 days after enrolment Double-distilled water (0.5 mL in 1mL syringe) for every potentially painful procedure during the first 7 days after enrolment
Outcomes	Primary outcome: score of motor development and vigor (MDV) and alertness and orientation (AO) domains of NAPI scale performed at 40 weeks PMA In addition, the highest HR and lowest SpO_2 obtained during the procedure were recorded until 30 s after the painful stimulus, for newborns in both groups (not reported)
Notes	We wrote to the authors and Dr Banga provided us with this information: The potentially painful procedures included: venipuncture, heel lance, peripheral venous catheterization, OG or NG tube insertion, intramuscular injection, suprapubic bladder tap, retinopathy of prematurity examination, removal of adhesive tapes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization using computer-generated random sequences was used with a static block size of 6 each
Allocation concealment (selection bias)	Low risk	Allocation sequence was generated and maintained confidentially by the co-investigator from department of Pharmacology. At the time of enrolment, the group allocation was telephonically conveyed to the research candidate, to ensure allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical-looking packets carrying sucrose and the double-distilled water, prepared and serially labelled according to confidential randomization code by pharmacy, were available at neonatal units. The primary care team members were responsible for administrating the intervention/control to the enrolled newborn according to the allocated serially numbered packet, unaware of the randomization
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The participants, the research candidate, and the primary care team members assessing the painful response were blinded to the group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 infants lost to follow-up in the sucrose group, intervention discontinued in 1 and 2 died. 5 infants lost to follow1up in the water group and 2 died
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Basnet 2010

Methods	RCT Painful intervention: venipuncture Study location: Neonatal ward of Tribhuvan University Teaching Hospital, Kathmandu, Nepal Study period: February to August 2006
Participants	50 term infants aged between 12 h to 8 days Mean post-natal age: 59.92 h no treatment group; 68.76 h sucrose group
Interventions	No treatment group (n = 25) Sucrose group (n = 25): received 2 ml of 30% sucrose orally 2 minutes before venipuncture
Outcomes	DAN score, duration of cry, number of infants crying
Notes	Data for DAN scores were reported as median and IQRs. Duration of cry was reported as mean and SD and was included in meta-analyses

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)	High risk	Authors did not report whether the opaque, sealed envelopes used to allocate participants were sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Personnel blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	One rating scale (DAN) listed in methods section and is reported in results table. The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Biran 2011

Methods	RCT Painful intervention: venipuncture

Biran 2011 *(Continued)*

	Study location: NICUs at Hôpital Armand Trousseau, Paris, France and Centre Hospitalier de Meaux, Meaux, France Study period: July to September 2007
Participants	76 preterm infants, mean (SD) PMA: sucrose group (n = 37): 32.6 (2.33) weeks; sucrose + EMLA group: (n = 39): 32.3 (2.01) weeks
Interventions	Sucrose group: 0.5 mL 30% sucrose solution orally and placebo cream Sucrose + EMLA group: 0.5 mL 30% sucrose solution orally and EMLA cream on the skin
Outcomes	DAN scale, PIPP score
Notes	Discussed adverse effects observed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization 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 and personnel blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes not reported for 4 infants because of problems with video recording
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Blass 1997

Methods	RCT Painful intervention: heel lance Study location: Tompkins Community Hospital, Ithaca, New York, USA Study period: not stated
Participants	72 newborn infants (PNA 22 h to 40 h)
Interventions	2 mL 12% sucrose (n = 8) 2 mL protein solution (Provimin) (n = 8)

Blass 1997 *(Continued)*

	2 mL lactose (n = 8) 2 mL dilute fat (coconut and soy oil blend) (n = 8) 2 mL concentrated fat (n = 8) 2 mL fat and lactose solution (n = 8) 2 mL Ross Special Formula (RSF - artificial milk) (n = 8) 2 mL Similac (artificial milk) (n = 8) Solutions were given via syringe over a 2-min period
Outcomes	Crying time (percentage of procedure time spent crying, percentage of time spent crying during 3-min recovery period, number of infants that cried 20% or more during each recovery minute)
Notes	Sucrose vs. water, Similac vs. water and RSF vs. water were compared using Mann-Whitney U test. Most results were presented in graph form and means were reported in the text and could not be combined in meta-analyses 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)	Unclear 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 However, Similac group was high risk as its appearance differed from sucrose or water
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Sucrose and water solutions blinded. However, Similac group was high risk as its appearance differed from sucrose or water
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Unclear risk	Several test solutions were gifts from Ross Laboratories

Blass 1999

Methods	RCT Painful intervention: heel lance Study location: Boston Medical Center, Boston, MA, USA Study period: not stated.
Participants	40 term newborn infants, 34 h to 55 h old
Interventions	All interventions given for 2 min prior to heel lance:

Blass 1999 *(Continued)*

	2 mL 12% sucrose over 2 min via syringe (n = 10) 2 mL 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)
Outcomes	Percentage of time spent crying during 3 min after heel lance, percentage of time spent grimacing, change in mean HR
Notes	Data were reported in graph forms only Results of ANOVA reported as P values only (we have contacted the authors to request additional information, but have received none) 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 alone groups blinded; pacifier + water, and pacifier + sucrose groups were blinded (although assessors could see pacifiers, they did not know which solution was being tested)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Sucrose and water alone groups blinded; pacifier + water, and pacifier + sucrose groups were blinded (although assessors could see pacifiers, they did not know which solution was being tested)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Boyle 2006

Methods	RCT Painful intervention: screening for ROP Study location: Neonatal Unit, Royal Infirmary of Edinburgh, Edinburgh, Scotland, UK and Neonatal Unit, Birmingham Heartlands Hospital, Birmingham, UK Study period: not stated
Participants	40 preterm infants < 32 weeks' PMA Sterile water group: mean PMA 27 weeks; mean PNA 45 days Sucrose group: mean PMA 29 weeks; mean PNA 43 days Water + pacifier group: mean PMA 30 weeks; mean PNA 41 days Sucrose + pacifier group: mean PMA 29 weeks; mean PNA 42 days

Boyle 2006 *(Continued)*

Interventions	2 min before start of eye examination: 1 mL sterile water (n = 10) 1 mL sucrose 33% (n = 10) 1 mL sterile water + pacifier (n = 9) 1 mL sucrose 33% + pacifier (n = 11) Water or sucrose was given by mouth using a syringe
Outcomes	PIPP during eye examination
Notes	Data were presented in graph form and reported as means and SDs 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)	High risk	Sealed opaque envelopes. Did not state if the envelopes were sealed and sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water alone groups blinded; pacifier + water, and pacifier + sucrose groups were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Sucrose and water alone groups blinded; pacifier + water, and pacifier + sucrose groups were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Bucher 1995

Methods	Randomized, double-blind, placebo-controlled, cross-over trial Painful intervention: heel lance Study location: Neonatal Clinic, Department of Obstetrics and Gynaecology, University Hospital, Zurich, Switzerland Study period: not stated
Participants	16 preterm infants (27 to 34 weeks' PMA), PNA approximately 42 days
Interventions	2 mL 50% sucrose via syringe 2 min before heel lance 2 mL distilled water via syringe 2 min before heel lance (n = 16, cross-over design)

Bucher 1995 *(Continued)*

	Each infant was assessed twice receiving2ml of sucrose 50%or 2 ml of distilled water in random order immediately before heel lance
Outcomes	Increase in HR (beats/min); recovery time for HR (s); recovery time for respirations (s); crying (percentage of total intervention); recovery time until crying stopped (s); oxygen saturation (maximum increase in kPa; maximum decrease in kPa; and difference between baseline and 10 min after end of intervention in kPa), and cerebral blood volume
Notes	Results were presented in graph form without mean values and SDs, in tables with medians with IQRs, or both. Used Wilcoxon signed rank test. Data for sucrose and placebo groups prior to cross-over were not presented 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 assessment (detection bias) All outcomes	Low risk	Sucrose and water solutions blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Carbajal 1999

Methods	RCT Painful intervention: venipuncture Study location: maternity ward, Poissy Hospital, Poissy, France Study period: April to end of June 1997
Participants	150 term newborn infants, 3 to 4 days old
Interventions	2 min prior to venipuncture the allocated solution was adminstered for 30 seconds by a sterile syringe into the infant's mouth No treatment (n = 25) 2 mL sterile water (n = 25)

Carbajal 1999 *(Continued)*

	2 mL 30% glucose (n = 25) 2 mL 30% sucrose (n = 25) Pacifier alone (n = 25) 2 mL 30% sucrose followed by pacifier (n = 25)
Outcomes	DAN scale during venipuncture, reported as median and IQR
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 and sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Low risk for sucrose and water solutions High risk for pacifier groups
Blinding of outcome assessment (detection bias) All outcomes	High risk	Low risk for sucrose and water solutions High risk for pacifier groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Cignacco 2012

Methods	RCT Painful intervention: repeated heel lances Study location: 3 NICUs in Switzerland Study period: 12 January to 31 December 2009
Participants	71 preterm infants between 24 and 32 weeks PMA
Interventions	Sucrose group (n = 24): sucrose 20% (0.2 mL/kg), administered orally ~2 min before the heel lance. If the infant seemed to be in pain during the heel lance phase, up to 2 additional doses of sucrose were administered and noted in the study chart Sucrose + facilitated tucking (FT) (n = 23): combination of sucrose and facilitated tucking; the FT was started at the beginning of the baseline phase and sucrose was given 2 min before the heel lance

Cignacco 2012 *(Continued)*

	FT (n = 24): FT was started at the beginning of the baseline phase, and the infant was 'tucked' through all 3 phases
Outcomes	BPSN: data collection occurred: at baseline (before any manipulation); at heel lance (skin preparation, heel stick, and haemostasis after blood was drawn); and during recovery (3 min after the heel lance) The BPSN contains 9 items: 3 are physiological (HR, respiratory rate, and oxygen saturation) and 6 are behavioural (grimacing, body movements, crying, skin colour, sleeping patterns, consolation)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization by using SPSS, version 16
Allocation concealment (selection bias)	Low risk	For each site, group assignments were sealed in opaque, consecutively numbered envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	When parents consented to participation, the envelope was opened by a study nurse
Blinding of outcome assessment (detection bias) All outcomes	High risk	The intervention was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all 71 randomized infants
Selective reporting (reporting bias)	Low risk	The trial was registered as: NCT00758511 In the registry it said that 25% sucrose would be used. In the paper it said that 20% sucrose was used. We did not see any other deviations from the protocol
Other bias	Low risk	Appears free of other bias

Codipietro 2008

Methods	RCT Painful intervention: heel lance Study location: Neonatal Unit of Agnelli Hospital, Pinerolo, Turin, Italy Study period: January to April 2007
Participants	51 term infants: mean PMA 39.3 weeks (SD 1.2) in breastfeeding group; 50 term infants: mean PMA 39.4 weeks (SD 1.1) in sucrose group
Interventions	1 mL 25% sucrose (n = 50) Breastfeeding (n = 51)

Codipietro 2008 *(Continued)*

Outcomes	PIPP during blood sampling, 2 min after heel lance, HR increase from baseline at 30 s following commencement of procedure, oxygen saturation decrease, duration of first cry, percentage crying time in first 2 min and during blood sampling Data reported as median and full range
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
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only assistants listening to voice recordings of cry for PIPP scoring were blind to intervention. High risk for PIPP-R outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported on all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Dilli 2014

Methods	RCT Painful intervention: screening for ROP Study location: Dr Sami Ulus Maternity and Children Training and Research Hospital, Ankara, Turkey Study period: July 2011 to June 2012
Participants	64 infants undergoing eye examination for ROP. The groups had similar PMA (28.5 ± 2.8 weeks), mean birthweight (1304 ± 466 g) or corrected PMA (35.4 ± 3.7 weeks) at examination
Interventions	All infants received topical anaesthetic (proxymetacaine, Alcaine) drop 0.5%: ALCON CANADA Inc, Mississauga, Canada) applied 30 s before the eye examination. In addition: Sucrose group (n= 32): received 0.5 mL/kg 24% sucrose with a pacifier Control group (n = 32): received 0.5 mL/kg sterile water with a pacifier
Outcomes	Mean PIPP score during examination

Dilli 2014 *(Continued)*

	Secondary outcome measurements were frequency of tachycardia (> 180 beats/min), bradycardia (< 100 beats/min), desaturations (< 85% for > 10 s) and crying time
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Low risk	Syringes of either 24% sucrose (A) or sterile water (B) were provided by the pharmacy in sealed envelopes. Both of the solutions were colourless
Blinding (performance bias and detection bias) All outcomes	Low risk	The parents, the nurse, the ophthalmologist and investigators were blinded to the group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All the infants were video-recorded until completion of the eye examination. Primary outcome measurement was PIPP score which was performed by the same investigator who had web-based training
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all 64 infants
Selective reporting (reporting bias)	Low risk	Clinical Trials.gov Identifier: NCT01811979. There did not seem to be any deviations from the protocol
Other bias	Low risk	Appears free of other bias

Elserafy 2009

Methods	Cross-over RCT Painful intervention: venipuncture Study location: NICU at King Faisal Specialist Hospital, Jeddah, Saudi Arabia Study period: January 2005 to May 2007
Participants	36 infants: median (range): 32 weeks' PMA (27 to 46), mean (SD) GA: 32.4 (2.0) - 2 different mean PMAs reported in the article
Interventions	0.5 mL sterile water with pacifier 0.5 mL sterile water without pacifier 0.5 mL 24% sucrose with pacifier 0.5 mL 24% sucrose without pacifier Pacifier alone Control group (the authors do not state what this grooup received - we assume no intervention)
Outcomes	Duration of cry, PIPP, HR, respiratory rate, glucose check

Elserafy 2009 *(Continued)*

Notes	All infants received all of the 6 interventions and so we could not use the results in meta-analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
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)	High risk	Consecutively numbered envelopes, but report did not specify whether they were opaque or sealed
Blinding (performance bias and detection bias) All outcomes	Low risk	Personnel were blinded to sucrose and water solutions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Gal 2005

Methods	Randomized, double-blind, placebo-controlled, cross-over study Painful intervention: screening for ROP Study location: Department of Neonatology, Women's Hospital, Greensboro, North Carolina, USA Study period: January 2003 to June 2004
Participants	23 preterm infants mean PMA 26.4 weeks (range 24 to 29), PNA 28 to 93 days
Interventions	Mydriatic eye drops (phenylephrine HCl 1%, cyclopentolate HCl 0.2%) and local anaesthetic eye drops (proxymetacaine HCl 0.5%: 2 drops) were given to both groups prior to examination. In addition infants received: Sucrose group: 2 mL 24% sucrose via syringe (n = 23) Water group: 2 mL sterile water via syringe (n = 23)
Outcomes	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 SDs after cross-over. Results for the 2 groups prior to cross-over were not available Results of paired t-tests were reported as P values Adverse events reported, but no adverse events experienced

Gal 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment allocation was made in groups of 6 based on the results from a dice roll
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 assessment (detection bias) All outcomes	Low risk	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 of the paper
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
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	Randomized, double-blind, controlled trial Painful intervention: venipuncture, arterial puncture, heel lance, intravenous cannulation, endotracheal tube introduction, endotracheal tube suctioning, gavage insertion for feeding, removal of electrode leads and tape Study location: NICU of the Hospital of Clinics, School of Medicine, University of São Paulo at Ribeirão Preto, Preto, Brasil Study period: April 2003 and September 2005
Participants	33 preterm infants, median PMA 30 weeks
Interventions	On day 1, no treatment was given to any neonate in order to collect baseline data. On days 2 to 4 solutions (sucrose or water) were administered to neonates before every painful procedure (listed above): 0.5 mL/kg 25% sucrose before every minor painful procedure listed above (n = 17) 0.5 mL/kg sterile water before every minor painful procedure listed above (n = 16)
Outcomes	Incidence of cry (percentage of neonates crying), HR (percentage of neonates with HR ≥ 160 beats/min), NFCS (percentage of neonates with score ≥ 3), Activated Behavioural State (percentage of neonates with score ≥ 4)
Notes	Pain was assessed over 4 days during morning blood collection (heel lance)

Gaspardo 2008 *(Continued)*

	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 were reported. NFCS results were reported in graph form only Adverse events were assessed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization sequence
Allocation concealment (selection bias)	Low risk	Solutions prepared by pharmacist labelled '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	Staff blinded to sucrose and water solutions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/ 44 enrolled infants were discharged from the NICU while the data collection was in progress and 33 infants completed the study
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Gibbins 2002

Methods	RCT Painful intervention: heel lance Study location: a University-affiliated metropolitan Level III NICU, Toronto, Ontario, Canada Study period: 16-month period during 1998-1999
Participants	190 preterm and term infants, mean PMA 33.7 weeks, under 7 days' PNA
Interventions	2 min prior to heel lance: Sucrose + NNS group (N = 64): 0.5 mL 24% sucrose via syringe to the anterior surface of the tongue followed by pacifier Sucrose group (N = 62): 0.5 mL 24% sucrose without pacifier Water + NNS group (N = 64): 0.5 mL sterile water with pacifier
Outcomes	PIPP at 30 s and 60 s after heel lance
Notes	1-way ANOVA to evaluate mean pain scores

Gibbins 2002 *(Continued)*

	Results were reported as means and SDs Adverse effects were evaluated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated using a centralized randomization 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	Staff were blinded to sucrose and water solutions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Facial coders were not informed about the purpose of the study, phases of the heel lance, or group allocation for the 2 pacifier groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 neonates were lost to follow-up due to equipment failure
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other biases

Gormally 2001

Methods	RCT, factorial design Painful intervention: heel lance Study location: Lakeshore General Hospital, Montreal, Quebec, Canada Study period: not stated
Participants	94 normally developing newborns, mean PMA 39.4 weeks on 2nd or 3rd day of life 9 infants did not complete the study for the following reasons: early discharge, nurse or testing room unavailability to obtain heel lance, infant removed from study prior to start date, technical difficulties
Interventions	No holding + sterile water given by pipette (n = 21) No holding + 0.25 mL 24% sucrose solution (0.06 g) given by pipette (n = 22) Holding + sterile water given by pipette (n= 20) Holding + 0.25 mL 24% sucrose solution (0.06 g) given by pipette (n = 22) All solutions given 3 times at 30-s intervals
Outcomes	Percentage of time crying, pain concatenation scores for facial activity, mean HR, mean vagal tone index, measurements prior to intervention and at 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 in numbers, only in graph form Adverse effects were not evaluated

Gormally 2001 *(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	Low risk	Sucrose and water solutions blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Facial coders were blind to solution assignment only but not to holding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for all infants who completed the study
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Grabska 2005

Methods	Prospective, randomized, blinded, placebo-controlled study Painful intervention: screening for ROP Study location: NICUs at Conneticut Children's Medical Center and John Dempsey Hospital, USA Study period: not stated
Participants	32 preterm infants with birthweight < 1.5 kg or PMA < 28 weeks PMA (mean ± standard deviation) 28 ± 1.6 weeks, PNA (mean ± standard deviation) 50.8 ± 20.3 days
Interventions	Sterile water (n = 16) 24% sucrose (n = 16): dose was adjusted according to weight: 0.5 mL (0.12 g) for infants < 1 kg; 1.0 mL (0.24 g) for infants 1 kg-1.5 kg; 1.5 mL (0.36 g) for infants > 1.5 kg-2 kg; 2.0 mL (0.48 g) for infants > 2 kg
Outcomes	HR, respiratory rate and oxygen saturation at baseline, post mydriatic, post study drug, during eye examination, post eye examination PIPP at baseline, during eye examination, post eye examination Crying time during eye examination Blood pressure at baseline, post mydriatic, 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

Grabska 2005 *(Continued)*

	Adverse events were evaluated and included choking, and transient oxygen desaturation

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	Pharmacy provided solutions in sealed envelopes after randomization, 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
Blinding of outcome assessment (detection bias) All outcomes	Low risk	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 randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Gray 2012

Methods	RCT Painful intervention: vaccination (hepatitis B) Study location: University of Chicago Medicalm Center, Chicago, Illinois, USA Study period: June to July 2007
Participants	47 healthy full-term infants undergoing vaccination
Interventions	Sucrose group (n = 15): 1.0 mL 25% sucrose solution administered via syringe Warmth group (n = 14): 100% radiant warmth from Ohmeda warmer on the manual setting Pacifier group (n = 15): hospital-issued pacifier held lightly to their mouths 3 infants were subsequently excluded from data analysis (1 in the sucrose group and 2 in the warmth group)
Outcomes	Cumulative crying time, mean HR, mean respiratory sinus arrhythmia, cumulative distribution of grimace time
Notes	All outcomes were provided in graph form only and could not be used in meta-analyses

Risk of bias

Gray 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	High risk	Infants were randomly assigned using a sealed envelope system into 1 of 3 groups: warmth (n = 14), sucrose (n = 15), pacifier (n = 15). Did not state whether the envelopes were sequentially numbered or not
Blinding (performance bias and detection bias) All outcomes	High risk	Infants in the warmth group had their clothing removed except for the diaper and were placed under an Ohmeda-Ohio 3000 Infant Warmer System. Infants in the other 2 study groups (sucrose and pacifier) remained in their bassinets (cots) clothed in a shirt, diaper, and hat
Blinding of outcome assessment (detection bias) All outcomes	High risk	The infant's face was videotaped for offline coding of grimace and cry. The research assistants could probably tell to which group the infant belonged
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 47 enrolled infants, 3 infants were subsequently excluded from data analysis due to technical problems with HR recording (1 in the sucrose group and 2 in the warmth group)
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Gray 2015

Methods	RCT Painful intervention: vaccination (hepatitis B) Study location: University of Chicago Hospital, Chicago, Illinois, USA Study period: July to August 2008
Participants	29 healthy, full-term newborns undergoing vaccination Exclusion criteria included preterm birth (< 37 weeks' completed PMA), birthweight < 2 kg, any Apgar score < 6, congenital abnormalities, medical complications, or drug exposure. Infants with previous oxygen administration, ventilatory support, or NICU admission were excluded
Interventions	Sucrose group (n = 15): 1.0 mL 24 % sucrose 2 min before vaccination Sucrose + warmth group (n = 14): 1.0 mL 24% sucrose 2 min before vaccination + radiant warmth from an infant warmer before the vaccination Infants in the sucrose + warmth group were placed under an Ohmeda Ohio Infant Warmer (Model No. 3000; GE Healthcare, Fairfield, CT), and their clothing was removed, except for a diaper (nappy)
Outcomes	Duration of cry and grimace (s), HR variability and HR
Notes	Duration of cry and grimace were provided as means and SDs and in graph form. Respiratory sinus arrhythmia and HR reported in graph form Both groups received sucrose

Gray 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "We randomly assigned each infant in the study to sucrose alone or sucrose plus warmer groups by using a sealed envelope randomisation system"
Allocation concealment (selection bias)	High risk	No information about whether the envelopes were opaque and sequentially numbered
Blinding (performance bias and detection bias) All outcomes	High risk	The study could not be blinded to warmth vs. no warmth
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Video tapes were analyzed by assessors blinded to group assignment – probably, but could the warmer be seen?
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported on all infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it. We could not find a Trils registration number
Other bias	Low risk	Appears free of other bias

Greenberg 2002

Methods	RCT Painful intervention: heel lance Study location: a moderate sized hospital in Southern California, USA Study period: not stated
Participants	84 term newborns, approximately 17 h 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 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 SDs. Means and SEs were provided for "time crying by group in seconds" Adverse effects were not evaluated

Risk of bias

Bias	Authors' judgement	Support for judgement

Greenberg 2002 *(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	High risk	Use of pacifier precluded blinding. No blinding between pacifier groups either, as one was moistened with water and one dipped in sugar packet
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome measurement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement indicating how many infants were recruited and how many dropped out
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Guala 2001

Methods	RCT Painful intervention: heel lance Study location: Hospital of Vigevano, Italy Study period: not stated
Participants	140 term (38 to 41 weeks' PMA)
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	HR before, during and 3 min after heel lance
Notes	ANOVA to evaluate HR across groups at each phase of the heel lance. Means and SDs 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

Guala 2001 *(Continued)*

Allocation concealment (selection bias)	High risk	Allocated by sealed opaque envelopes. Did not state if the envelopes were sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Staff were blinded to sucrose and water solutions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 infants were allocated to each group and results for all infants were presented
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Haouari 1995

Methods	Randomized, double-blind, placebo-controlled trial Painful intervention: heel lance Study location: Leeds General Infirmary, Leeds, UK Study period: 6 months (dates not provided)
Participants	60 term (37 to 42 weeks' PMA) infants, 1 to 6 days of age
Interventions	2 mL 12.5% sucrose 2 min prior to heel lance (n = 15) 2 mL 25% sucrose 2 min prior to heel lance (n = 15) 2 mL 50% sucrose 2 min prior to heel lance (n = 15) 2 mL sterile water 2 min prior to heel lance (n = 15) All solutions were given by syringe on the tongue over < 1 min
Outcomes	Total time (s) crying over 3 min following heel lance, time of first cry (s) following heel lance, percentage change in 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 IQRs. Changes in HR were expressed in means and SDs 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	Preprepared solutions in coded bottles

Haouari 1995 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions administered blinded to staff
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Harrison 2003

Methods	Randomized, blinded, controlled trial Painful intervention: heel lance Study location: Royal Children's Hospital, University of Melboourne, Victoria, Australia Study period: May 2000 to July 2001
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 hospitalized infants Mean (SD) PMA of placebo group: 36.7 weeks (3.3) Mean (SD) PMA of treatment group: 36.8 weeks (3.7)
Interventions	1 mL water 2 min prior to heel lance (n = 46) 1 mL 25% sucrose 2 min prior to heel lance (n = 53) For infants weighing ≤ 1500 g the dose was reduced to 0.5 mL
Outcomes	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 HR and oxygen 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

Harrison 2003 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomization 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 assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	NNS 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	RCT Painful intervention: circumcision Study location: General Care Nursery of the University of Chicago Hospitals, Chicago, Ill, USA Study period: not stated
Participants	119 full-term male neonates undergoing circumcision, PMA ≥ 38 weeks, PNA ≥ 12 h
Interventions	No treatment (n = 40) DPNB (0.8 mL 1% lidocaine) (n = 40) Pacifier dipped in and packed with gauze soaked in 50% sucrose (n = 39)
Outcomes	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 were reported as mean and SD. Mean HRs 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**

Herschel 1998 *(Continued)*

Random sequence generation (selection bias)	Low risk	Shuffled opaque unmarked envelopes to generate sequence
Allocation concealment (selection bias)	High risk	Group assignments contained in opaque unmarked envelopes. Did not state if the envelopes were sequentially numbered
Blinding (performance bias and detection bias) All outcomes	High risk	Intervention was not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessment was blinded. Outcome not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was 1 exclusion: an infant randomized to sucrose was not circumcised. After the operator visualized the location of the meatus, she thought the surgery was contraindicated
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Isik 2000a

Methods	RCT Painful intervention: heel lance Study location: Marmara University Hospital, Istanbul, Turkey Study period: August 1997 to May 1998
Participants	113 healthy newborns PMA: 37 to 42 weeks, median PNA: 2 days (range 2 to 5 days)
Interventions	2 mL 30% sucrose (n = 28) 2 mL 10% glucose (n = 29) 2 mL 30% glucose (n = 28) 2 mL 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 HR 3 min after heel lance; mean recovery time for HR; percentage 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 percentage 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

Isik 2000a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Could not tell if intervention was blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Could not tell if HR assessment was blinded; however, it was stated that assessment of crying was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No clear statement given. Indicated that any baby that cried prior to the heel lance 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)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Johnston 1997

Methods	RCT Painful intervention: heel lance Study location: University-affiliated level III NICU, Canada Study period: not stated
Participants	85 preterm infants (25 to 34 weeks' PMA), 2 to 10 days of age
Interventions	0.05 mL 24% sucrose via syringe into the mouth just prior to heel lance (n = 27) 0.05 mL 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 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 sterile water via syringe into the mouth just prior to heel lance (n = 20)
Outcomes	HR, oxygen saturation, behavioural facial actions, behavioural state; NFCS baseline and at 3 x 30-s blocks
Notes	Data were analyzed using MANOVA (facial action). For HR repeated measures ANOVA was used with mean values but no SDs presented in graph form For state repeated measures ANOVA was performed and no univariate means and SDs were presented Oxygen 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

Johnston 1997 *(Continued)*

Allocation concealment (selection bias)	High risk	Sequentially numbered envelopes, but did not specify whether envelopes were opaque
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "The research nurse who actually conducted the heel stick procedure was not naive as to the interventions". "Not only was it obvious whether or not the infant was on the rocking bed, the nurse participated in preparing the infants for the conditions"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Similarily, in instances where the pulse oximeter signal was lost and heart rate was recorded by hand, the researcher collecting the data knew to which group the infant belonged". "The research assistant who coded the behavioral data in the laboratory did not know the purpose of the study, the nature of the interventions, nor the infants' group assignment"
Incomplete outcome data (attrition bias) All outcomes	High risk	The original design called for 28 infants/group based on anticipated effect size; however Table 1 shows that sample size of each group varied from 14 to 27; not equal groups
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Johnston 1999

Methods	RCT Painful intervention: heel lance Study location: Level III NICU, Canada Study period: not stated
Participants	48 preterm neonates, mean PMA of 31 weeks (range 25 to 34 weeks) within 10 days of birth
Interventions	Interventions given by syringe 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 24% sucrose as a single dose, followed by 2 doses of sterile water (n = 15) 3 doses 0.05 mL 24% sucrose (n = 17) 3 doses 0.05 mL sterile water (n = 16)
Outcomes	PIPP, measured over 5 x 30-s blocks of time
Notes	Repeated measures ANOVA was used to evaluate the effect of single vs. repeated doses of sucrose Means and SDs 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
Allocation concealment (selection bias)	High risk	Once parental consent was obtained, the research assistant opened the next sealed study envelope that contained the computer-generated random as-

Johnston 1999 *(Continued)*

		signment to 1 of 3 treatment groups: single sucrose, repeated sucrose, and sterile water. Trial report did not state whether or not the envelopes were opaque
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 syringes with the solutions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The video tapes were later coded according to the NFCS in the university laboratory by research assistants who were blind to the purpose of the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Johnston 2002

Methods	RCT Painful intervention: multiple invasive procedures Study location: 3 level III university-affiliated NICUs in Canada Study period: 27 months (dates not stated)
Participants	103 preterm infants completed the study (107 infants entered the study; 2 infants died and 2 were withdrawn) Sucrose group: mean (SD) PMA: 28.18 weeks (1.72) Water (control) group: mean (SD) PMA 28.05 weeks (2.06)
Interventions	Sucrose or water was administered orally up to 3 times, 2 min apart, for every invasive procedure during a 7-day period: 0.1 mL 24% sucrose (n = 51) 0.1 mL water (n = 52)
Outcomes	Neurobehavioural development assessed by the sub scales of alertness and orientation and motor development and vigour of the NAPI, Score for Neonatal Acute Physiology (SNAP) and Neuro-Biological Risk Score (NBRS)
Notes	Data could not be used for meta-analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random computer-generated program

Johnston 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Did not specify how allocation was done
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Research assistants not blinded to group, but blinded to purpose of study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Research assistants not blinded to group, but blinded to purpose of study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 infants were withdrawn from the study during the week of intervention and another 2 infants died
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Kaufman 2002

Methods	RCT Painful intervention: circumcision Study location: normal newborn Nursery of the Boston Univeristy Medical Centre, Boston, MA, USA Study period: March 1999 to August 2000
Participants	57 male 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-s intervals
Notes	Results were reported graphically. A 2-factor analysis of variance evaluated raw and percentage 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

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 make them indistinguishable

Kaufman 2002 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions were prepared and coded by pharmacy department and stored in individual darkened vials, each containing 60 mL aliquots. Investigators, research assistants, and hospital staff who participated in the circumcision did not know the contents of a given vial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators who were unaware of the experimental condition scored the audio-video tapes using software
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how many infants were included in the analyses
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Kristoffersen 2011

Methods	RCT, cross-over design Painful intervention: NG intubation Study location: NICU at St Olav's University Hospital, Trondheim, Norway Study period: January 2005 to June 2008
Participants	24 preterm infants, 28 to 32 weeks' PMA
Interventions	Each infant acted as his or her own control over a 3-week period 6 times. On these occasions, 6 different treatment combinations were given in randomized order: Pacifier or no pacifier, combined with no fluid, sterile water, or 30% sucrose
Outcomes	PIPP scores
Notes	Infants acted as their own controls

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 that
Blinding of outcome assessment (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 that

Kristoffersen 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	2 infants were transferred to another hospital and did not complete the study. 24 infants completed the study and they had complete observations. The 6 treatment combinations resulted in 144 discreet events being observed
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Leng 2013

Methods	RCT Painful intervention: heel lance Study location: Children's Hospital of Chongqing Medical University, Chongqing 400014, China Study period: not stated
Participants	560 full-term neonates (male 295, female 265) PMA 37 to 42 weeks; weight at birth 2500 g to 4000 g; Apgar scores at 1 min and 5 min after birth averaged Inclusion criteria: ≥ 8 points; age 3 to 28 days; had not undergone surgery; baseline HR 120-140 beats/min; oxygen saturation ≥ 0.90; planned screening for congenital metabolic disease Exclusion criteria: neonates presenting with asphyxia, congenital heart disease, and neuromuscular disease during birth; oxygen inhalation; hyperglycaemia; fasting; received sedative injection within last 48 h; fructose intolerance; maternal methadone dependence; vertebral injury
Interventions	The infants were randomized to 7 groups: Placebo group (plain boiled water) 10% glucose 25% glucose 50% glucose 12% sucrose 24% sucrose 30% sucrose The solutions were administered through a syringe dripping into the neonate's mouth 2 min before heel lance
Outcomes	The heel lance procedure was recorded by video. HR, oxygen saturation and pain scores were assessed at 1 min before heel lance and 3, 5 and 10 min after heel lance. Results were reported as means and full ranges.
Notes	The article was translated for us by Mr David Corpman

Risk of bias

Bias	Authors' judgement	Support for judgement

Leng 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	A table of random numbers was used
Allocation concealment (selection bias)	Unclear risk	A lottery method was used to assign the 7 groups to a boiled water placebo control group (placebo group), glucose groups (10%, 25%, and 50% concentration (mass concentration)), and sucrose groups (12%, 24%, and 30% concentration)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no statement that staff and assessors were blinded to intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The heel lance procedure was recorded by video. HR, oxygen saturation and pain scores were assessed at 1 min before heel lance and 3, 5 and 10 min after the heel lance. It is not stated if the assessors were blinded to intervention groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for 80 infants in each group
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Leng 2015

Methods	RCT Painful intervention: heel lance Study location: Children's Hospital of Chongqing Medical University, Chongqing, and Hunan Children's Hospital, Hunan, Shenzhen Children's Hospital, Shenzhen, and Chengdu Women's & Children's Central Hospital, Chengdu, China Study period: 25 June 2012 to 25 February 2013
Participants	New born infants (n = 671) with PMA between 37 and 42 weeks at birth; PNA between 3 and 28 days; birthweight 2500 g to 4000 g; Apgar score ≥ 8 at 5 min after birth; resting HR 120-140 beats/min and resting oxygen saturation ≥ 95%; and requiring neonatal congenital metabolism disease screening or blood glucose test
Interventions	The interventions in the 4 groups were as follows: Sucrose + routine care group: 2 mL 24% sucrose administered to the infant's mouth by syringe 2 min before the heel lance procedure Sucrose + NNS: 2 mL 24% sucrose administered to the infant's mouth by syringe 2 min before the heel lance procedure, and then a standard silicone newborn pacifier was placed into the infant's mouth until the end of the process Sucrose + swaddling: infants were swaddled with a cotton blanket, upper but not lower limb movements were restricted by the blanket, and then 2 mL 24% sucrose administered to the infant's mouth by syringe 2 min before the heel lance procedure. The lower limbs were swaddled right after the heel lance procedure until the end of the process

Leng 2015 *(Continued)*

	Sucrose + NNS + swaddling): infants were swaddled with a cotton blanket, upper but not lower limb movements were restricted by the blanket, then 2 mL 24% sucrose administered into the infant's mouth by syringe before the heel lance procedure, then a standard silicone newborn pacifier was placed into the infant's mouth, the lower limbs were swaddled right after the heel lance procedure until the end of the process
Outcomes	Revised NFCS, increase in HR (%), decrease in oxygen saturation (%). There was no significant difference in the frequency of adverse effects (fall in HR or oxygen saturation) across groups. No adverse events were observed during the procedure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each infant was assigned a random digit by using a random number table generated with SPSS19.0
Allocation concealment (selection bias)	Unclear risk	A simple calculation utilizing the random digit was used to determine a remainder (remainder = random digit/4), which was then used to decide which group the infant belonged to. For example, if the remainder was 1, then the infant was assigned to the sucrose group. If the remainder was 2, then the infant was assigned to the sucrose + NNS group. If the remainder was 3 then the infant was assigned to the sucrose + swaddling group. If the remainder was 0 then the group assigned was the sucrose + NNS + swaddling group. Randomization codes were kept in a secure location that could not be accessed by study personnel
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "Although we made efforts to limit bias from the coder, there is a possibility that the coder could still have distinguished the different groups by assessing with or without NNS". Nurses performing heel sticks were blinded to study and infant's clinical information
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Although we made efforts to limit bias from the coder, there is a possibility that the coder could still have distinguished the different groups by assessing with or without NNS"
Incomplete outcome data (attrition bias) All outcomes	Low risk	It appears that outcome data were reported on all infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Liaw 2011

Methods	RCT Painful intervention: IM injection Study location: a neonatal nursery at a medical centre in Taipei, Taiwan Study period: not stated

Liaw 2011 *(Continued)*

Participants	165 newborns, ≥ 36 weeks PMA receiving IM injections. Birthweight ≥ 2200 g, Apgar score ≥ 7 at 1 and 5 min after birth
Interventions	20% sucrose orally NNS Routine care
Outcomes	NFCS, cry duration, HR and respiratory rate
Notes	We reported on cry duration in the sucrose and the routine care groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Each infant enrolled in the study was randomly assigned to 1 of 3 pain relief methods by a statistician blind to the study purpose and using random allocation software
Blinding (performance bias and detection bias) All outcomes	High risk	The senior research nurse was trained to follow the nursery's standard procedures for IM injections of hepatitis vaccine. The IM injection procedures were controlled to be administered within 1 min in all newborns of the 3 groups. The other research nurse was trained to offer NNS or oral sucrose adeptly to infants in the experimental groups before the IM injection procedures
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The other research assistant, blinded to the study purpose and the infants' clinical information and intervention groups, was trained to code facial actions, to score pain using the NFCS and to measure cry duration. Facial actions and cry duration were recorded using a real-time colour video recorder. Video signals were directly transmitted to a computer, and a time code was recorded and entered into videotapes by software The NNS group was probably known to the research assistant
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other biases

Liaw 2013

Methods	RCT Painful intervention: heel lance Study location: Level III NICU and a neonatal special care unit at a medical centre in Taipei, Taiwan Study period: not stated

Liaw 2013 *(Continued)*

Participants	110 infants (PMA 26.4 to 37 weeks) needing heel lances
Interventions	3 interventions were used in different combinations: NNS + FT (n = 22); FT + sucrose (n = 21); NNS + sucrose (n = 21); NNS + sucrose + FT (n = 23) Sucrose intervention: infants were fed 0.2 mL–2.0 mL 20% sucrose through a syringe 2 min before the heel lance procedures. Volume depended on the infant's PMA (PMA 26 to 28 weeks: 0.2 mL; PMA 28.1 to 30 weeks: 0.5 mL; PMA 30.1 to 32 weeks: 1 mL; PMA 32.1 to 37 weeks: 1.5 mL; PMA > 37 weeks: 2.0 mL) NNS intervention: infants were given a standard silicone newborn pacifier to stimulate sucking 1 min before touching the foot to initiate heel lance procedures FT intervention: infants were placed in a flexed posture and gently held by the intervener's warm hands without strongly restraining the infant's head and body, one hand on the infant's head, and the other on the trunk Control group: routine care (n = 23)
Outcomes	Infants' behavioural states (quiet sleep, active sleep, transition state, active awake, quiet awake, fussing or crying)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated Infants meeting the study criteria were randomly assigned to control and treatment interventions by a statistician blind to the study purpose using Clinstat block randomization
Allocation concealment (selection bias)	Low risk	See random sequence generation
Blinding (performance bias and detection bias) All outcomes	High risk	We could not see how staff and assessors could be blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	We could not see how staff and assessors could be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Marin Gabriel 2013

Methods	RCT

Marin Gabriel 2013 *(Continued)*

	Painful intervention: heel lance Study location: Hospital Puerta de Hierro-Majadahonda, Madrid, Spain Study period: not stated
Participants	136 healthy term neonates (PMA 37 to 41 weeks)
Interventions	Sucrose group (N = 32; analyzed): 2 mL 24% sucrose given into mouth with a sterile syringe 2 min before heel lance to neonates laid supine on a cot; procedure was done in presence of mother Sucrose + skin-to-skin contact (SSC) group (n = 35; analyzed): neonates held prone between their mother's breasts at least 5 min before sampling and 2 mL 24% sucrose was given into mouth with a sterile syringe 2 min before heel lance SSC group (n = 31? Written to authors, could be 32): neonates held prone between their mother's breasts at least 5 min before sampling Breastfeeding (BF) + SSC group (n = 29; analyzed): neonates were held prone with skin-to-skin contact with mother; BF started at last 5 min before heel lance and was maintained during sampling Mothers were allowed to speak and touch their babies in all groups
Outcomes	NIPS; HR; crying time (s); crying in blood sampling; number of heel lances (%) Data presented as medians and IQRs, HR as means with SDs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	High risk	Randomization was by closed envelopes and 268 opaque (but not sequentially numbered) envelopes with the group assignment were prepared at the beginning of the study and mixed. Parents selected 1 envelope
Blinding (performance bias and detection bias) All outcomes	High risk	Nurses and parents were not blinded to the treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Nurses and parents were not blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the sucrose group 1 infant was not analyzed because of technical problem. In the BF + SSC group 3 infants were excluded from the analysis because of non-effective BF, 2 because of incorrect SSC and 1 because of technical problem. All participants from the sucrose + SSC group were included. In the SSC group there were technical problem in 1 infant but Figure 1 in the trial report indicates that 31/33 infants were analyzed, and we do not know what happened to this 1 infant
Selective reporting (reporting bias)	Low risk	Trial registration number (ClinicalTrials.gov): NCT01576432. There did not seem to be any deviations from the protocol in the full report
Other bias	Low risk	Appears free of other bias

Mathai 2006

Methods	Randomized study (blinded for cry but not for DAN) Painful intervention: heel lance Study location: transitional care unit and postnatal ward of a large, teaching hospital, Mumbai, India Study period: not stated
Participants	104 term neonates > 24 h old Sucrose group mean PNA = 48 h Distilled water group mean PNA = 44 h
Interventions	2 mL 20% sucrose (n = 17) 2 mL distilled water (n = 15) 2 mL expressed breast milk (n = 18) 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 (s) (i.e. until baby took first inspiration after beginning of cry), total cry (s); HR and oxygen saturation (SpO_2) before heel prick and 2 and 4 min after heel prick
Notes	Results were graphed and reported as means and SDs (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. 1 observer left the room during the intervention to be able to assess the DAN score blindly. A second observer was in the room during the interventions and was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	1 observer left the room during the intervention to be able to assess the DAN score blindly. A second observer was in the room during the interventions and was not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Physiological parameters (HR, oxygen saturation) not reported, but were listed as outcomes variables in the Methods sections
Selective reporting (reporting bias)	Unclear risk	Physiological parameters (HR, oxygen saturation) not reported, but were listed as outcomes variables in the Methods sections

Mathai 2006 *(Continued)*

Other bias	Low risk	Appears free of other bias

McCullough 2008

Methods	Randomized, double-blind, controlled trial Painful intervention: NG tube insertion Study location: Department of Child Health, Rotherham General Hospital, Rotherham, South Yorkshire, UK Study period: not stated
Participants	20 preterm infants, mean PMA 30 weeks Sucrose group: mean PNA 23 days Water group: mean PNA 27 days
Interventions	Total of 51 NG tube insertions. Each infant was randomised to either the water or sucrose group prior to each insertion. This was not a cross-over study. In each instance where NG tube insertion was required, the infant was randomised separately and independently of any previous allocation to receive either placebo (sterile water) or 24% sucrose solution 0.5 mL to 2 mL 24% sucrose (n = 26) 0.5 mL to 2 mL sterile water (n = 25)
Outcomes	Incidence of crying, HR, oxygen saturation, NFCS (median)
Notes	Incidence of crying reported as percentage of neonates who cried. HR and oxygen saturation measured as change (in beats/min and percentage 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 water 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 administered in a blinded manner
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessments
Incomplete outcome data (attrition bias)	Unclear risk	No information provided about why enrolled infants did not participate in the study

McCullough 2008 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Unclear risk	Infants were randomised several times - could they be "remembering" their previous experience, which may affect the results?

Milazzo 2011

Methods	Double-blind, RCT Painful intervention: arterial puncture Study location: a 40-bed, Level III, NICU of a 564-bed community-based hospital in midwest USA Study period: 12-month period (Dates not reported)
Participants	47 neonates, 30 to 36 weeks' PMA, 48 h old, nil by mouth status, and medical requirement for an arterial puncture
Interventions	Sucrose group (n = 24): 0.5 mL solution oral sucrose (Sweet-Ease, preservative-free, 24% sucrose solution 99044, Children's Medical Ventures, Norwell, Massachusetts) given in a 1 mL syringe 1-3 min before arterial puncture. A pacifier was then held in place lightly and infant's extremities swaddled by nurses assigned to infant's care. Arterial puncture was performed by another nurse Control group (n = 23): a pacifier was held in place lightly and infant's extremities swaddled by nurses assigned to infant's care. Arterial puncture was performed by another nurse
Outcomes	NIPS, HR, oxygen saturation (%)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment to groups was done using a computer randomization scheme
Allocation concealment (selection bias)	High risk	Envelopes were sealed, but not sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Immediately prior to the therapeutically required arterial puncture, the study investigator left the infant's room while the nurse caring for the infant opened the sealed envelope containing the randomization assignment to treatment group. Infants assigned to the sucrose solution treatment group were then given a 0.5 mL solution of oral sucrose in a 1-mL syringe by the nurse caring for the infant. Infants assigned to the placebo group did not receive any oral solution The investigator was then called back to the infant's bedside, remaining blinded to treatment group assignment, and obtained baseline study data (NIPS; HR; oxygen saturation) immediately after the arterial puncture needle was inserted and again 1 min after the arterial puncture procedure was completed For infants assigned to the sucrose treatment group, the time from sucrose administration to arterial puncture was at least 1 min but not more than 3 min.

Milazzo 2011 *(Continued)*

		Group assignment codes were not revealed to study investigators until study enrolment was completed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See blinding of participants and personnel. Group assignment codes were not revealed to study investigators until study enrolment was completed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were presented for 47/49 infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Mitchell 2004

Methods	Randomized, double-blind, placebo-controlled trial Painful intervention: screening for ROP Study location: level-3 university-affiliated NICU, Monroe, Louisiana, USA Study period: February 2002 to August 2002
Participants	30 preterm infants Sucrose group: mean PMA 26.5 weeks, mean PNA 8.5 weeks Water group: mean PMA 27.3 weeks, mean PNA 8.2 weeks
Interventions	Sucrose group (n = 15): pacifier and 3 doses of 0.1 mL 24% sucrose drops Water group (n = 15): pacifier and 3 doses of 0.1 mL sterile water drops Both groups received proxymetacaine hydrochloride 0.5% and were swaddled before the eye examination
Outcomes	PIPP at baseline; at eye drops instillation; during examination of left eye and at 30 s, 60 s, 90 s 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 randomization sequence
Allocation concealment (selection bias)	High risk	Allocated using sealed envelopes, but did not specify whether envelopes were opaque or sequentially numbered

Mitchell 2004 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions administered blinded to staff Nurse administering interventions was aware of group allocation. All other personnel and investigators were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Montoya 2009

Methods	Randomized, double-blind, controlled trial Painful intervention: venipuncture Study location: Unidad de Cuidado Intensivo Neonatal, Clinica Universitaria Bolivariana, Medellin, Colombia Study period: January to June 2008
Participants	111 preterm and term infants: 55 in sucrose group, 56 in water group
Interventions	1 mL 12% sucrose 1 mL water
Outcomes	NIPS score
Notes	Trial report was written in Spanish

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	Staff were blinded to the solutions used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Trial report did not mention blinding of outcome assessors

Montoya 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data reported on all 111 randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Mucignat 2004

Methods	Randomized, prospective, cross-over study Painful intervention: SC injection Study location: Service de Néonatologie, Hôpital Armand-Trousseau, Paris, France Study period: 1 April to 31 August 2002
Participants	33 preterm neonates, < 33 weeks' PMA Mean ± SD PMA at birth: 30 ± 6 weeks Mean ± SD PMA at injection: 32 ± 6 weeks
Interventions	NNS group: non-nutritive pacifier Sucrose + NNS group: 0.2 mL to 0.5 mL 30% sucrose with pacifier EMLA + NNS group: local application of EMLA cream with pacifier Sucrose + EMLA + NNS group: 0.2 mL to 0.5 mL 30% sucrose with EMLA and pacifier
Outcomes	DAN and NFCS scores; HR, respiratory rate and oxygen saturation (%) measured before, during and after injection
Notes	Fisher test, ANOVA of fixed-effect and the Tukey method were used to compare groups Results were reported as means and SDs Each infant acted as its own control. For each consecutive EPO injection, patients were randomised between four groups of intervention. The numbers of injections reported for the different interventions in Table 1 of the trial report varied from 41 to 86. NNSgroup; n = 41; Sucrose + NNS group; n = 86; EMLA + NNS group; n = 71; and Sucrose + EMLA + NNS group; n = 67. Data could not be used in RevMan-analyses 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)	High risk	Interventions could not be blinded

Mucignat 2004 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Did not state that outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Each infant acted as its own control. The numbers reported for the different interventions in Table 1 vary from 41 to 86
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	High risk	Unequal distribution of allocated and received treatments amongst injections: NNS; n = 41, EMLA + NNS; n = 71, sucrose + NNS; n = 86, sucrose + EMLA + NNS; n = 67

O'Sullivan 2010

Methods	Randomized, prospective, placebo-controlled study Painful intervention: screening for ROP Study location: Dublin, Ireland Study period: not stated
Participants	40 preterm infants Water group: mean PMA ± SD = 29.5 ± 2.3 weeks, mean corrected age at first eye examination ± SD = 33.1 ± 1.2 weeks Sucrose group: mean PMA ± SD = 29.8 ± 2.4 weeks, mean corrected age at first eye examination ± SD = 33.0 ± 1.1 weeks
Interventions	Sucrose group: 0.2 mL 24% sucrose given by mouth using a syringe and a pacifier (N = 20) Water group: 0.2 mL sterile water given by mouth using a syringe and a pacifier (N = 20) Both groups were swaddled
Outcomes	N-PASS; HR and oxygen saturation at baseline; number of episodes 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 randomization process used
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque and sealed envelopes used
Blinding (performance bias and detection bias)	Low risk	Only pharmacist was aware of the identify of solutions, all other personnel were blinded

O'Sullivan 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Ogawa 2005

Methods	Randomized, double-blind, placebo-controlled trial Painful intervention: heel lance and venipuncture Study location: NICU of Osaka Medical College, Osaka, Japan Study period: November 1999 to March 2000
Participants	100 healthy, full-term infants ≥ 37 weeks' PMA
Interventions	1 mL sterile water 2 min before heel lance (n = 25) 1 mL 50% sucrose 2 min before heel lance (n = 25) 1 mL sterile water 2 min before venipuncture (n = 25) 1 mL 50% sucrose 2 min before venipuncture (n = 25)
Outcomes	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
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 SDs. P values were 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)	High risk	100 sealed envelopes. Did not state if they were opaque and sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions were administered blindly

Ogawa 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data provided for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appeears free of other bias

Okan 2007

Methods	Randomized, blinded, cross-over trial Painful intervention: heel lance Study location: NICU, Istanbul, Turkey Study period: not stated
Participants	31 preterm infants: mean (SD) PMA 30.5 weeks (2.7); PNA 20 days (16)
Interventions	2 mL sterile water 2 mL 20% sucrose 2 mL 20% glucose All solutions were given 2 min before heel lance. The infants were tested 3 times in a cross-over manner
Outcomes	HR, respiratory rate, oxygen saturation and NFCS score at baseline, heel lance and at 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 analyzed using the Friedman test Results were reported as means and SDs Adverse effects were not evaluated

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)	High risk	Allocated by sealed envelopes. Solutions contained in identical bottles coded by nurse who was not 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 were provided blinded to staff

Okan 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Videotape records were later analyzed by two observers who were not aware of which solution was used. Each observer assessed the data independently and could not communicate their findings to the other."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported on all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Overgaard 1999

Methods	Double-blind RCT Painful intervention: heel lance Study location: Department of Obstetrics and Gynaecology, Aalborg University Hospital, Aalborg, Denmark Study period: 3 months (dates not provided)
Participants	100 newborn term infants, mean age 6 days (range 4 to 9)
Interventions	2 mL 50% sucrose solution via syringe into the mouth over 30 s, 2 min prior to heel lance (n = 50) 2 mL sterile water via syringe into the mouth over 30 s, 2 min prior to heel lance (n = 50)
Outcomes	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 HR at 0 min and 1 min, change in oxygen saturation at 0 min and 1 min
Notes	Results were reported as medians and 5% and 95% percentiles - we did not attempt to convert to means and SDs. Four infants were excluded after randomisation due to failure of the videotaping leaving 96 newborns for analysis; sucrose n = 49; placebo n = 47 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
Blinding (performance bias and detection bias) All outcomes	Low risk	Sucrose and water solutions were administered blinded to investigators and parents
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessments

Overgaard 1999 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 infants were excluded due to failure of videotaping, leaving 96 newborns for analysis
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Pandey 2013

Methods	RCT Painful intervention: OG tube insertion Study location: NICUs of Kalawati Saran Children's Hospital, Lady Hardinge Medical College, New Delhi, India Study period: not stated
Participants	120 clinically stable preterm infants (< 37 weeks PMA) were enrolled within the first 7 postnatal days, they had not received any painful stimulus 30 min prior to intervention, and required routine OG tube insertion. 105 infants were analyzed
Interventions	1 mL 24% sucrose administered to the tongue 2 min before OG tube insertion. Total number randomized: n = 60; final analysis n = 53 1 mL distilled water administered to the tongue 2 min before OG tube insertion. Total number randomized: n = 60; final analysis n = 52
Outcomes	The primary outcome was the response to the pain, assessed by the PIPP scale, prior to the procedure, during the procedure, and at 30 s, 1 min and 2 min postprocedure Secondary outcomes were the maximum HR and minimum oxygen saturation recorded during the procedure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used block randomization with computer generated random sequences and a block size of 4
Allocation concealment (selection bias)	Low risk	Allocation concealment was done by the hospital pharmacy which packed 2 mL of the sucrose and the double distilled water into syringes and provided opaque sealed envelopes sequentially labelled according to randomization code
Blinding (performance bias and detection bias) All outcomes	Low risk	2 min prior to the procedure, 1 mL of the solution marked with infant's serial number was administered orally to the infant by a healthcare provider (blinded to the contents of the solution)

Pandey 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	A consultant of the unit, who was unrelated to the study and was blinded to the study methodology, evaluated the video-recordings and assigned the PIPP scores
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 infants were excluded from the sucrose group as the monitor malfunctioned, and 1 infant in the sucrose group went into sudden cardiorespiratory arrest and had to be excluded. In the water group the OGT was displaced before the 2 min post procedure PIPP scores could be assigned for 3 infants, and the monitor malfunctioned for 5 infants. 53 infants were analyzed in the sucrose group and 52 in the water group (88% of enrolled infants)
Selective reporting (reporting bias)	Low risk	The protocol for the study was available to us and there did not seem to be any deviation from the protocol. ClinicalTrials.gov (Registration number: NCT 00949104)
Other bias	Low risk	Appears free of other bias

Potana 2015

Methods	RCT Stressful intervention: echocardiography Study location: a level III NICU in Gujarat, India Study period: August to November 2013
Participants	104 neonates with established enteral feeding, not on any respiratory support and with PMA between 32 and 42 weeks requiring echocardiography Exclusion criteria: neonates who were nil by mouth, had poor neurological status, and those who were paralysed or sedated with pharmacological agents
Interventions	Sucrose group: Arbineo 24% w/v oral solution, dose: 1 mL for infants 32 to 40 weeks PMA, 2 mL for infants > 40 weeks PMA, administered 2 min prior to echocardiography by a dropper Control group: no medication or placebo
Outcomes	PIPP, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated using GraphPad software
Allocation concealment (selection bias)	High risk	Sealed opaque envelopes but not stated if they were sequentially numbered
Blinding (performance bias and detection bias) All outcomes	High risk	Could not be blinded

Potana 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators performing the video analysis were blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled infants were analyzed
Selective reporting (reporting bias)	Unclear risk	The study was not entered into a trials registry and the protocol for the study was not available to us. We could not judge if there was a deviation from the protocol or not
Other bias	Low risk	Appears free of other bias

Ramenghi 1996a

Methods	Randomized, double-blind, placebo-controlled, cross-over study Study intervention: heel lance Study location: Leeds General Infirmary, Leeds, UK Study period: not stated
Participants	15 infants (32 to 34 weeks' PMA) > 24 h of age
Interventions	1 mL 25% sucrose via syringe into mouth 2 min prior to heel lance 1 mL sterile water via syringe into mouth via syringe 2 min before heel lance Cross-over design
Outcomes	Duration of first cry (s) following heel lance, percentage of time crying 5 min after heel lance, HR (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, percentage cry over 5 min and HR. For composite behavioural outcome scores data were presented in graph form only with no indication if data represented medians or means. Wilcoxon matched pairs signed rank test used to evaluate outcomes Adverse effects were evaluated. Cross-over study and results from the first assignment to sucrose or water were not reported. No data available to use in meta-analyses

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 staff were blinded to sucrose and water solutions
Blinding of outcome assessment (detection bias)	Unclear risk	Unsure of whether outcome assessments were performed blinded

Ramenghi 1996a *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Ramenghi 1996b

Methods	Randomized, single-blind, placebo-controlled trial Painful intervention: heel lance Study location: Leeds General Infirmary, Leeds, UK Study period: not stated
Participants	60 infants (37 to 42 weeks' PMA) 2 to 5 days old
Interventions	2 mL 25% sucrose via syringe into mouth 2 min prior to heel lance (n = 15) 2 mL 50% sucrose via syringe into mouth 2 min prior to heel lance (n =15) 2 mL commercial sweet-tasting solution (Calpol) via syringe into mouth 2 min prior to heel lance (N = 15) 2 mL sterile water via syringe into mouth 2 min prior to heel lance (n = 15)
Outcomes	Duration of first cry (s) following heel lance, percentage time crying over 3 min following heel lance, percentage change in HR over 7 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 IQRs for the pain score. For cry duration and percentage crying over 3 min the data were presented as medians and IQRs. Percentage change in HR was reported in graph form without indicating whether the data represented means or medians with SDs 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	Investigators were blind to the nature of the sucrose and water solutions, but the Calpol could not be disguised because of its pink colour
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessments were performed blinded to groups for sucrose and water but not for Calpol

Ramenghi 1996b *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Ramenghi 1999

Methods	Randomized, double-blind, placebo-controlled, cross-over trial for the mode of delivery of sucrose or water by mouth or intragastrically Painful intervention: heel lance Study location: Leeds General Infirmary, Leeds, UK Study period: Dates not provided
Participants	30 preterm infants (PMA 32 to 36 weeks, PNA < 24 h)
Interventions	Each infant received either sucrose or water and was not crossed over for the solution received, only for the method of delivery Sucrose group (n = 15): 25% sucrose solution (volume not reported) given via syringe into the mouth or via NG tube 2 min prior to first heel lance, and via the alternate route for the second heel lance within 48 h Water group (n = 15) : sterile water via syringe into the mouth or via NG tube 2 min prior to first heel lance and via the alternate route for the second heel lance within 48 h Cross-over design
Outcomes	Percentage 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 IQR and total range 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	Did not describe measures taken to ensure blinding of intervention and outcome assessment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Did not describe measures taken to ensure blinding of intervention and outcome assessment

Ramenghi 1999 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported on all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Rogers 2006

Methods	Randomized, double-blind trial Painful intervention: bladder catheterization Study location: a single tertiary-care dedicated paediatric emergency department, USA Study period: June 2003 to November 2004
Participants	83 infants ≤ 90 days old, born at least 34 weeks' PMA were enrolled and randomized, 3 infants were withdrawn after randomization Separated into 3 age groups: • 1-30 days • 31-60 days • 61-90 days
Interventions	2 mL 24% sucrose via syringe 2 min before bladder catheterization (n = 40) 2 mL sterile water via syringe 2 min before bladder catheterization (n = 40)
Outcomes	DAN scale, percentage 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 SDs. P values were 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
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	Staff blinded to sucrose and water solutions
Blinding of outcome assessment (detection bias)	Low risk	Research nurses were blinded to the treatment allocation

Rogers 2006 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	83 infants were enrolled and randomized, but 3 were withdrawn after randomizations as a result of inappropriate enrolment or withdrawal of consent
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Rush 2005

Methods	Prospective RCT Painful intervention: screening for ROP Study location: NICU at a university-affiliated hospital, Amarillo, Texas, USA Study period: not stated
Participants	30 infants < 32 weeks' GA or weighing < 1500 g Sucrose group mean GA 29.57 weeks (range 26 to 32) Control group mean GA 28.8 weeks (range 25 to 31)
Interventions	Sucrose group: 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 Control: no swaddling, no sucrose and not held by nurse All infants received eye drop instillation of 0.5% proxymetacaine and 1% tropicamide, then 15 min later eye drop instillation of 0.5% tropicamide and 2.5% phenylephrine All eye drops were instilled into both infant's eyes before the ROP examination
Outcomes	Pulse rate, respiratory rate and oxygen saturation at baseline (30 min before instillation of proxymetacaine), 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
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias)	High risk	No blinding to interventions

Rush 2005 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	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	Appears free of other bias

Rushforth 1993

Methods	Randomized, double-blind, placebo-controlled study Painful intervention: heel lance Study setting: Leeds General Infirmary, Leeds, UK Study period: not stated
Participants	52 infants, 37 to 42 weeks' PMA, 2 to 7 days old
Interventions	2 mL 7.5% sucrose administered by a dropper into the mouth over a 1-min period prior to heel lance (n = 26) 2 mL 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 analyzed blindly at a later date
Notes	Results 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	Unclear risk	Not clear whether staff were blinded to sucrose and water solutions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessments

Rushforth 1993 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Simonse 2012

Methods	RCT Painful intervention: heel lance Study location: neonatal ward of Amphia Hospital, a secondary health care centre in Breda, the Netherlands Study period: January 2010 to May 2011
Participants	71 preterm infants, PMA 32 to 36 6/7 weeks at birth undergoing heel lance with an automated piercing device
Interventions	Sucrose group (n= 25; 24 analyzed): neonates lay in their cots and received 1 mL to 2 mL 24% sucrose solution 2 min before the heel lance, combined with NNS and Newborn Individualized Developmental Care and Assessment Breastfed group (n = 23; all analyzed): infants were breastfed while held in mothers' arms, heel lance was performed after continuous sucking was observed (i.e. during feeding) Bottle-fed group (n = 23; all analyzed): infants were bottle-fed breast milk. The non-breast feeding group infants were held in arms of an experienced nurse and were given supplemental breast milk by a sterile syringe and heel lance was performed after continuous sucking was observed
Outcomes	PIPP score; COMFORTneo Score, HR and SpO_2
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization sequence was created by using a fixed block size of 8 for a maximum of 75 neonates with a 1:1:1 allocation
Allocation concealment (selection bias)	Low risk	Neonates were allocated to 1 of the 3 groups according to the method of sequentially numbered and opaque sealed envelopes created by an independent employee and masked for the investigator
Blinding (performance bias and detection bias) All outcomes	High risk	It was not possible to blind investigators for the allocated intervention
Blinding of outcome assessment (detection bias)	High risk	It was not possible to blind investigators for the allocated intervention

Simonse 2012 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 infant was excluded from the sucrose group
Selective reporting (reporting bias)	Low risk	This trial was registered at www.clinicaltrials.gov (identifier NCT01276366). There did not seem to be any deviations from the protocol
Other bias	Low risk	Appears free of other bias

Slater 2010

Methods	Randomized, prospective study Painful intervention: heel lance Study location: Elizabeth Garret Anderson Wing, University College Hospital, London, UK Study period: 25 February 2009 to 25 March 2010
Participants	59 infants; 29 assigned to sucrose group and 30 to water group 44 term infants 37 to 43 weeks' PMA, < 8 days old were included in the analysis of the primary outcome (pain-specific brain activity recorded with electroencephalography and identified by principal component analysis)
Interventions	Sucrose group (n = 20): 0.5 mL 24% sucrose given via syringe Water group (n = 24): 0.5 mL sterile water
Outcomes	HR change, 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 randomized code
Allocation concealment (selection bias)	Low risk	Only the hospital pharmacy had access to the randomization codes that could be used to identify the solution. A sealed copy of the randomization 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
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias)	High risk	59 infants were enrolled, but the primary outcome was ascertained in 44 infants (75%)

Slater 2010 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Stang 1997

Methods	Prospective, randomized, double-blind, placebo-controlled trial Painful intervention: circumcision Study location: Fairview Riverside Medical Center, Minneapolis, Minnesota, USA Study period: 1993 to 1994
Participants	80 healthy term male newborns, mean PMA 39.5 weeks, mean PNA 31.5 h
Interventions	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 (scores prior to 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 SDs 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 assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessments

Stang 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data results did not specify number of infants with data
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Stevens 1999

Methods	Randomized, cross-over, controlled trial Painful intervention: heel lance Study location: NICUs of 3 metropolitan university-affiliated teaching hospitals and 1 children's hospital in Canada and the USA Study period: a 15-month period (dates not given)
Participants	122 preterm neonates, 27 to 31 weeks' PMA, < 28 days old
Interventions	Each infant received all 4 interventions in a random order (serving as his/her own control); there was 1 control intervention and 3 treatment 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 (control)
Outcomes	PIPP
Notes	Repeated measures ANOVA and ANCOVA used to evaluate efficacy of treatment interventions Means and SDs provided for pain scores prior to cross-over for sucrose + pacifier and water + pacifier Adverse effects were evaluated The first author provided us with unpublished information regarding the study methods.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence
Allocation concealment (selection bias)	Low risk	Allocation was enclosed in sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	The study solutions were prepared in each of the study units by the Pharmacist and labelled as Study Solution 1 and 2. The research nurses (who performed the heel lance and administered each intervention) drew up the solution specified in the intervention sequence from a dark coloured bottle, so were blind to which solution (e.g. water or 24% sucrose) was used. Nurses were not blind to the prone positioning or control
Blinding of outcome assessment (detection bias)	Low risk	The study nurse collected all of the data (e.g. videotaped facial expressions, recorded cry) and was blind to study solutions; the data coders were also

Stevens 1999 *(Continued)*

All outcomes		blinded to which study solution was used - but NOT to the prone positioning or control, as they could visualize this on the videotapes. The data analysts were blinded to all of the interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants
Selective reporting (reporting bias)	Low risk	The primary author assured us that there were no deviations from the protocol
Other bias	Low risk	Appears free of other bias

Stevens 2005a

Methods	Prospective RCT Painful intervention: heel lance and other procedures Study location: 1 tertiary-level NICU in Canada Study period: not stated
Participants	66 preterm infants, 26 to 30 weeks' PMA, < 72 h PNA
Interventions	No intervention (N = 22) 0.1 mL 24% sucrose via syringe and pacifier (n = 23) 0.1 mL sterile water via syringe and pacifier (n = 21) Solutions were given 2 min before every procedure during the first 28 days of life
Outcomes	PIPP, neonatal clinical outcomes and neurobiological risk scores
Notes	Actual PIPP scores (mean, standard deviation) were not reported. PIPP scores were analyzed 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 reported as '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	Staff were blinded to sucrose and water solutions
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessments

Stevens 2005a *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 infants dropped out of the study prior to any data collection
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Storm 2002

Methods	RCT Painful intervention: heel lance Study location: Section of Neonatology, Department of Paediatrics, the National Hospital, Oslo, Norway Study period: not reported
Participants	48 preterm infants, median PMA 32 weeks, median PNA 14 days
Interventions	2 mL 15% sucrose (n = 12) 1 mL 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 Oral solutions were administered via syringe into infant's mouth 2 min prior to heel lance NG tube solutions (milk) 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, HR
Notes	Paired non-parametric tests (Wilcoxon test) used to compare the infant's intervention and control session No median or IQR 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. Randomly divided into 4 groups
Blinding (performance bias and detection bias) All outcomes	Unclear risk	2 groups fasting; 2 groups fed (milk) during the last hour prior to heel lanceup via NG tube
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Did not provide any information about blinding of assessor

Storm 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on number of participants included in the Methods or Results sections. Results in figures and P values only. Presented no data that could be meta-analysed
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us, so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Suhrabi 2014

Methods	RCT Painful intervention: vaccination pain (hepatitis B) Study location: Shahid Mostafa Khomini Hospital of Ilam, Islamic Republic of Iran Study period: May 2013 to June 2013
Participants	90 full-term neonates, who were not receiving analgesics, not receiving nutrition during 30 min before vaccination and absence of diarrhoea and common cold
Interventions	The hepatitis B vaccine was injected 2 min after administration of sucrose, glucose or no treatment and pain severity measured by the NIPS scale during 1-2 min Sucrose group (n = 30): 2 mL 25% sucrose through a syringe in 30 s Glucose group (n = 30): 2 mL 25% glucose through a syringe in 30 s Control group (n = 30): no intervention
Outcomes	NIPS during 1-2 min after vaccine injection
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The cases were randomly (simple randomization method) divided into 3 groups of 30 neonates each
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) All outcomes	High risk	The cases were randomly (simple randomization method) divided into 3 groups of 30 neonates each
Blinding of outcome assessment (detection bias) All outcomes	High risk	The cases were randomly (simple randomization method) divided into 3 groups of 30 neonates each
Incomplete outcome data (attrition bias) All outcomes	Low risk	NIPS reported on all 90 infants

Suhrabi 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	The registered protocol was available to us and there did not seem to have been any deviation from the protocol. IRCT 201304096790N3). Date registered: 22 May 2013. Registration timing: Registration while recruiting
Other bias	Low risk	Appears free of other bias

Taddio 2008

Methods	Double-blind, RCT Painful intervention: IM injections, venipunctures and heel lances Study location: Mount Sinai Hospital, Toronto, Ontario, Canada Study period: 15 September 2003 to 27 July 2004
Participants	240 newborns, mean PMA 38.7 to 39.9 weeks, mean PNA 0.5 h to 0.8 h
Interventions	2 mL 24% sucrose given to newborns of non-diabetic mothers (n = 60) 2 mL sterile water given to newborns of non-diabetic mothers (n = 60) 2 mL 24% sucrose given to newborns of diabetic mothers (n = 60) 2 mL sterile water given to newborns of diabetic mothers (n = 60) Solutions were given before all IM injections, venipunctures and heel lances during the first 2 days of life
Outcomes	PIPP score during procedure
Notes	Student's t-test used to compare average PIPP scores between groups. Post hoc analyses were performed after adjusting for baseline characteristics by use of a general linear model for IM injection and venipuncture and linear mixed-model analysis for heel lances. Adverse events were analyzed 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table: allocation was done on a 1:1:1 basis
Allocation concealment (selection bias)	Low risk	Centralized at the hospital pharmacy. Solutions carried in identical bottles only labelled with patient identification
Blinding (performance bias and detection bias) All outcomes	Low risk	Staff were blinded to sucrose and water solutions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessments blinded

Taddio 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Taddio 2011

Methods	RCT Painful intervention: venipuncture Study location: Mother and Infant Unit, Mount Sinai Hospital, Toronto, Ontario, Canada Study period: 20 August 2007 to 22 February 2009
Participants	330 infants mean PMA (SD) 39.5 weeks (1.2) Liposomal lidocaine group (n = 110) mean PMA (SD) 39.6 weeks (1) Sucrose group (n = 110) mean PMA (SD) 39.6 weeks (1.3) Sucrose liposomal lidocaine group (n = 110) mean PMA (SD) 39.6 weeks (1.3)
Interventions	Liposomal lidocaine group: 1 g liposomal lidocaine 4% cream to the dorsum of the hand, occluded by a dressing (Tegaderm) for 30-40 min Sucrose group: 2 mL 24% sucrose solution, administered by mouth using a syringe over 1-2 min Sucrose liposomal lidocaine group: both sucrose and liposomal lidocaine as described above 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 (s),observer-rated pain using a visual analogue scale (VAS) (0 to 10 cm), HR (beats/min), oxygen saturation (%)
Notes	Reported no significant adverse effects

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	Concealment of treatment allocation was achieved by carrying out randomization and dispensing functions offsite
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and personnel blinded

Taddio 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy outcomes were not reported in 9 infants and safety outcomes were not repotted in 2 infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Thakkar 2016

Methods	RCT Painful intervention: heel lance Study location: tertiary-level NICU in Western India Study period; 1 year, dates not stated
Participants	Participants were full-term infants (≥37 weeks PMA), with birthweight > 2200 g, > 24 h old and were exclusively breastfed Exclusion criteria: neonates with history of birth asphyxia, sepsis, meningitis, respiratory distress, congenital malformations, receiving nil by mouth, being mechanically ventilated and who received any pharmacological agent for analgesia in the 72 h before enrolment
Interventions	Sucrose group (n = 45): 30% sucrose solution delivered by sterile syringe Sucrose + NNS (n = 45): 30% sucrose solution delivered by sterile syringe plus NNS NNS group (n = 45): sterile gauze was held gently in neonate's mouth and the palate tickled to stimulate sucking No treatment group (n = 45): received no treatment
Outcomes	PIPP, total crying time. Results presented as medians and IQRs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random-sequence numbers
Allocation concealment (selection bias)	High risk	Opaque sealed envelopes were used. Did not say if the envelopes were sequentially numbered
Blinding (performance bias and detection bias) All outcomes	High risk	Staff knew if the infants were given sucrose by syringe or if they were given NNS or no intervention. Quote: " ... blinding was not possible because the interpreter was performing the procedure"

Thakkar 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	" ... blinding was not possible because the interpreter was performing the procedure"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Tutag Lehr 2015

Methods	RCT Painful intervention: heel lance Study location: Hutzel Harper University Hospital, Detroit, MI, USA Study period 2005 to 2007
Participants	56 term infants ≤ 7 days old: appropriate for PMA (weight between 5th to 95th percentile) scheduled to undergo routine heel lance for newborn metabolic screening
Interventions	Sucrose group (n = 29): infants received 2.0 mL 24% sucrose orally Water group (n = 27): infants received sterile water orally Feedings were withheld 2.0 h prior to heel lance to minimize risk of aspiration. No infant received NNS (pacifiers) during the study
Outcomes	Primary outcomes: mean skin blood flow; NIPS Skin blood flow, perfusion units measured by Laser Doppler Imager during heel lance HR, RR, oxygen saturation in blood
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated block method
Allocation concealment (selection bias)	Low risk	Pharmacy Investigational Drug Service team at Hutzel Harper University Hospital maintained the double-blinded randomization sequence
Blinding (performance bias and detection bias) All outcomes	Low risk	A computer-generated block method assigned infants to receive either 2 mL 24% sucrose or 2 mL sterile water placebo prior to heel lance
Blinding of outcome assessment (detection bias)	Low risk	Doses were dispensed in plastic oral syringes

Tutag Lehr 2015 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the sucrose group (n = 30) 1 infant was excluded secondary to withdrawn consent. In the placebo group (n = 30) 3 infants were not included: 1 had a significant Laser Doppler Imager scan artefact, 1 received oral acetaminophen prior to heel lance, and 1 developed persistent tachypnoea prior to the study
Selective reporting (reporting bias)	Unclear risk	We could not determine whether this study was registered in a trials registry, so we could not tell if there were any deviations from the protocol
Other bias	Low risk	Appears free of other bias.

Unceta-Barranechea 2008

Methods	Prospective RCT Painful intervention: heel lance Study location: Maternity Unit Hospital de Basurto, Bilbao, Vizcaya, Spain Study period: 3 months in 2007
Participants	150 term infants
Interventions	2 mL 24% sucrose with NNS NNS with water Control: facilitated tucking
Outcomes	Modified 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	Staff were blinded to sucrose and water solutions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was unclear if outcome assessments were performed staff blinded to interventions
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomized infants

Unceta-Barranechea 2008 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Unclear risk	Appears free of other bias

Yilmaz 2010

Methods	RCT Painful intervention: heel lance Study location: Trabzon Delivery and Children's Diseases Hospital, Erzurum, Turkey Study period: February 2007 to January 2008
Participants	120 infants GA 37 to 42 weeks Sucrose group (n = 30): mean PMA (SD) 39.10 weeks (0.71) Mother's milk group (n = 30): mean PMA (SD) 39.10 weeks (1.03) Pacifier group (n = 30): mean PMA (SD) 39.20 weeks (0.93) Control group (n = 30): mean PMA (SD) 39.67 weeks(0.80)
Interventions	Sucrose group: 2 mL 20% sucrose via syringe 2 min before the procedure (using a syringe with the needle removed and avoiding contact of the syringe with the mouth and lips) Mother's milk group: 2 mL mother's milk via syringe 2 min before the procedure (using a syringe with the needle removed and avoiding contact of the syringe with the mouth and lips) Pacifier group: given a pacifier Control group: newborns were in their mothers' lap; no interventions were made before the painful procedure
Outcomes	NIPS score, HR, respiratory rate, crying time. Data were presented according to different procedure times and could not be used in meta-analyses
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Did not specify method of randomization
Allocation concealment (selection bias)	Unclear risk	Did not specify method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Did not report on blinding of personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Did not report on blinding of outcome assessors

Yilmaz 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Örs 1999

Methods	RCT Painful intervention: heel lance Study location: Marmara University Hosppital, Istanbul, Turkey Study period: September 1996 to January 1997
Participants	102 healthy term infants, PMA 37 to 42 weeks, median PNA 1.6 days (range 1 to 15 days)
Interventions	2 mL 25% sucrose (n = 35) 2 mL human milk (n = 33) 2 mL sterile water (n = 34) Solution 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; percentage change in HR 1, 2, and 3 min after heel lance
Notes	Kruskal-Wallis 1-way ANOVA used to assess differences between groups Medians and IQRs reported for 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 were administered blinded to staff, but human milk was probably not blinded to staff
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data provided on all randomized infants

Örs 1999 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The study protocol was not available to us so we could not judge whether there were any deviations from it
Other bias	Low risk	Appears free of other bias

Abbreviations
BF = breastfeeding
BPSN = Bernese Pain Scale for Neonates
DAN = Douleur Aiguë du Nouveau-né Scale
DPNB = dorsal penile nerve block
EMLA = eutectic mixture of local anaesthetic (a topical mixture of lidocaine (2.5%) and prilocaine (2.5%) cream)
HR = heart rate
IM = intramuscular
IQR = interquartile range(s)
min = minute(s)
NAPI = Neurobehavioural Assessment of Preterm Infants
NFCS = Neonatal Facial Coding System
NG = nasogastric
NICU = neonatal intensive care unit
NIPS = Neonatal Infant Pain Scale
N-PASS = Neonatal Pain Agitation and Sedation Scale
NNS = non-nutritive sucking
PIPP = Premature Infant Pain Profile
PMA = postmenstrual age
PNA = postnatal age
RCT = randomised controlled trial
RR = respiratory rate
ROP = retinopathy of prematurity
SC = subcutaneous
SD = standard deviation
SpO_2 = oxygen saturation
SSC = skin to skin contact
w/v = weight by volume

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

Study	Reason for exclusion
Abad 1993	Available as an abstract only
Abad 2001	Although this was an RCT, 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
Akman 2002	The word 'random' does not appear anywhere in the text. It is unlikely that this is an RCT
Aziznejad 2013	The age of the infants was 8.5 months
Barbier 1994	Study did not include the use of sucrose
Barr 1993	Although an RCT, the authors did 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 were presented

Study	Reason for exclusion
Barr 1995	Excluded based on 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 so, 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 was an RCT the number of neonates in each group was not stated
Blass 1995	This was a controlled trial without randomisation. The number of patients in each group was 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	PNA 0 to 6 months
Dilli 2009	PNA 0 to 48 months. A group < 1 month old could not be separated
Efe 2007	Study not fully randomised
Fernandez 2003	The noxious stimulus was heel stroke, which is non-invasive
Gibbins 2000	Available as an abstract only
Gormally 1996	Available as an abstract only
Graillon 1997	An RCT cross-over study in which no painful stimulus was applied to the neonates
Harrison 2011	Not an RCT
Isik 2000b	Available as an abstract only
Johnston 2000	Available as an abstract only
Joung 2010	Non-randomised study
Lewindon 1998	The infants in this study were too old for inclusion in this review (mean age 17.1 weeks)
Mandel 2012	All infants received sucrose
Mellah 1999	Randomised double blind cross-over study. Data analyzed by paired t-test. Results from the first exposure to sucrose or placebo could not be isolated
Mohan 1998	Control group was not randomised
Ozdogan 2010	This was a quasi-randomised trial. "Healthy newborns (n = 142) were consecutively allocated to one of the six groups: ..."
Ramenghi 2002	Immunisations performed at 2, 3 or 4 months, so infants were too old for this review
Razmus 2004	Study not fully randomised

Study	Reason for exclusion
Reis 2003	Mean PNA 9.5 weeks
Sahebihag 2011	Infants were too old for this review
Scaramuzzo 2013	Dr Scaramuzzo informed us that "our randomisation method was simply one yes-one not". This was therefore a quasi-randomised trial which we did not include in the review
Skogsdal 1997	This study used glucose and breast milk as the interventions
Stevens 1997b	Available as an abstract only
Stevens 2000	Available as an abstract only
Taddio 2000	Not an RCT and included older infants
Taddio 2003	Infants did not receive a painful procedure
Taddio 2009b	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

Abbreviations
PNA = postnatal age
RCT = randomised controlled trial

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

Moradi 2012a

Methods	
Participants	
Interventions	
Outcomes	
Notes	Study awaiting classification - written in Persian

Moradi 2012b

Methods	
Participants	
Interventions	
Outcomes	
Notes	Study awaiting classification – written in Persian

Singh 2001

Methods	
Participants	
Interventions	
Outcomes	
Notes	We have not been able to locate a copy of the article at libraries in Canada or the US.

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

Campbell-Yeo 2013

Trial name or title	Trial of repeated analgesia with kangaroo care (TRAKC)
Methods	RCT
Participants	Infants < 36.0 weeks PMA
Interventions	Kangaroo mother care Sucrose Kangaroo mother care + sucrose
Outcomes	PIPP; NAPI
Starting date	June 2012
Contact information	Marsha Campbell-Yeo, RN, NNP, PhD; Marsha.CampbellYeo@iwk.nshealth.ca
Notes	ClinicalTrials.gov Identifier: NCT01561547

ISRCTN59514984

Trial name or title	RCT of sucrose analgesia for repeated capillary blood sampling
Methods	RCT Painful intervention: repeated capillary blood sampling
Participants	PMA or PNA not provided
Interventions	Sucrose Water
Outcomes	Outcome measures not provided
Starting date	September 2006

ISRCTN59514984 *(Continued)*

Contact information	Dr Simon Mitchell, SMH Central Manchester & Manchester Children's University Hospitals St Mary's Hospital for Women & Children Oxford Road Manchester M13 0JH UK
Notes	ISRCTN59514984

ISRCTN73259137

Trial name or title	Kangaroo mother care combined with sucrose to reduce pain responses in preterm infants
Methods	RCT Painful intervention: venipuncture
Participants	1. PMA between 28 and 36 weeks 2. PNA < 28 days
Interventions	Kangaroo mother care + sucrose Sucrose
Outcomes	Pain responses measured by: • PIPP • changes in HR • changes in oxygen saturation • changes in behavioural state • percentage of time displaying facial actions • HR variability • recovery time Primary outcome measures were taken at baseline (30 s before venipuncture); during skin cleansing; needle stick and blood harvesting; compression after needle removal; and rest (up to 5 min after the end of the procedure)
Starting date	March 2007
Contact information	Ms Ananda Fernandes, Praceta Falcão Resende 1 R/Ch Coimbra 3000-164 Portugal +351 (0)917 500 541 Email: amfernandes@esenfc.pt
Notes	ISRCTN73259137

Montanholi 2012

Trial name or title	Effect of skin-to-skin compared to sucrose for pain relief in infants undergoing repeated painful procedures: randomised clinical trial
Methods	RCT
Participants	Newborns 4 to 12 h old with PMA ≥ 36 weeks
Interventions	The therapeutic intervention is skin-to-skin contact and the control interventions is 25% sucrose
Outcomes	NFCS
Starting date	June 2013
Contact information	Liciane Langona Montanholi Av. Bandeirantes, 3900, City: Ribeirão Preto/Brazil Zip Code: 14040-902 Telephone: +55 16 3602 3411 Email: licianelm@gmail.com Affiliation: Escola de Enfermagem de Ribeirão Preto- Universidade de São Paulo
Notes	RBR-7nynr7

NCT01190995

Trial name or title	Role of repeated painful procedures in preterm neonates on short term neuro behavioural outcome
Methods	RCT
Participants	Infants up to 28 days of age
Interventions	24% sucrose Placebo
Outcomes	Short-term neurobehavioral status at enrolment in the study and at 40 weeks post-conceptional age using the NAPI scale
Starting date	July 2010
Contact information	Vikram Datta, MD., Lady Hardinge Medical College, New Delhi, Delhi1, India, 110001 Email: drvikramdatta@gmail.com
Notes	ClinicalTrials.gov Identifier: NCT01190995

NCT01438008

Trial name or title	Pilot study of sucrose to reduce pain in sick babies
Methods	RCT

NCT01438008 *(Continued)*

Participants	Infants who are inpatients of the NICU: • who are receiving a continuous intravenous infusion of an opioid analgesic such as morphine or fentanyl at a maximum dose equivalent to 20 µg/kg/h of morphine following either abdominal (gastrointestinal or renal) or thoracic surgery and; • who require heel lance for medically required blood sampling, and; • who are eligible to receive sucrose as per the hospital's sucrose policy for infants.
Interventions	24% sucrose solution
Outcomes	PIPP; total crying time: skin conductance activity
Starting date	May 2012
Contact information	Denise Harrison, Children's Hospital of Eastern Ontario
Notes	ClinicalTrials.gov Identifier NCT01438008

NCT01552993

Trial name or title	Registration and treatment of pain during eye examination of prematurity
Methods	RCT
Participants	Ages eligible for study: 31 to 37 weeks
Interventions	Paracetamol mixture 20 mg/kg + pacifier + glucose Pacifier + sucrose
Outcomes	Pain - time frame 5 minutes using PIPP
Starting date	March 2012
Contact information	Hakon Bergseng, PhD Email: hakon.bergseng@stolav.no
Notes	ClinicalTrials.gov Identifier: NCT01552993

NCT01742520

Trial name or title	Neurodevelopmental outcomes of preterm infants treated for pain management with repeated doses of sucrose 24%
Methods	RCT
Participants	Preterm infants born 27-33 weeks PMA
Interventions	Breast milk or formula prior to every painful procedure Multiple doses of sucrose 1-3 min prior to every invasive procedure

NCT01742520 *(Continued)*

Outcomes	Primary outcome measures: neurodevelopmental outcomes at 6 month corrected age; Griffith mental developmental scale (gross and fine motor, language, performance, social) and general movements by Prechtel Secondary outcome measures: neurodevelopment at 15 weeks corrected age; Griffith mental developmental scaled (gross and fine motor, language, performance, social) and general movements by Prechtel
Starting date	January 2013
Contact information	Dr Iris Morag, Sheba Medical Center Email: irismorag@gmail.com
Notes	ClinicalTrials.gov Identifier: NCT01742520

NCT01800318

Trial name or title	Does noninvasive electrical stimulation of acupuncture points (NESAP) reduce heel stick pain in infants?
Methods	RCT
Participants	Infants up to 3 days of age
Interventions	Sham NESAP with 24% oral sucrose NESAP with oral water NESAP with 24% oral sucrose Sham NESAP with oral water
Outcomes	Changes from baseline PIPP; change in salivary cortisol after heel stick; change in HR variability during heel stick; change in HR; change in oxygen saturation; duration of crying after TENS unit initiated; duration of crying during heel stick
Starting date	March 2013
Contact information	Richard W Hall MD University of Arkansas
Notes	ClinicalTrials.gov Identifier: NCT01800318

NCT01894659

Trial name or title	Oral sucrose versus glucose for procedural pain in premature neonates
Methods	RCT
Participants	Preterm neonates ≤ 34 weeks PMA and ≤ 7 days of age postnatally
Interventions	Oral sucrose versus glucose for procedural pain in premature neonates
Outcomes	Urinary markers of ATP utilization, oxidative stress and cell injury

NCT01894659 *(Continued)*

Starting date	February 2014
Contact information	Danilyn Angeles, PhD, Loma Linda University, 909-558-7563; Email: dangeles@ll.edu
Notes	ClinicalTrials.gov Identifier: NCT01894659

NCT01931020

Trial name or title	Analgesic effect of oral 25% glucose versus oral 24% sucrose for pain relief during heel lance in preterm neonates
Methods	RCT
Participants	Infants at 34 to 37 weeks PMA
Interventions	Sucrose 1 mL of 24% sucrose administered prior to heel lance vs. 1 mL of 25% glucose administered prior to heel lance
Outcomes	Painful response:PIPP 30 s after heel lance Duration of crying Within 2 min following the procedure
Starting date	July 2013
Contact information	Vikram Datta, MD., Lady Hardinge Medical College, New Delhi, Delhi1, India, 110001; Email: drvikramdatta@gmail.com
Notes	ClinicalTrials.gov Identifier: NCT01931020

NCT02133716

Trial name or title	Efficacy of breast milk expressed and sucrose in procedural pain in preterm (LACTEET)
Methods	RCT
Participants	Preterm infants (PMA 25 to 37 weeks and body weight < 2500 g)
Interventions	Expressed breast milk vs. oral 24% sucrose
Outcomes	PIPP; percentage of crying
Starting date	October 2013
Contact information	Laura Collados Gómez, Hospital University Gregorio Marañon, Madrid, Spain, 28007
Notes	ClinicalTrials.gov Identifier: NCT02133716

NCT02344368

Trial name or title	The effect of sucrose on pain relief during venous blood sampling in preterm infants
Methods	RCT
Participants	Preterm infants weighing > 1000 g
Interventions	The aim of this study is to find the minimal effective dose of 25% sucrose to reduce pain during a single venous blood sampling procedure: 0.2 mL or 0.5 mL
Outcomes	Pain assessed by PIPP-R. Pain score related to the blood sampling will be performed twice: at skin puncture and immediately after the needle has been removed
Starting date	January 2015
Contact information	Contact: Laila Kristoffersen (Email: laila.kristoffersen@ntnu.no); Contact: Håkon Bergseng, MD PhD (Email: hakon.bergseng@ntnu.no); St Olavs hospital, Trondheim, Norway
Notes	NCT02344368

Passariello 2014

Trial name or title	Efficacy of oral sucrose in newborns exposed to painful stimuli
Methods	RCT
Participants	All infants (< 1 month of age) admitted to the Unit of Neonatal Intensive Care of Monaldi Hospital, Naples, Italy.
Interventions	24% sucrose oral solution administered during capillary and arterial blood sample taking, directly by a disposable plastic vial at dosage of 1.5 mL for newborns with a birthweight > 3 kg and 1 mL for newborns with a birthweight < 3 kg Sterile water administered directly by a disposable plastic vial during capillary and arterial blood sample taking
Outcomes	Skin conductance algesimeter was used to monitor pain. Skin conductance activity was measured for 3 min before, during, and for 3 min after the intervention
Starting date	June 2013
Contact information	Dr Annalisa Passariello Address Via S. Pansini 5-80100-Naples. University of Naples “Federico II”. Italy Phone +39 3395077349 Email: annalisa_passariello@libero.it
Notes	ACTRN12614000164695

Philip 2012

Trial name or title	Effectiveness of human breast milk, table sugar vs sterile water for pain relief in premature infants undergoing a heel prick procedure in nursery of Christian Medical College and Hospital, Vellore

Philip 2012 *(Continued)*

Methods	RCT
Participants	Haemodynamically stable preterm (28 to 36 weeks PMA) infants, aged 0 to 28 days, who tolerate feeds, and are admitted to the nursery and undergo heel-prick procedure
Interventions	24% sucrose (0.6 mL/kg body weight) to be given orally over 15 s (single dose) Expressed breast milk (0.6 mL/kg body weight) Placebo (sterile water 0.6 mL/kg body weight)
Outcomes	Preintervention PIPP score (infant at rest) and postintervention pain at 0, 2, and 5 min using PIPP scale
Starting date	June 2012
Contact information	Ms Sophia Philip, College of Nursing, Christian Medical College, Vellore, Tamil Nadu 632004 India. Phone: 9894143708. Email: sopiantony@gmail.com
Notes	CTRI/2012/06/002730

Roue 2013

Trial name or title	Prevention of the procedural pain in the newborn (ACTISUCROSE)
Methods	RCT
Participants	Newborns with PMA of 37 to 42 weeks
Interventions	20% saccharose Breastfeeding
Outcomes	Increase of the total concentration of haemoglobin (delta HbT) measured by the spectrometer during the intravenous injection
Starting date	June 2013
Contact information	Jean-Michel Roue, University Hospital, Brest, France
Notes	NCT02109263

Shah 2015

Trial name or title	Comparing efficacy of music therapy, sucrose and combination of the two in neonates for pain relief during heel prick procedure
Methods	RCT. This is a cross-over study with each neonate getting all 3 interventions in random order. There will be a minimum of 40 minutes of 'wash-out' period between interventions

Shah 2015 *(Continued)*

Participants	Newborns ≥ 32 weeks, stable clinical condition with no need of CPAP/high flow/ventilation; age 0 h to 28 days
Interventions	Music therapy Oral 24% sucrose 0.5 mL with no music Oral 24% sucrose with music therapy
Outcomes	PIPP score, HR stability, saturation stability
Starting date	Anticipated date of first participant enrolment 1 June 2015
Contact information	Dr Swapnil Shah, Department of Neonatology, Royal North Shore Hospital, Reserve Road, St Leonards NSW 2065, Australia. Phone: +61 2 9463 2141 Fax: +61 2 9463 2004 Email: swapnilshah12@yahoo.co.in
Notes	

Stevens 2014

Trial name or title	Sucrose practices for pain in neonates
Methods	RCT
Participants	Newborns up to 2 weeks of age. Infants 24 to 42 weeks PMA at birth, admitted to the NICU, and scheduled to receive a heel lance
Interventions	0.1 mL 24% sucrose concurrent opioids 0.5 mL 24% sucrose concurrent opioids 1.0 mL 24% sucrose concurrent opioids 0.1 mL 24% sucrose no opioids 0.5 mL 24% sucrose no opioids 1.0 mL 24% sucrose no opioids
Outcomes	The primary outcome is pain intensity measured using the PIPP-R to assess change from baseline to 30 s post painful procedure
Starting date	July 2013
Contact information	Bonnie Stevens, RN, PhD Email: bonnie.stevens@sickkids.ca
Notes	ClinicalTrials.gov Identifier: NCT02134873

Abbreviations
ATP = adenosine triphosphate
CPAP = continuous positive airway pressure
PMA = post menstrual age
HR = heart rate
min = minute(s)
NAPI = Neurobehavioural Assessment of Preterm Infants

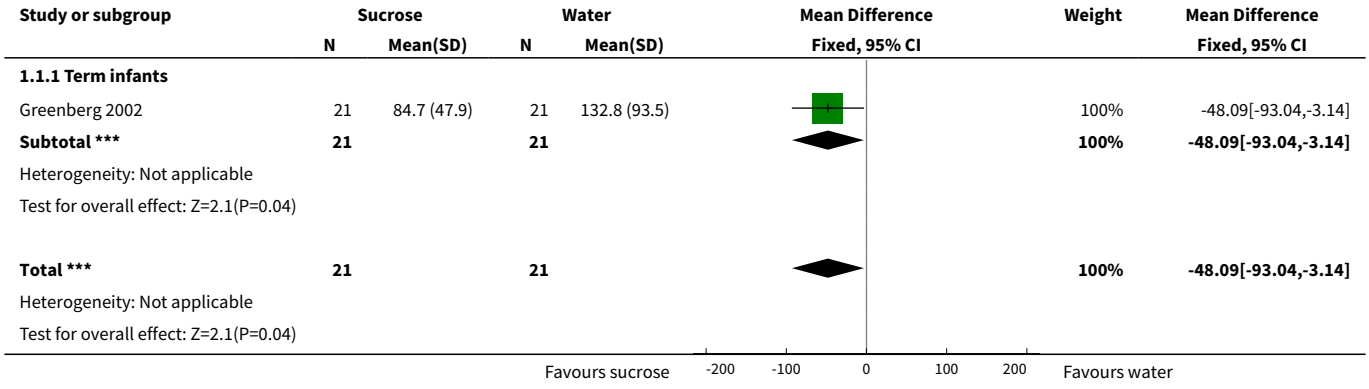
NESAP = Non−invasive Electrical Stimulation of Acupuncture Points
NFCS = Neonatal Facial Coding System
NICU = neonatal intensive care unit
PIPP = Premature Infant Pain Profile
PIPP-R = Premature Infant Pain Profile-Revised
PMA = postmenstrual age
PNA = postnatal age
RCT = randomised controlled trial
TENS = transcutaneous electrical nerve stimulation

DATA AND ANALYSES

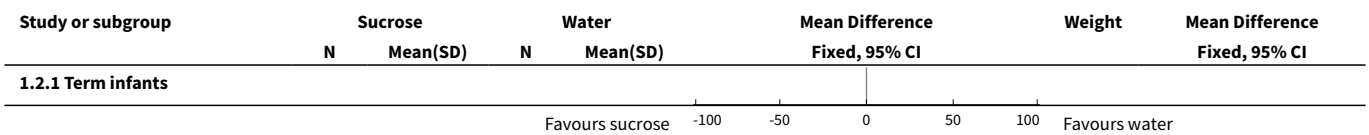
Comparison 1. Heel lance (term infants): sucrose (12% to 12.5%) versus water/routine care

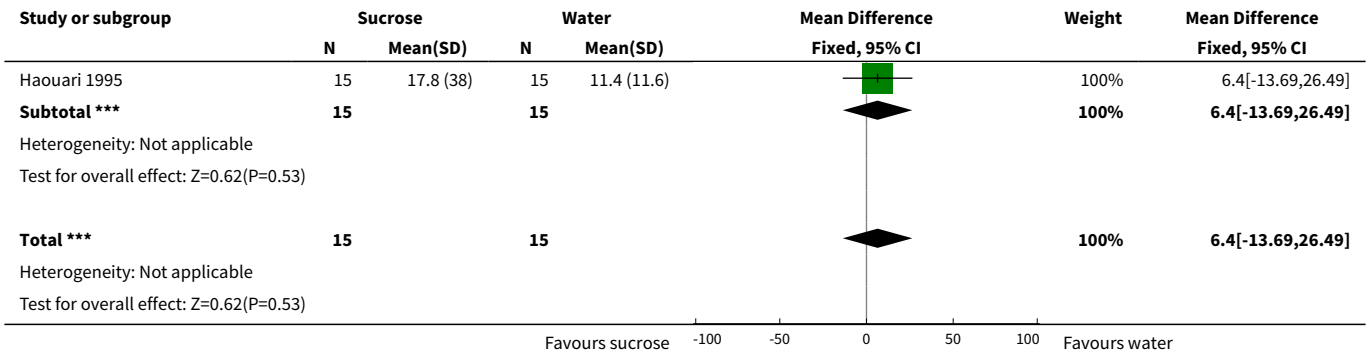
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total crying time (s)	1	42	Mean Difference (IV, Fixed, 95% CI)	-48.09 [-93.04, -3.14]
1.1 Term infants	1	42	Mean Difference (IV, Fixed, 95% CI)	-48.09 [-93.04, -3.14]
2 Percentage change in heart rate 1 min after heel lance	1	30	Mean Difference (IV, Fixed, 95% CI)	6.4 [-13.69, 26.49]
2.1 Term infants	1	30	Mean Difference (IV, Fixed, 95% CI)	6.4 [-13.69, 26.49]

Analysis 1.1. Comparison 1 Heel lance (term infants): sucrose (12% to 12.5%) versus water/routine care, Outcome 1 Total crying time (s).



Analysis 1.2. Comparison 1 Heel lance (term infants): sucrose (12% to 12.5%) versus water/routine care, Outcome 2 Percentage change in heart rate 1 min after heel lance.



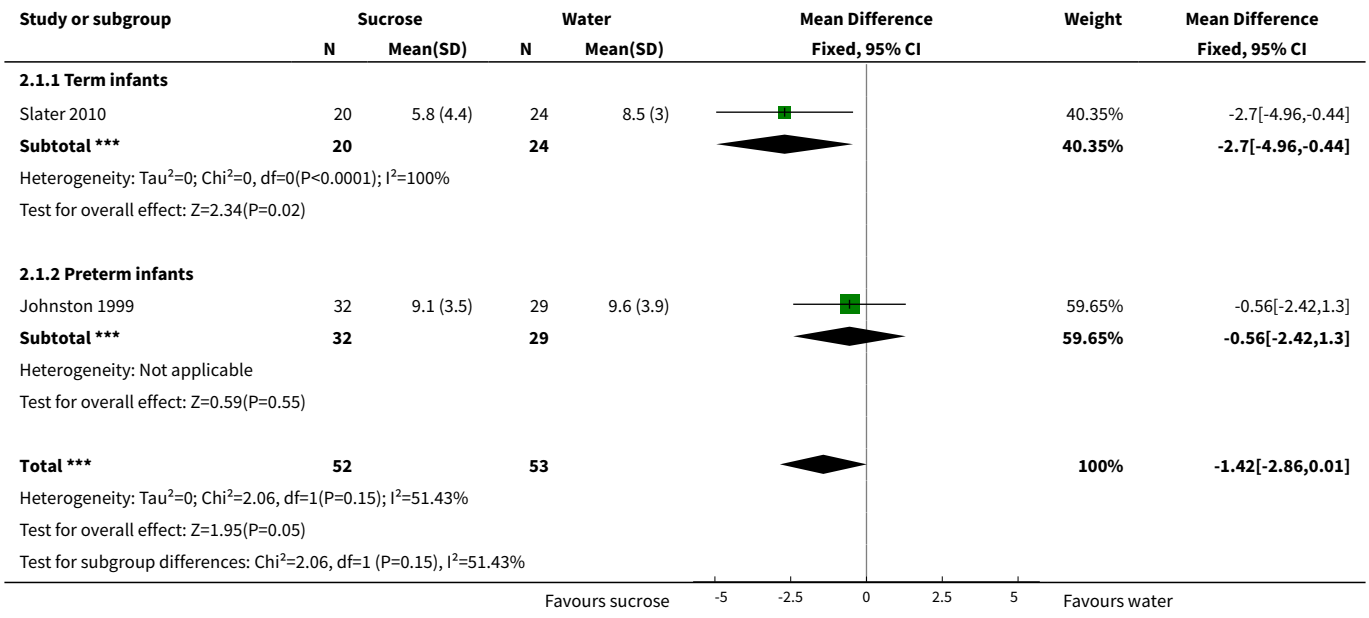


Comparison 2. Heel lance: sucrose (20% to 33%) versus water

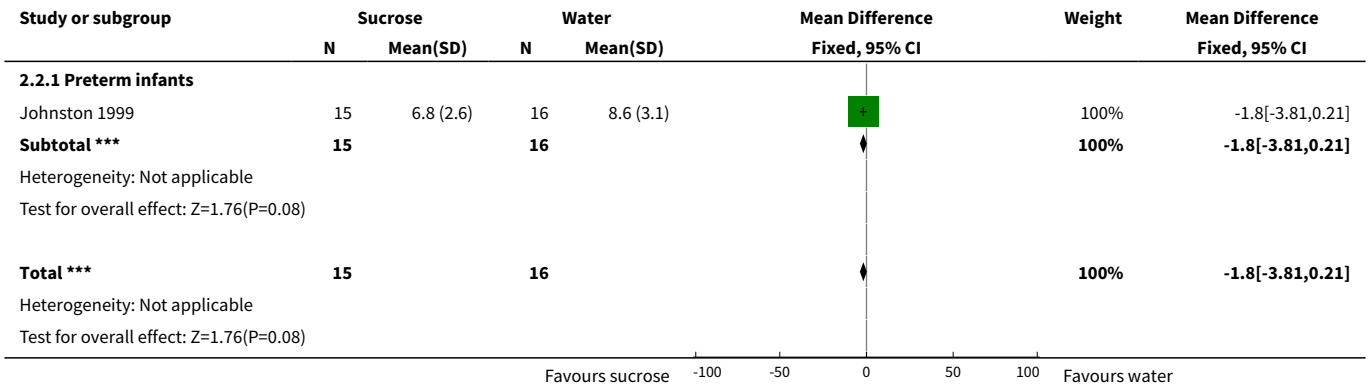
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PIPP at 30 s after heel lance	2	105	Mean Difference (IV, Fixed, 95% CI)	-1.42 [-2.86, 0.01]
1.1 Term infants	1	44	Mean Difference (IV, Fixed, 95% CI)	-2.70 [-4.96, -0.44]
1.2 Preterm infants	1	61	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-2.42, 1.30]
2 PIPP at 60 s after heel lance	1	31	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-3.81, 0.21]
2.1 Preterm infants	1	31	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-3.81, 0.21]
3 PIPP score during heel lance (1st heel lance)	1	107	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.52, 1.52]
3.1 Newborns of diabetic mothers	1	107	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.52, 1.52]
4 DAN score at 30 s after heel lance	1	32	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-8.58, 4.78]
4.1 Term infants	1	32	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-8.58, 4.78]
5 NIPS during heel lance	1	56	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-2.42, -1.58]
5.1 Term infants	1	56	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-2.42, -1.58]
6 Duration of first cry (s)	2	142	Mean Difference (IV, Fixed, 95% CI)	-8.63 [-19.88, 2.61]
6.1 Term infants	1	32	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-17.40, 7.40]
6.2 Preterm infants	1	110	Mean Difference (IV, Fixed, 95% CI)	-25.41 [-52.06, 1.24]
7 Total crying time	2	88	Mean Difference (IV, Fixed, 95% CI)	-22.11 [-32.52, -11.70]
7.1 Term infants	2	88	Mean Difference (IV, Fixed, 95% CI)	-22.11 [-32.52, -11.70]
8 Heart rate (beats/min) during heel lance	2	96	Mean Difference (IV, Fixed, 95% CI)	-0.81 [-8.57, 6.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Term infants	2	96	Mean Difference (IV, Fixed, 95% CI)	-0.81 [-8.57, 6.94]
9 Percentage change in heart rate 1 min after heel lance	2	86	Mean Difference (IV, Fixed, 95% CI)	0.90 [-5.81, 7.61]
9.1 Term infants	2	86	Mean Difference (IV, Fixed, 95% CI)	0.90 [-5.81, 7.61]
10 Respiratory rate (breaths/min) during heel lance	1	56	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-7.64, 5.64]
10.1 Term infants	1	56	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-7.64, 5.64]
11 Oxygen saturation (%) during heel lance	1	56	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-12.79, 2.79]
11.1 Term infants	1	56	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-12.79, 2.79]
12 Skin blood flow during heel lance (perfusion units (PU))	1	56	Mean Difference (IV, Fixed, 95% CI)	-32.0 [-68.87, 4.87]
12.1 Term infants	1	56	Mean Difference (IV, Fixed, 95% CI)	-32.0 [-68.87, 4.87]
13 Nociceptive-specific brain activity (mean weight)	1	44	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.05, 0.09]
13.1 Term infants	1	44	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.05, 0.09]

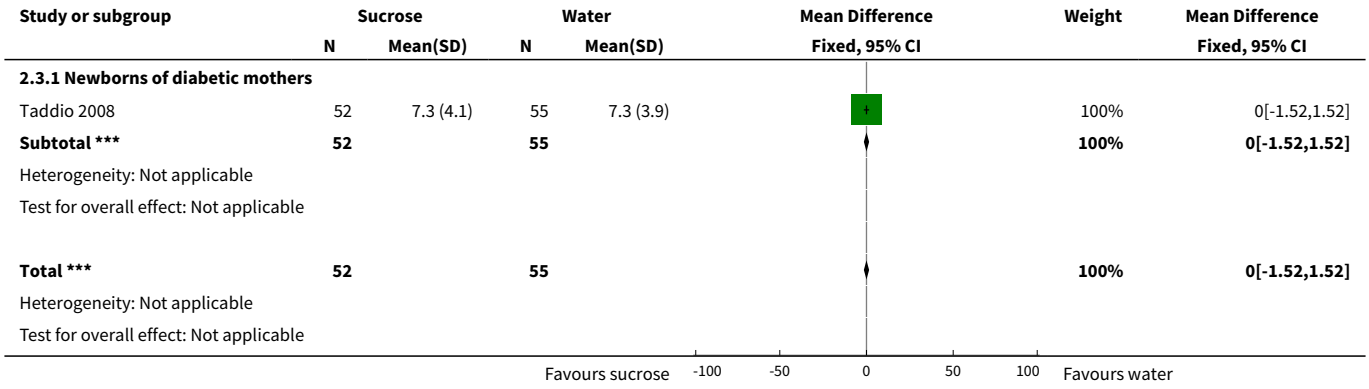
Analysis 2.1. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 1 PIPP at 30 s after heel lance.



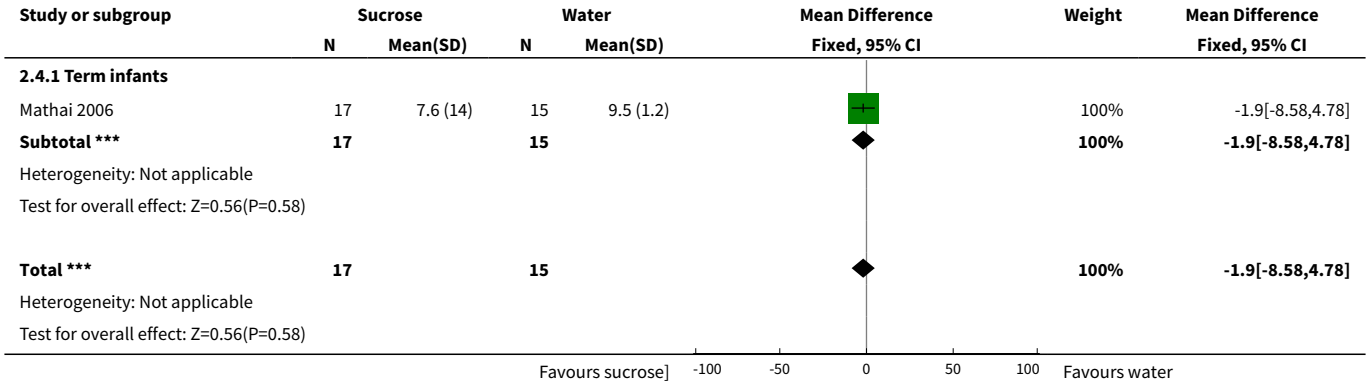
Analysis 2.2. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 2 PIPP at 60 s after heel lance.



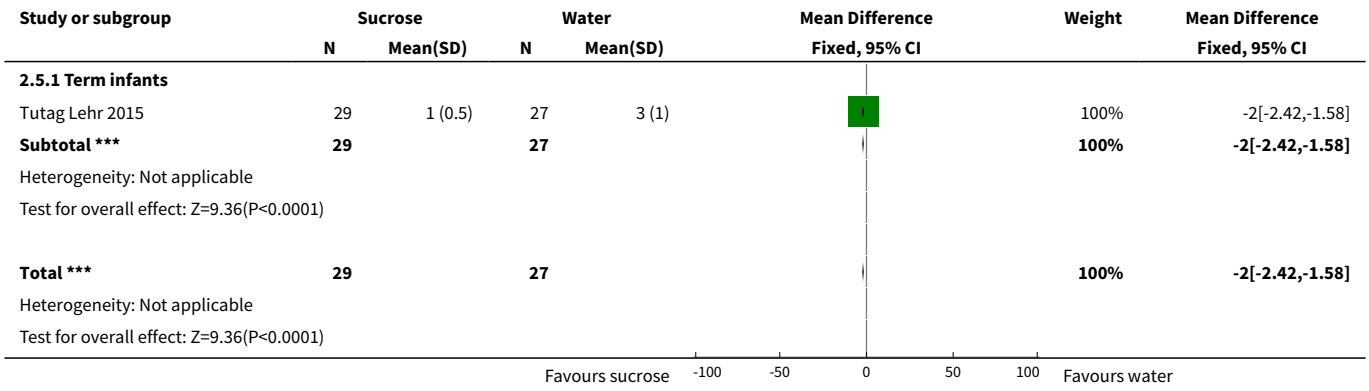
Analysis 2.3. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 3 PIPP score during heel lance (1st heel lance).



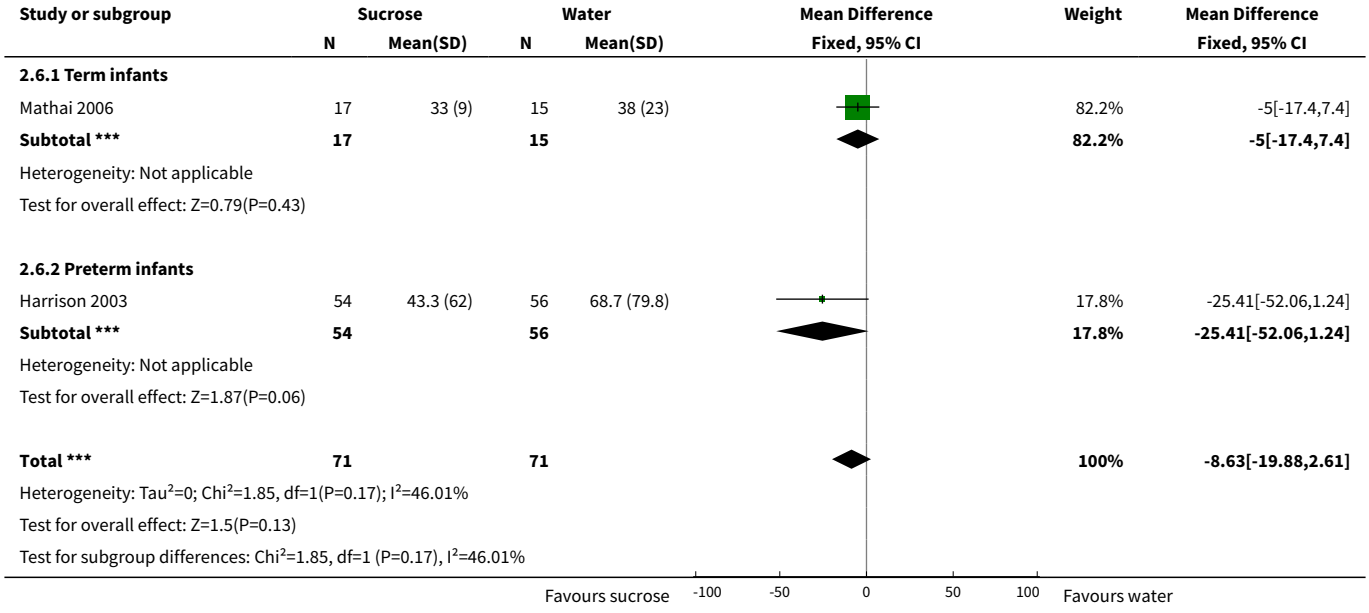
Analysis 2.4. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 4 DAN score at 30 s after heel lance.



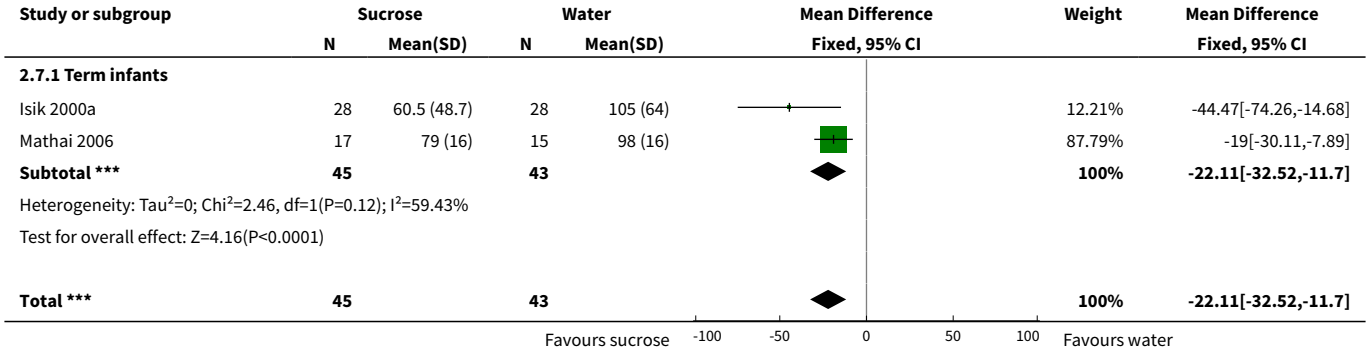
Analysis 2.5. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 5 NIPS during heel lance.

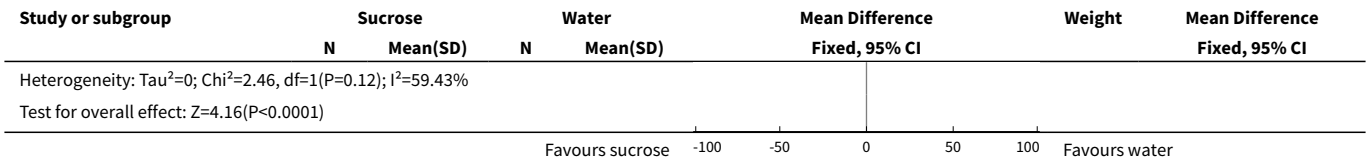


Analysis 2.6. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 6 Duration of first cry (s).

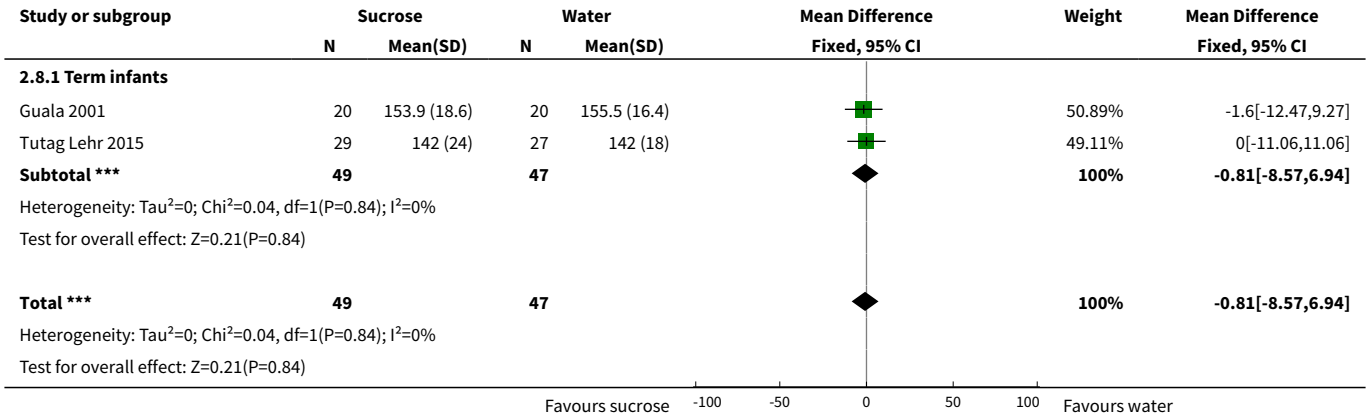


Analysis 2.7. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 7 Total crying time.

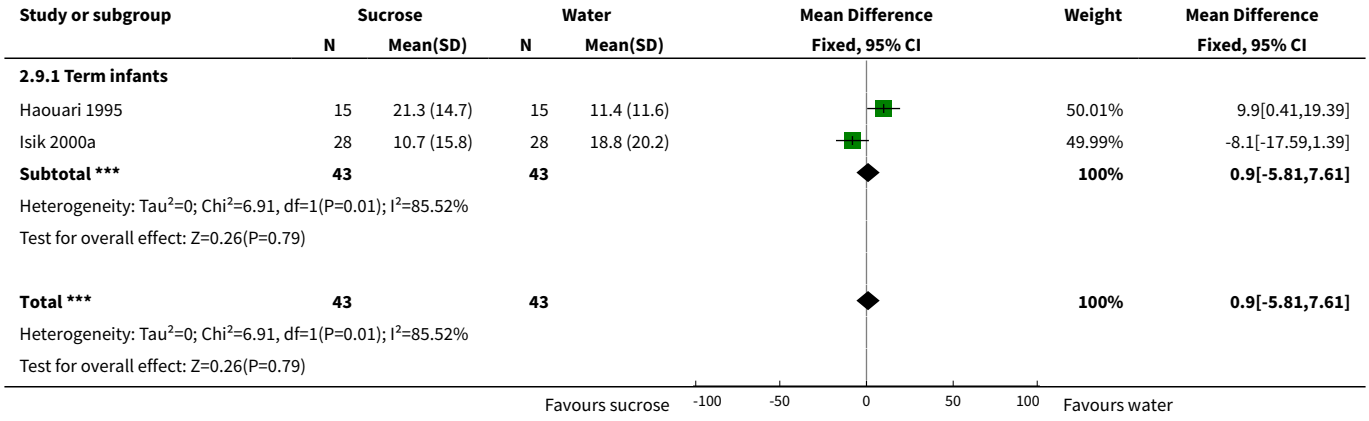




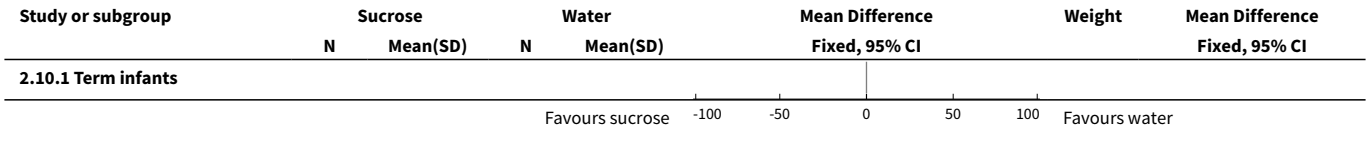
Analysis 2.8. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 8 Heart rate (beats/min) during heel lance.

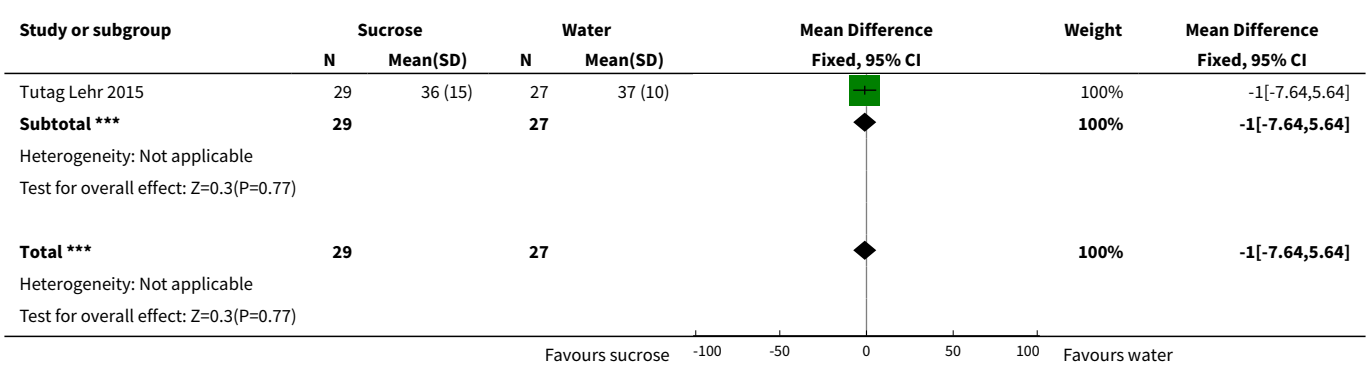


Analysis 2.9. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 9 Percentage change in heart rate 1 min after heel lance.

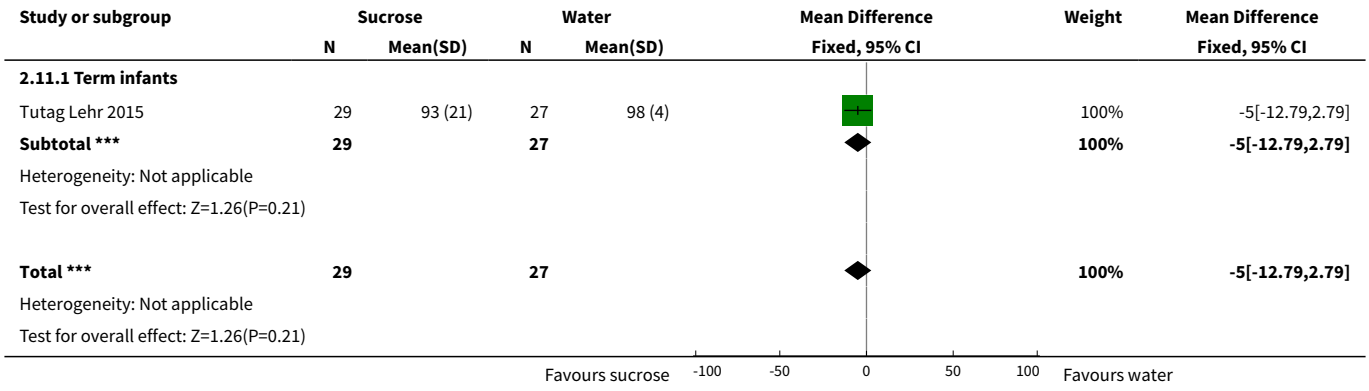


Analysis 2.10. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 10 Respiratory rate (breaths/min) during heel lance.

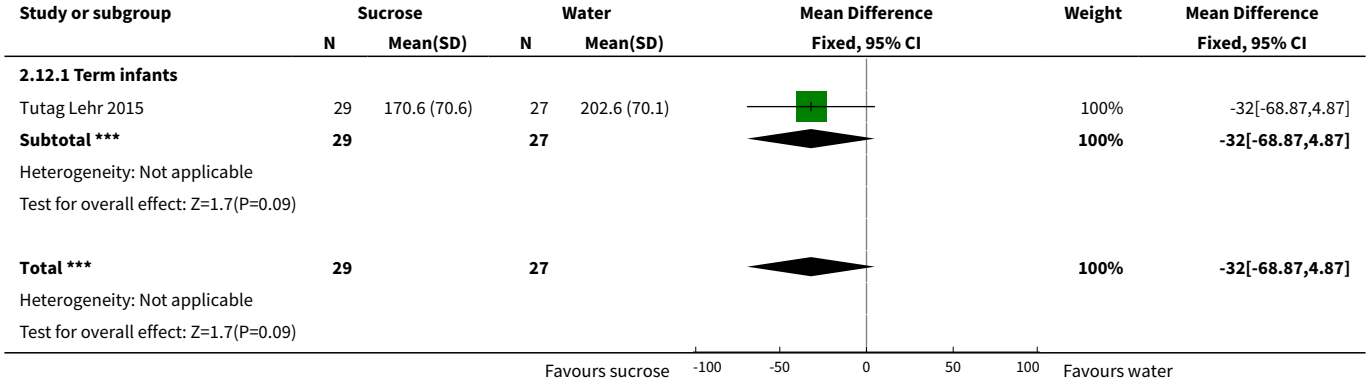




Analysis 2.11. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 11 Oxygen saturation (%) during heel lance.

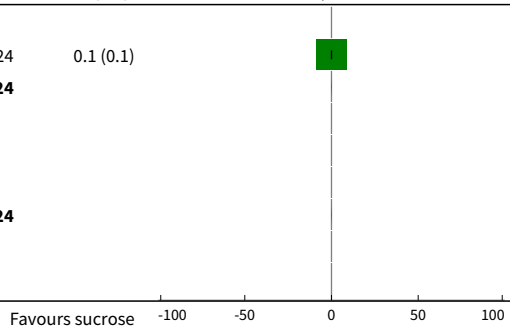


Analysis 2.12. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 12 Skin blood flow during heel lance (perfusion units (PU)).



Analysis 2.13. Comparison 2 Heel lance: sucrose (20% to 33%) versus water, Outcome 13 Nociceptive-specific brain activity (mean weight).

Study or subgroup	Sucrose N	Sucrose Mean(SD)	Water N	Water Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.13.1 Term infants							
Slater 2010	20	0.1 (0.1)	24	0.1 (0.1)		100%	0.02[-0.05,0.09]
Subtotal ***	**20**		**24**			**100%**	**0.02[-0.05,0.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.58(P=0.56)							
Total ***	**20**		**24**			**100%**	**0.02[-0.05,0.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.58(P=0.56)							

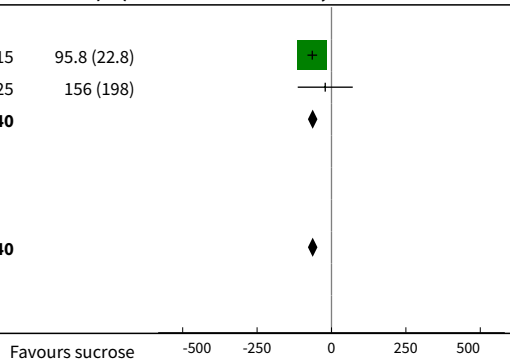


Comparison 3. Heel lance: sucrose (50%) versus water

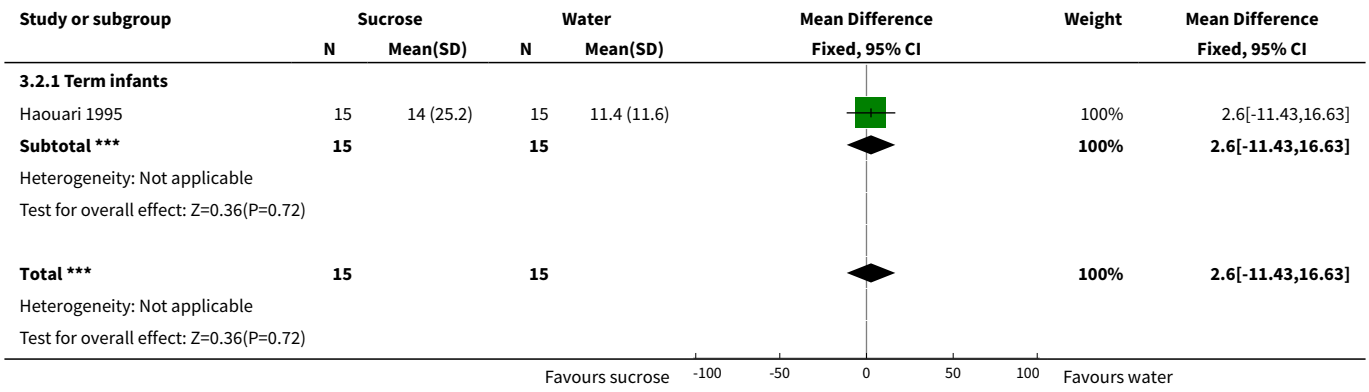
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of first cry (s)	2	80	Mean Difference (IV, Fixed, 95% CI)	-63.20 [-79.20, -47.19]
1.1 Term infants	2	80	Mean Difference (IV, Fixed, 95% CI)	-63.20 [-79.20, -47.19]
2 Percentage change in heart rate 1 min after heel lance	1	30	Mean Difference (IV, Fixed, 95% CI)	2.60 [-11.43, 16.63]
2.1 Term infants	1	30	Mean Difference (IV, Fixed, 95% CI)	2.60 [-11.43, 16.63]

Analysis 3.1. Comparison 3 Heel lance: sucrose (50%) versus water, Outcome 1 Duration of first cry (s).

Study or subgroup	Sucrose N	Sucrose Mean(SD)	Water N	Water Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.1.1 Term infants							
Haouari 1995	15	31.3 (22.6)	15	95.8 (22.8)		97%	-64.5[-80.75,-48.25]
Ogawa 2005	25	135 (128)	25	156 (198)		3%	-21[-113.42,71.42]
Subtotal ***	**40**		**40**			**100%**	**-63.2[-79.2,-47.19]**
Heterogeneity: Tau^2=0; Chi^2=0.83, df=1(P=0.36); I^2=0%							
Test for overall effect: Z=7.74(P<0.0001)							
Total ***	**40**		**40**			**100%**	**-63.2[-79.2,-47.19]**
Heterogeneity: Tau^2=0; Chi^2=0.83, df=1(P=0.36); I^2=0%							
Test for overall effect: Z=7.74(P<0.0001)							



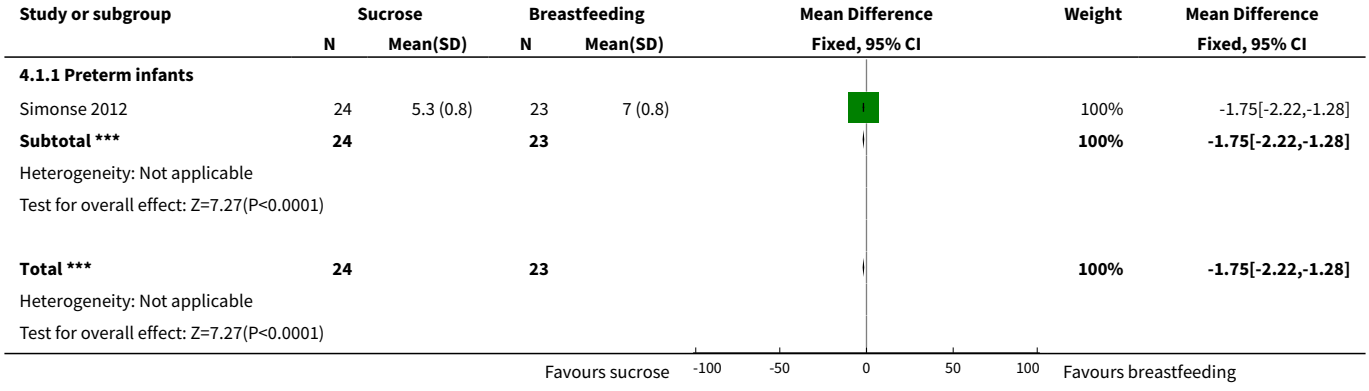
Analysis 3.2. Comparison 3 Heel lance: sucrose (50%) versus water, Outcome 2 Percentage change in heart rate 1 min after heel lance.



Comparison 4. Heel lance: sucrose (24%) versus breastfeeding

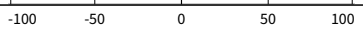
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 PIPP	1	47	Mean Difference (IV, Fixed, 95% CI)	-1.75 [-2.22, -1.28]
1.1 Preterm infants	1	47	Mean Difference (IV, Fixed, 95% CI)	-1.75 [-2.22, -1.28]
2 Comfort score	1	47	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-3.06, -2.14]
2.1 Preterm infants	1	47	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-3.06, -2.14]

Analysis 4.1. Comparison 4 Heel lance: sucrose (24%) versus breastfeeding, Outcome 1 PIPP.



Analysis 4.2. Comparison 4 Heel lance: sucrose (24%) versus breastfeeding, Outcome 2 Comfort score.

Study or subgroup	Sucrose N	Sucrose Mean(SD)	Breastfeeding N	Breastfeeding Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.2.1 Preterm infants							
Simonse 2012	24	16 (0.8)	23	18.6 (0.8)		100%	-2.6[-3.06,-2.14]
Subtotal ***	**24**		**23**			**100%**	**-2.6[-3.06,-2.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=11(P<0.0001)							
Total ***	**24**		**23**			**100%**	**-2.6[-3.06,-2.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=11(P<0.0001)							

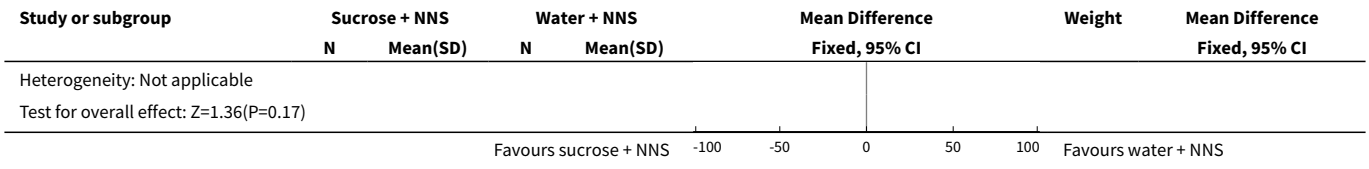


Comparison 5. Heel lance: sucrose (24%) + NNS versus water + NNS, or pacifier dipped in sucrose versus pacifier dipped in water

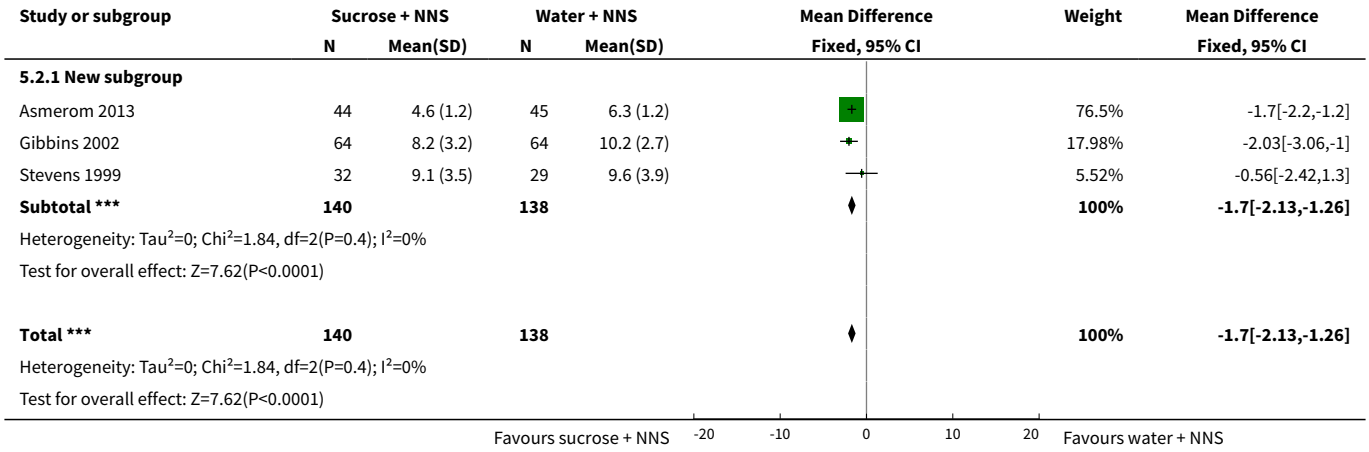
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NFCS	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.47, 0.27]
1.1 Term infants	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.47, 0.27]
2 PIPP 30 s after heel lance (mainly preterm infants)	3	278	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-2.13, -1.26]
2.1 New subgroup	3	278	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-2.13, -1.26]
3 PIPP 60 s after heel lance	2	164	Mean Difference (IV, Fixed, 95% CI)	-2.14 [-3.34, -0.94]
4 Crying time (s)	2	142	Mean Difference (IV, Fixed, 95% CI)	-1.41 [-9.87, 7.04]
4.1 Term infants	2	142	Mean Difference (IV, Fixed, 95% CI)	-1.41 [-9.87, 7.04]

Analysis 5.1. Comparison 5 Heel lance: sucrose (24%) + NNS versus water + NNS, or pacifier dipped in sucrose versus pacifier dipped in water, Outcome 1 NFCS.

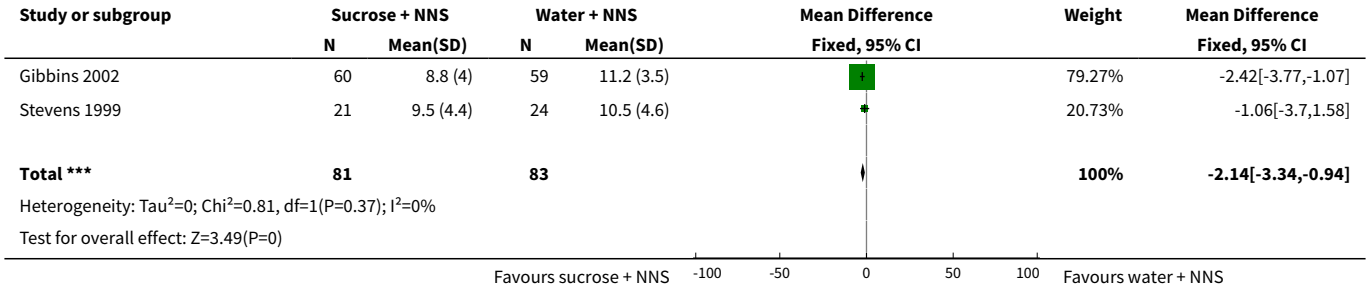
Study or subgroup	Sucrose + NNS N	Sucrose + NNS Mean(SD)	Water + NNS N	Water + NNS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.1.1 Term infants							
Unceta-Barranechea 2008	50	1.5 (2.1)	50	2.1 (2.3)		100%	-0.6[-1.47,0.27]
Subtotal ***	**50**		**50**			**100%**	**-0.6[-1.47,0.27]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.36(P=0.17)							
Total ***	**50**		**50**			**100%**	**-0.6[-1.47,0.27]**



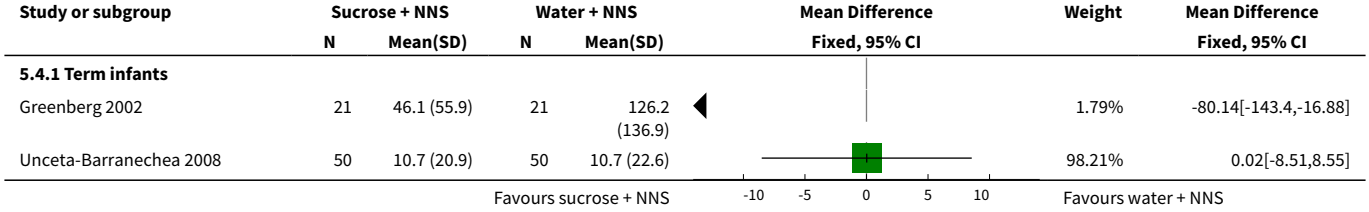
Analysis 5.2. Comparison 5 Heel lance: sucrose (24%) + NNS versus water + NNS, or pacifier dipped in sucrose versus pacifier dipped in water, Outcome 2 PIPP 30 s after heel lance (mainly preterm infants).

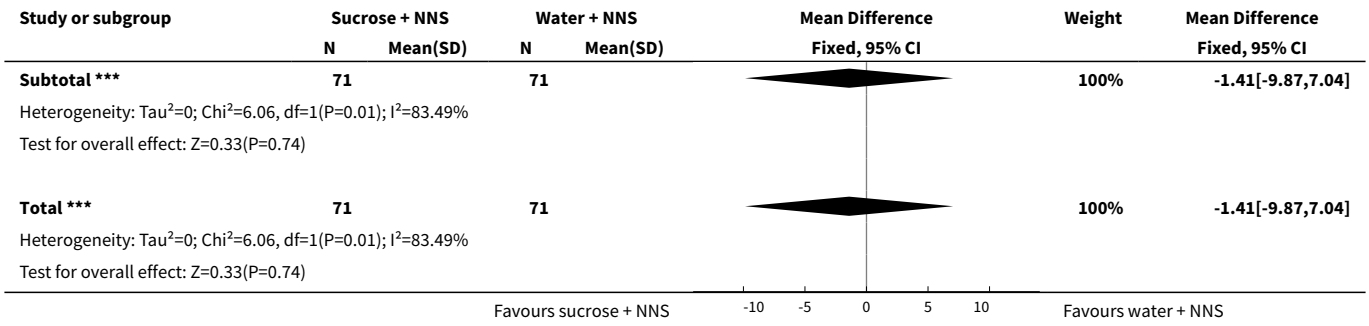


Analysis 5.3. Comparison 5 Heel lance: sucrose (24%) + NNS versus water + NNS, or pacifier dipped in sucrose versus pacifier dipped in water, Outcome 3 PIPP 60 s after heel lance.



Analysis 5.4. Comparison 5 Heel lance: sucrose (24%) + NNS versus water + NNS, or pacifier dipped in sucrose versus pacifier dipped in water, Outcome 4 Crying time (s).

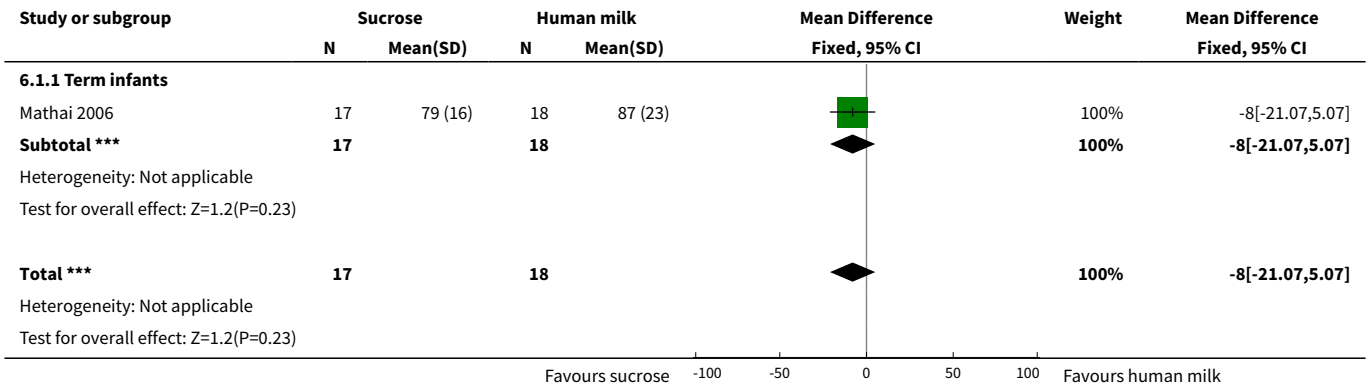




Comparison 6. Heel lance: sucrose (20%) versus human milk

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Crying time (s)	1	35	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-21.07, 5.07]
1.1 Term infants	1	35	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-21.07, 5.07]

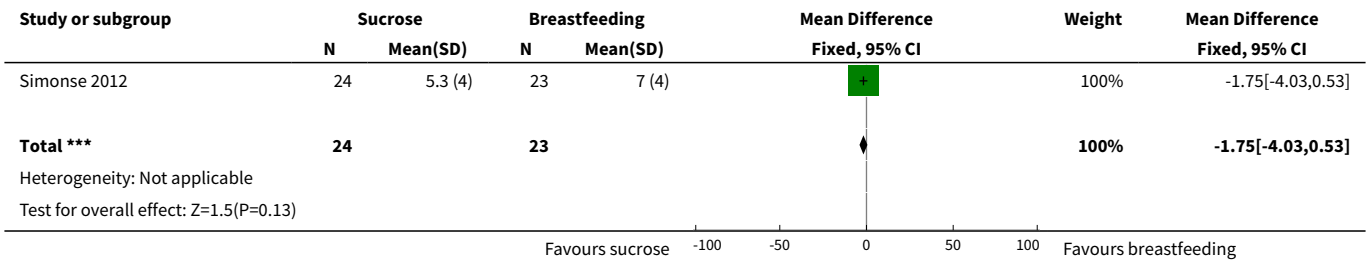
Analysis 6.1. Comparison 6 Heel lance: sucrose (20%) versus human milk, Outcome 1 Crying time (s).



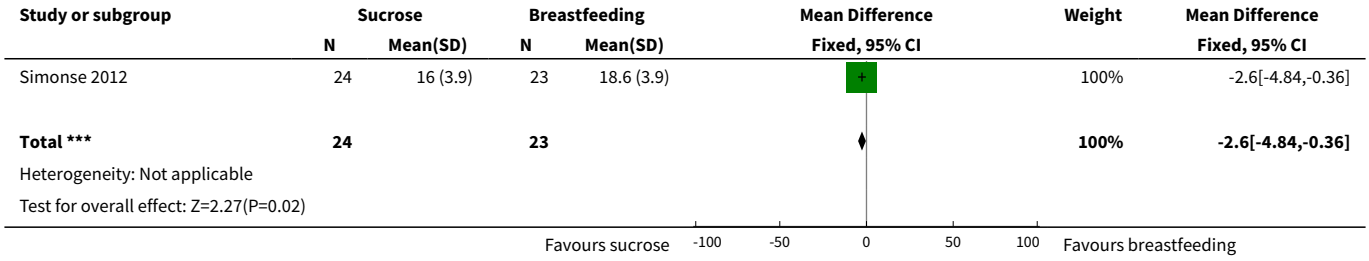
Comparison 7. Heel lance: sucrose (24%) + NNS+ NIDCAP support versus breast milk (by breastfeeding)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PIPP score	1	47	Mean Difference (IV, Fixed, 95% CI)	-1.75 [-4.03, 0.53]
2 COMFORTneo score	1	47	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-4.84, -0.36]

Analysis 7.1. Comparison 7 Heel lance: sucrose (24%) + NNS+ NIDCAP support versus breast milk (by breastfeeding), Outcome 1 PIPP score.



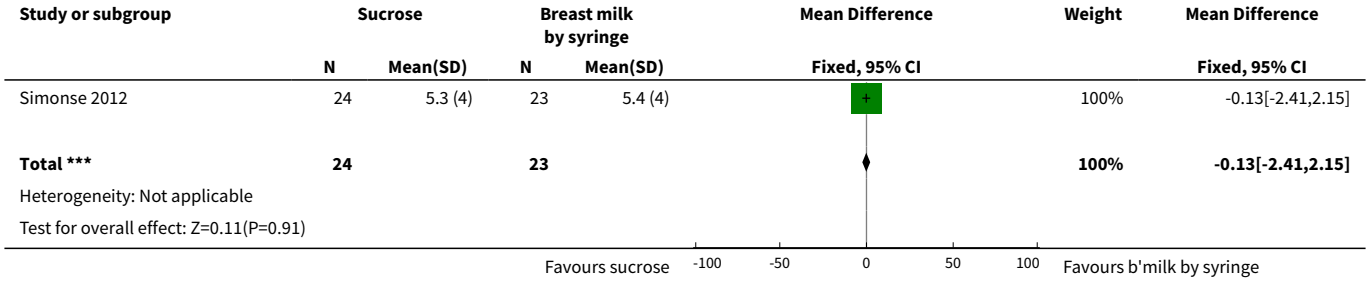
Analysis 7.2. Comparison 7 Heel lance: sucrose (24%) + NNS+ NIDCAP support versus breast milk (by breastfeeding), Outcome 2 COMFORTneo score.



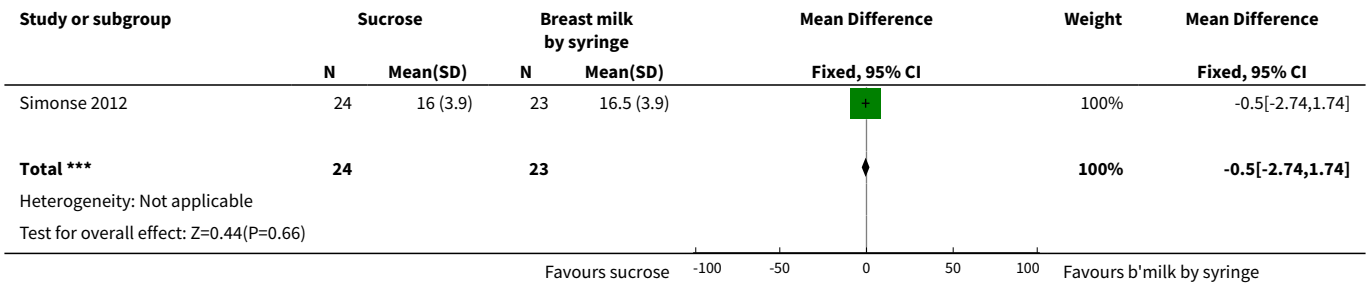
Comparison 8. Heel lance: sucrose (24%) + NNS + NIDCAP support versus breast milk (by syringe)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PIPP score	1	47	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-2.41, 2.15]
2 COMFORTneo score	1	47	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-2.74, 1.74]

Analysis 8.1. Comparison 8 Heel lance: sucrose (24%) + NNS + NIDCAP support versus breast milk (by syringe), Outcome 1 PIPP score.



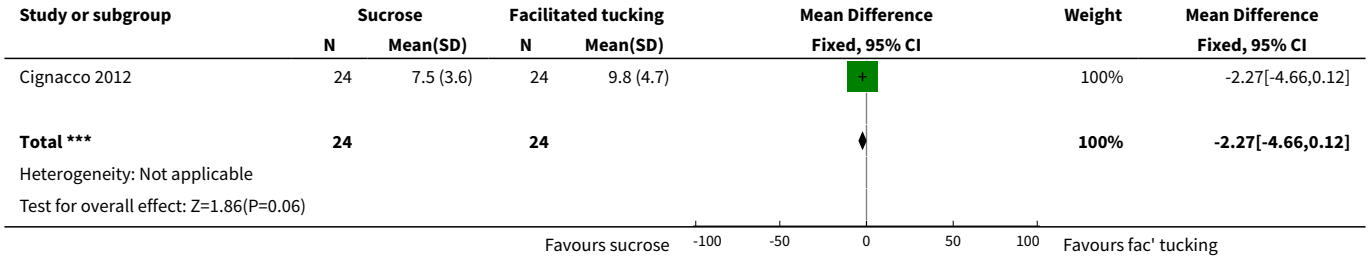
Analysis 8.2. Comparison 8 Heel lance: sucrose (24%) + NNS + NIDCAP support versus breast milk (by syringe), Outcome 2 COMFORTneo score.



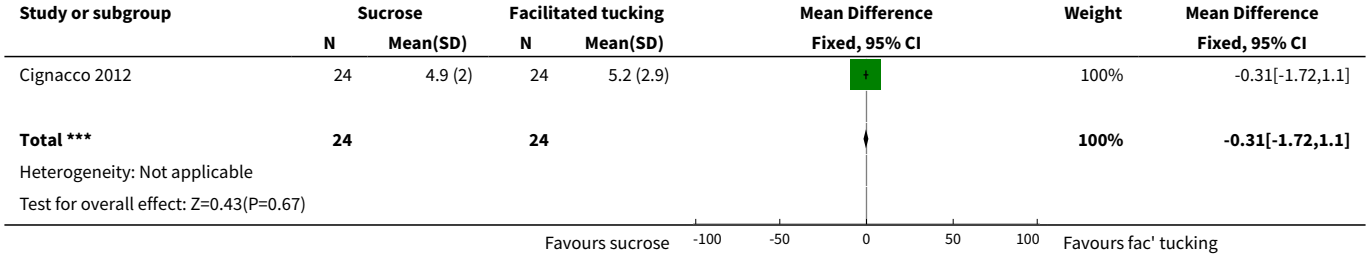
Comparison 9. Repeated heel lances: sucrose (20%) versus facilitated tucking

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total Bernese Pain Scale for Neonates during heel lance	1	48	Mean Difference (IV, Fixed, 95% CI)	-2.27 [-4.66, 0.12]
2 Total Bernese Pain Scale for Neonates during recovery	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-1.72, 1.10]

Analysis 9.1. Comparison 9 Repeated heel lances: sucrose (20%) versus facilitated tucking, Outcome 1 Total Bernese Pain Scale for Neonates during heel lance.



Analysis 9.2. Comparison 9 Repeated heel lances: sucrose (20%) versus facilitated tucking, Outcome 2 Total Bernese Pain Scale for Neonates during recovery.

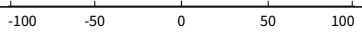


Comparison 10. Repeated heel lances: sucrose (20%) versus facilitated tucking + sucrose (20%)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total Bernese Pain Scale for Neonates during heel lance (preterm infants)	1	47	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-2.16, 2.06]
2 Total Bernese Pain Scale for Neonates during recovery (preterm infants)	1	47	Mean Difference (IV, Fixed, 95% CI)	0.64 [-0.73, 2.01]

Analysis 10.1. Comparison 10 Repeated heel lances: sucrose (20%) versus facilitated tucking + sucrose (20%), Outcome 1 Total Bernese Pain Scale for Neonates during heel lance (preterm infants).

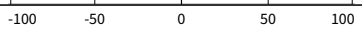
Study or subgroup	Sucrose N	Sucrose Mean(SD)	FT+ sucrose N	FT+ sucrose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cignacco 2012	24	7.5 (3.6)	23	7.5 (3.8)		100%	-0.05[-2.16,2.06]
Total ***	**24**		**23**			**100%**	**-0.05[-2.16,2.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.05(P=0.96)							



Favours sucrose — Favours FT + sucrose

Analysis 10.2. Comparison 10 Repeated heel lances: sucrose (20%) versus facilitated tucking + sucrose (20%), Outcome 2 Total Bernese Pain Scale for Neonates during recovery (preterm infants).

Study or subgroup	Sucrose N	Sucrose Mean(SD)	FT+ sucrose N	FT+ sucrose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cignacco 2012	24	4.9 (2)	23	4.2 (2.7)		100%	0.64[-0.73,2.01]
Total ***	**24**		**23**			**100%**	**0.64[-0.73,2.01]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.92(P=0.36)							



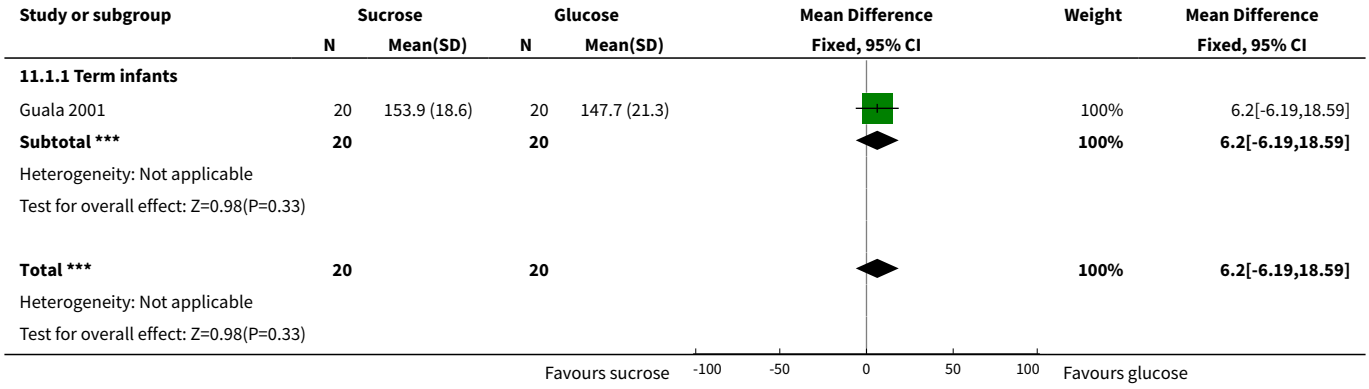
Favours sucrose — Favours FT + sucrose

Comparison 11. Heel lance: sucrose (30% to 33%) versus glucose (30% to 33%)

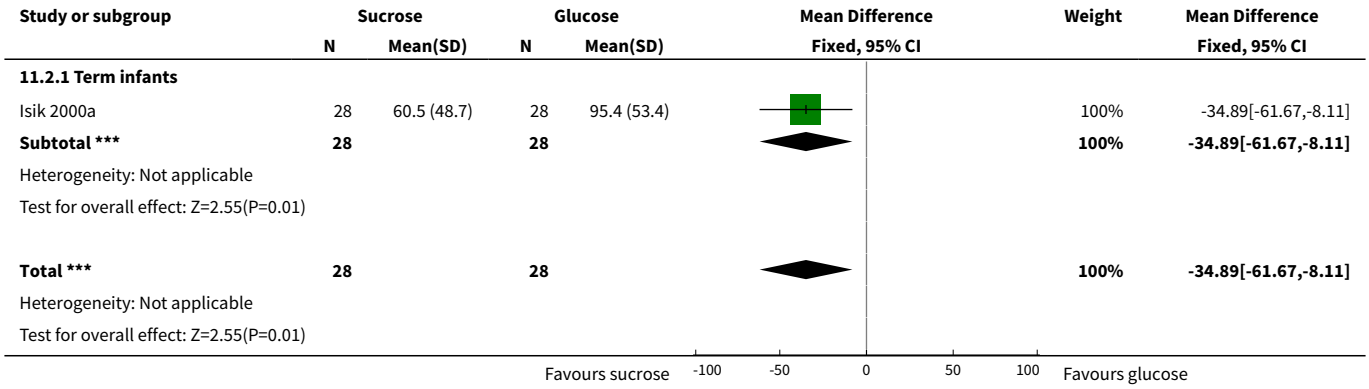
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heart rate (beats/min) during heel lance	1	40	Mean Difference (IV, Fixed, 95% CI)	6.20 [-6.19, 18.59]
1.1 Term infants	1	40	Mean Difference (IV, Fixed, 95% CI)	6.20 [-6.19, 18.59]
2 Crying time (s)	1	56	Mean Difference (IV, Fixed, 95% CI)	-34.89 [-61.67, -8.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Term infants	1	56	Mean Difference (IV, Fixed, 95% CI)	-34.89 [-61.67, -8.11]
3 Percentage change in heart rate 1 min after heel lance	1	56	Mean Difference (IV, Fixed, 95% CI)	-6.58 [-14.85, 1.69]
3.1 Term infants	1	56	Mean Difference (IV, Fixed, 95% CI)	-6.58 [-14.85, 1.69]

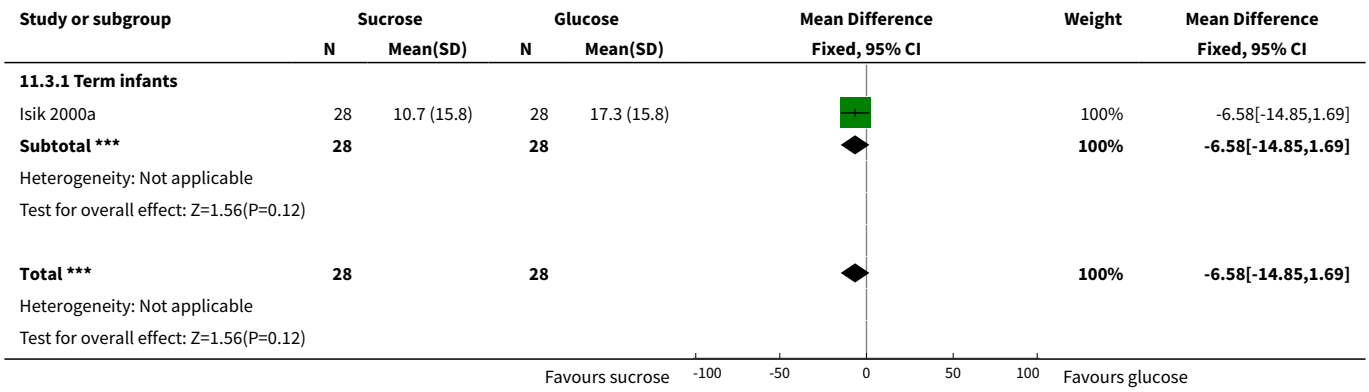
Analysis 11.1. Comparison 11 Heel lance: sucrose (30% to 33%) versus glucose (30% to 33%), Outcome 1 Heart rate (beats/min) during heel lance.



Analysis 11.2. Comparison 11 Heel lance: sucrose (30% to 33%) versus glucose (30% to 33%), Outcome 2 Crying time (s).



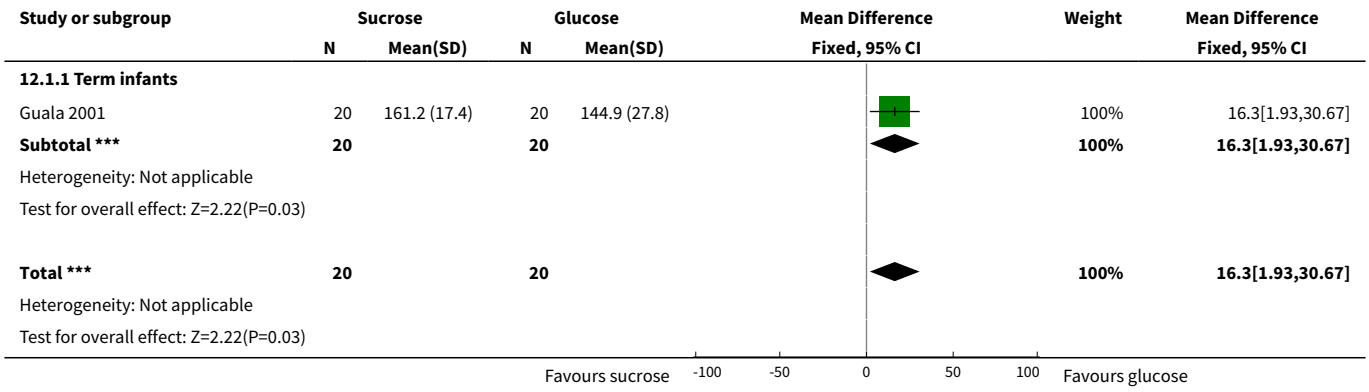
Analysis 11.3. Comparison 11 Heel lance: sucrose (30% to 33%) versus glucose (30% to 33%), Outcome 3 Percentage change in heart rate 1 min after heel lance.



Comparison 12. Heel lance: sucrose (50%) versus glucose (50%)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heart rate (beats/min) during heel lance	1	40	Mean Difference (IV, Fixed, 95% CI)	16.30 [1.93, 30.67]
1.1 Term infants	1	40	Mean Difference (IV, Fixed, 95% CI)	16.30 [1.93, 30.67]

Analysis 12.1. Comparison 12 Heel lance: sucrose (50%) versus glucose (50%), Outcome 1 Heart rate (beats/min) during heel lance.



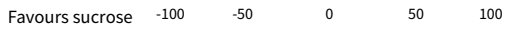
Comparison 13. Heel lance (term infants): sucrose (24%) versus laser acupuncture

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NIPS score	1	42	Mean Difference (IV, Fixed, 95% CI)	-0.86 [-1.43, -0.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Crying time (s)	1	42	Mean Difference (IV, Fixed, 95% CI)	-51.29 [-73.11, -29.47]

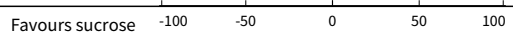
Analysis 13.1. Comparison 13 Heel lance (term infants): sucrose (24%) versus laser acupuncture, Outcome 1 NIPS score.

Study or subgroup	Sucrose N	Sucrose Mean(SD)	Laser acupuncture N	Laser acupuncture Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Abbasoglu 2015	21	3.7 (1)	21	4.5 (0.9)		100%	-0.86[-1.43,-0.29]
Total ***	**21**		**21**			**100%**	**-0.86[-1.43,-0.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.96(P=0)							



Analysis 13.2. Comparison 13 Heel lance (term infants): sucrose (24%) versus laser acupuncture, Outcome 2 Crying time (s).

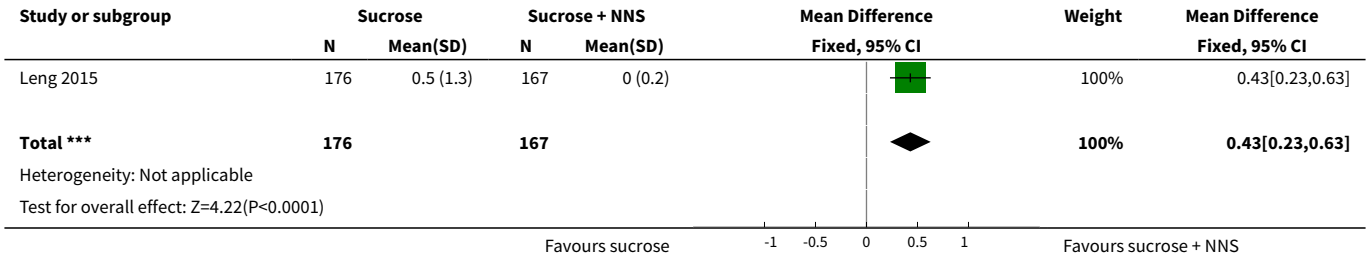
Study or subgroup	Sucrose N	Sucrose Mean(SD)	Laser acupuncture N	Laser acupuncture Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Abbasoglu 2015	21	46.7 (37.8)	21	98 (34.2)		100%	-51.29[-73.11,-29.47]
Total ***	**21**		**21**			**100%**	**-51.29[-73.11,-29.47]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.61(P<0.0001)							



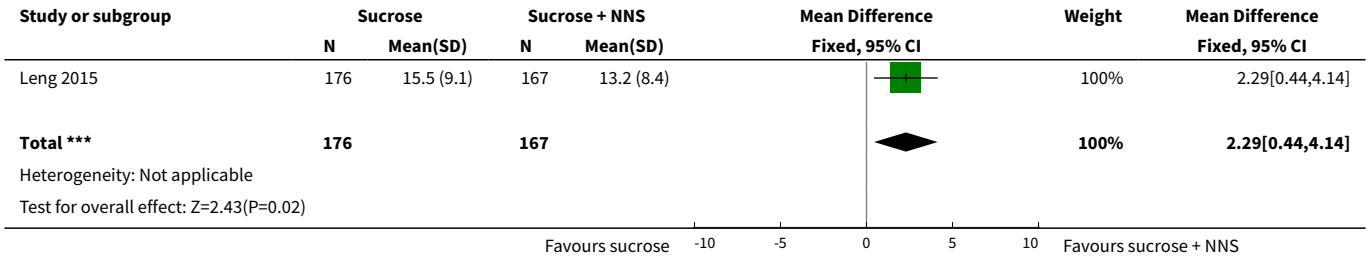
Comparison 14. Heel lance: sucrose (24%) versus sucrose (24%) + NNS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Revised NFCS	1	343	Mean Difference (IV, Fixed, 95% CI)	0.43 [0.23, 0.63]
2 Percentage increase in heart rate	1	343	Mean Difference (IV, Fixed, 95% CI)	2.29 [0.44, 4.14]
3 Decrease in oxygen saturation in blood (%)	1	343	Mean Difference (IV, Fixed, 95% CI)	0.48 [0.10, 0.86]

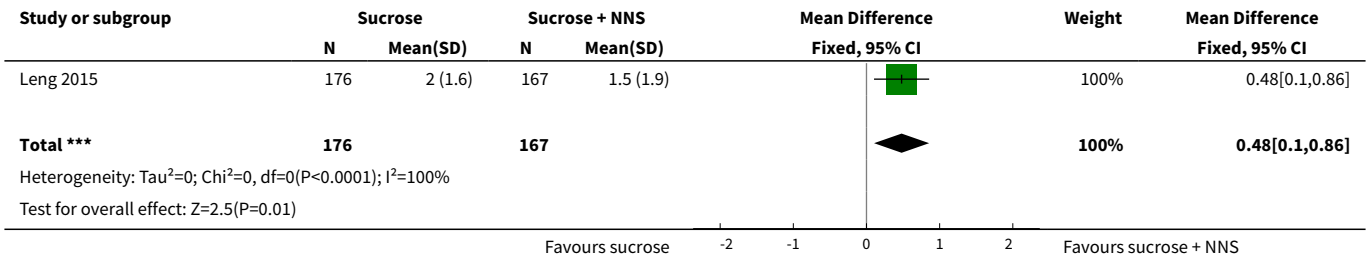
Analysis 14.1. Comparison 14 Heel lance: sucrose (24%) versus sucrose (24%) + NNS, Outcome 1 Revised NFCS.



Analysis 14.2. Comparison 14 Heel lance: sucrose (24%) versus sucrose (24%) + NNS, Outcome 2 Percentage increase in heart rate.



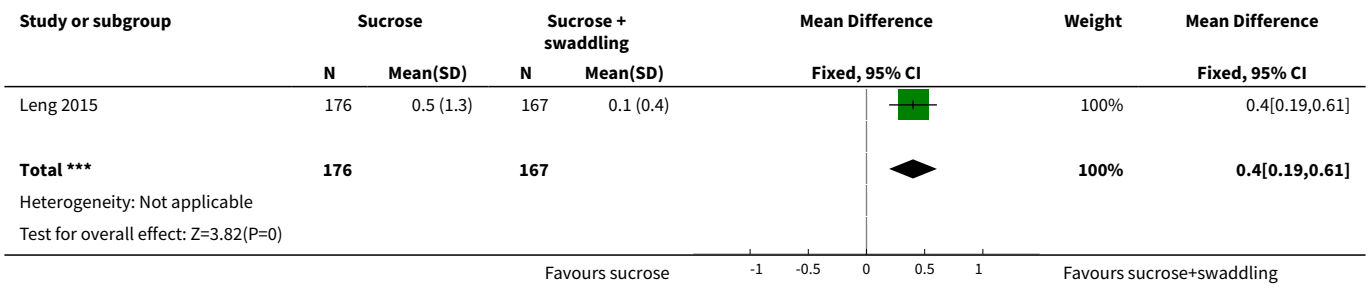
Analysis 14.3. Comparison 14 Heel lance: sucrose (24%) versus sucrose (24%) + NNS, Outcome 3 Decrease in oxygen saturation in blood (%).



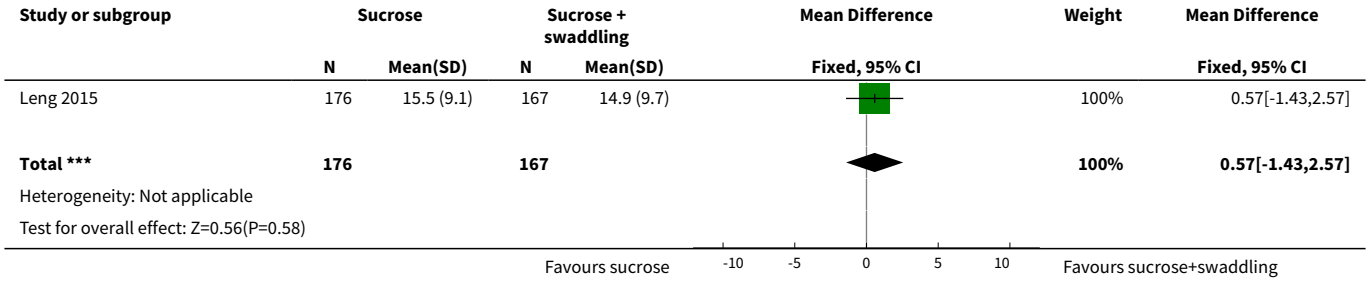
Comparison 15. Heel lance: sucrose (24%) versus sucrose (24%) + swaddling

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Revised NFCS	1	343	Mean Difference (IV, Fixed, 95% CI)	0.4 [0.19, 0.61]
2 Percentage increase in heart rate	1	343	Mean Difference (IV, Fixed, 95% CI)	0.57 [-1.43, 2.57]
3 Decrease in oxygen saturation in blood (%)	1	343	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.07, 0.67]

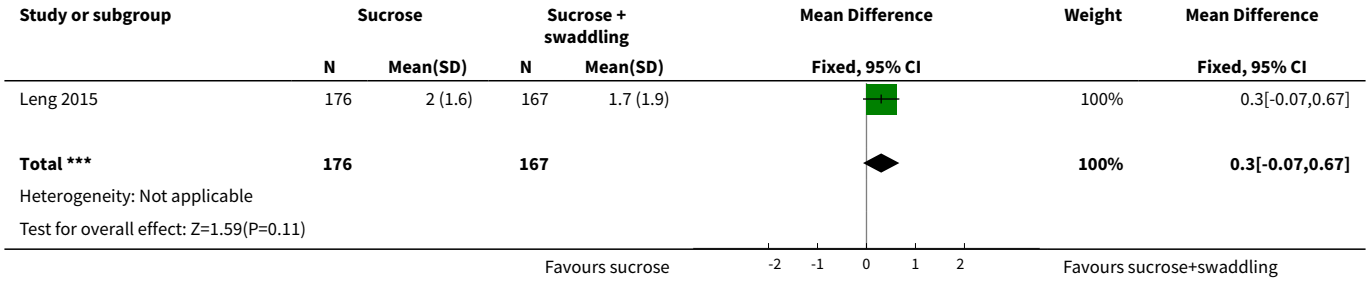
Analysis 15.1. Comparison 15 Heel lance: sucrose (24%) versus sucrose (24%) + swaddling, Outcome 1 Revised NFCS.



Analysis 15.2. Comparison 15 Heel lance: sucrose (24%) versus sucrose (24%) + swaddling, Outcome 2 Percentage increase in heart rate.



Analysis 15.3. Comparison 15 Heel lance: sucrose (24%) versus sucrose (24%) + swaddling, Outcome 3 Decrease in oxygen saturation in blood (%).



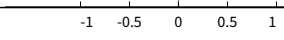
Comparison 16. Heel lance: sucrose (24%) versus sucrose (24%) + NNS + swaddling

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Revised NFCS	1	337	Mean Difference (IV, Fixed, 95% CI)	0.43 [0.23, 0.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Percentage increase in heart rate	1	337	Mean Difference (IV, Fixed, 95% CI)	3.25 [1.43, 5.07]
3 Decrease in oxygen saturation in blood (%)	1	337	Mean Difference (IV, Fixed, 95% CI)	0.79 [0.44, 1.14]

Analysis 16.1. Comparison 16 Heel lance: sucrose (24%) versus sucrose (24%) + NNS + swaddling, Outcome 1 Revised NFCS.

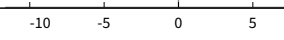
Study or subgroup	Sucrose		Sucrose + NNS + swaddling		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Leng 2015	176	0.5 (1.3)	161	0 (0.2)		100%	0.43[0.23,0.63]
Total ***	**176**		**161**			**100%**	**0.43[0.23,0.63]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.21(P<0.0001)							



Favours sucrose — Favours sucr +NNS+swaddle

Analysis 16.2. Comparison 16 Heel lance: sucrose (24%) versus sucrose (24%) + NNS + swaddling, Outcome 2 Percentage increase in heart rate.

Study or subgroup	Sucrose		Sucrose + NNS + swaddling		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Leng 2015	176	15.5 (9.1)	161	12.2 (8)		100%	3.25[1.43,5.07]
Total ***	**176**		**161**			**100%**	**3.25[1.43,5.07]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.5(P=0)							



Favours sucrose — Favours sucr +NNS+swaddle

Analysis 16.3. Comparison 16 Heel lance: sucrose (24%) versus sucrose (24%) + NNS + swaddling, Outcome 3 Decrease in oxygen saturation in blood (%).

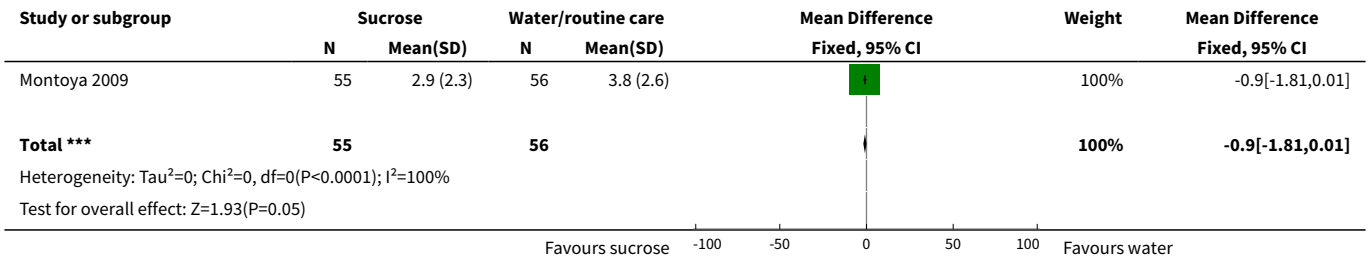
Study or subgroup	Sucrose		[sucrose + NNS + S]		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Leng 2015	176	2 (1.6)	161	1.2 (1.6)		100%	0.79[0.44,1.14]
Total ***	**176**		**161**			**100%**	**0.79[0.44,1.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.49(P<0.0001)							

[sucrose] — [sucrose + NNS +S]

Comparison 17. Venipuncture: sucrose (12%) versus water

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NIPS score in term and preterm infants	1	111	Mean Difference (IV, Fixed, 95% CI)	-0.9 [-1.81, 0.01]

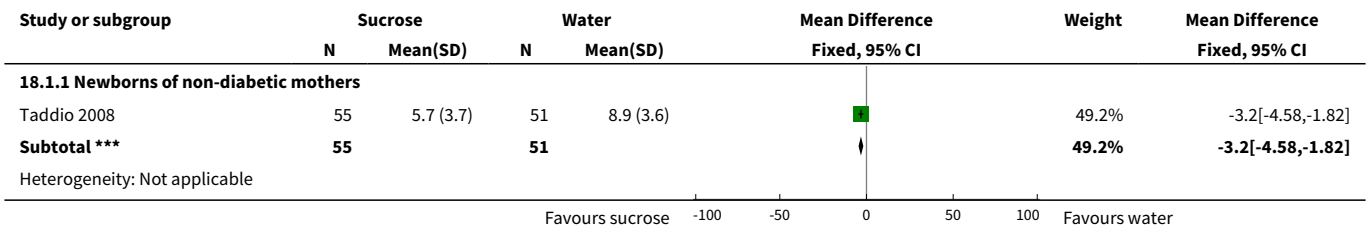
Analysis 17.1. Comparison 17 Venipuncture: sucrose (12%) versus water, Outcome 1 NIPS score in term and preterm infants.

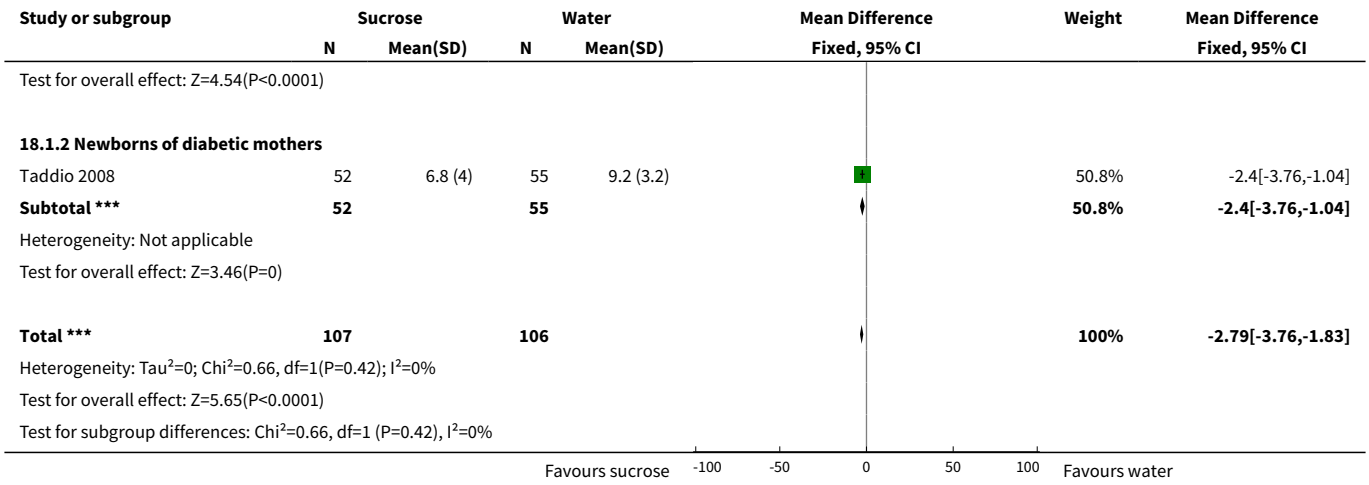


Comparison 18. Venipuncture: sucrose (24% to 30%) versus control (sterile water or no treatment)

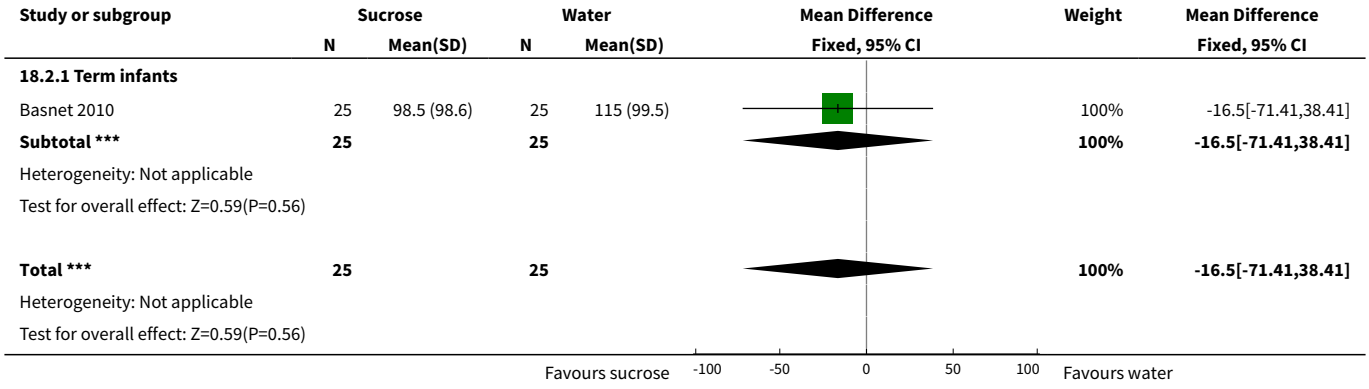
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PIPP score during venipuncture	1	213	Mean Difference (IV, Fixed, 95% CI)	-2.79 [-3.76, -1.83]
1.1 Newborns of non-diabetic mothers	1	106	Mean Difference (IV, Fixed, 95% CI)	-3.2 [-4.58, -1.82]
1.2 Newborns of diabetic mothers	1	107	Mean Difference (IV, Fixed, 95% CI)	-2.40 [-3.76, -1.04]
2 Duration of cry (s)	1	50	Mean Difference (IV, Fixed, 95% CI)	-16.5 [-71.41, 38.41]
2.1 Term infants	1	50	Mean Difference (IV, Fixed, 95% CI)	-16.5 [-71.41, 38.41]

Analysis 18.1. Comparison 18 Venipuncture: sucrose (24% to 30%) versus control (sterile water or no treatment), Outcome 1 PIPP score during venipuncture.





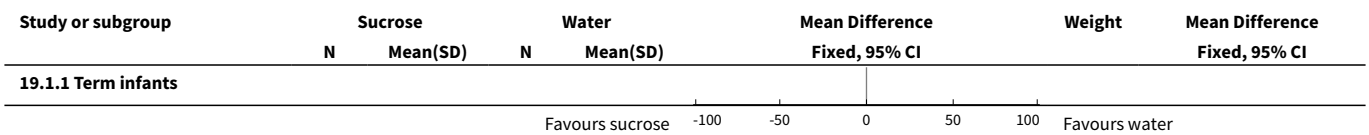
Analysis 18.2. Comparison 18 Venipuncture: sucrose (24% to 30%) versus control (sterile water or no treatment), Outcome 2 Duration of cry (s).

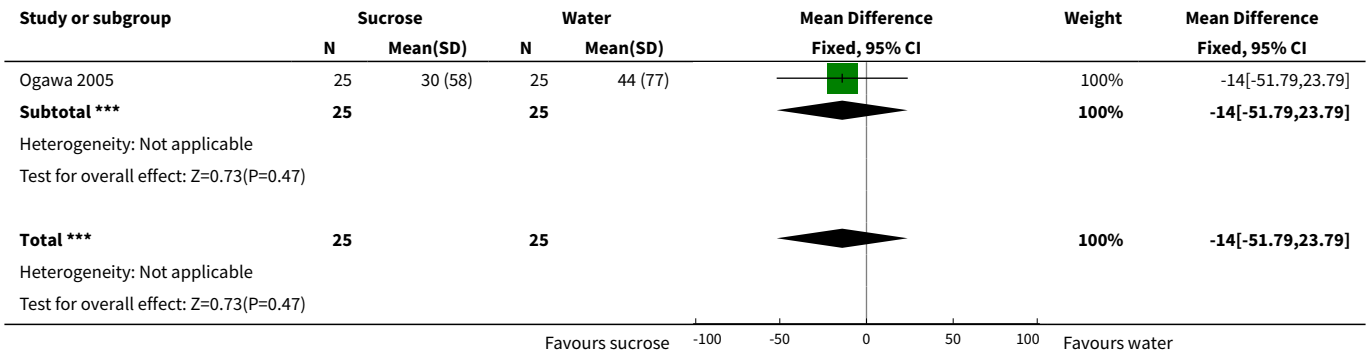


Comparison 19. Venipuncture: sucrose (50%) versus water

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of first cry (s)	1	50	Mean Difference (IV, Fixed, 95% CI)	-14.0 [-51.79, 23.79]
1.1 Term infants	1	50	Mean Difference (IV, Fixed, 95% CI)	-14.0 [-51.79, 23.79]

Analysis 19.1. Comparison 19 Venipuncture: sucrose (50%) versus water, Outcome 1 Duration of first cry (s).



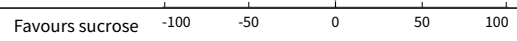


Comparison 20. Venipuncture: sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/Liposomal lidocaine cream on the skin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PIPP score	1	76	Mean Difference (IV, Fixed, 95% CI)	1.30 [-0.12, 2.72]
1.1 Preterm infants	1	76	Mean Difference (IV, Fixed, 95% CI)	1.30 [-0.12, 2.72]
2 PIPP score during recovery period	1	76	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.73, 1.93]
3 DAN score during venipuncture	1	76	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.26, 2.34]
3.1 Preterm infants	1	76	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.26, 2.34]
4 DAN score during recovery period	1	76	Mean Difference (IV, Fixed, 95% CI)	1.40 [0.03, 2.77]
5 Facial grimacing score	1	213	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-13.48, 3.48]
6 Observer-rated pain (VAS) (cm)	1	213	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-1.55, 0.15]
7 Mean crying times during all procedures (s)	2	289	Mean Difference (IV, Fixed, 95% CI)	1.83 [-10.42, 14.09]
7.1 Term infants	1	213	Mean Difference (IV, Fixed, 95% CI)	0.0 [-13.79, 13.79]
7.2 Preterm infants	1	76	Mean Difference (IV, Fixed, 95% CI)	8.69 [-17.97, 35.35]
8 Heart rate (beats/min)	1	213	Mean Difference (IV, Fixed, 95% CI)	5.0 [0.39, 9.61]
9 Oxygen saturation %	1	213	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.33, 0.73]

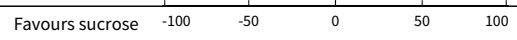
Analysis 20.1. Comparison 20 Venipuncture: sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/Liposomal lidocaine cream on the skin, Outcome 1 PIPP score.

Study or subgroup	Sucrose N	Sucrose Mean(SD)	Sucrose + EMLA N	Sucrose + EMLA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
20.1.1 Preterm infants							
Biran 2011	37	8.5 (3.1)	39	7.2 (3.2)		100%	1.3[-0.12,2.72]
Subtotal ***	**37**		**39**			**100%**	**1.3[-0.12,2.72]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.8(P=0.07)							
Total ***	**37**		**39**			**100%**	**1.3[-0.12,2.72]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.8(P=0.07)							



Analysis 20.2. Comparison 20 Venipuncture: sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/Liposomal lidocaine cream on the skin, Outcome 2 PIPP score during recovery period.

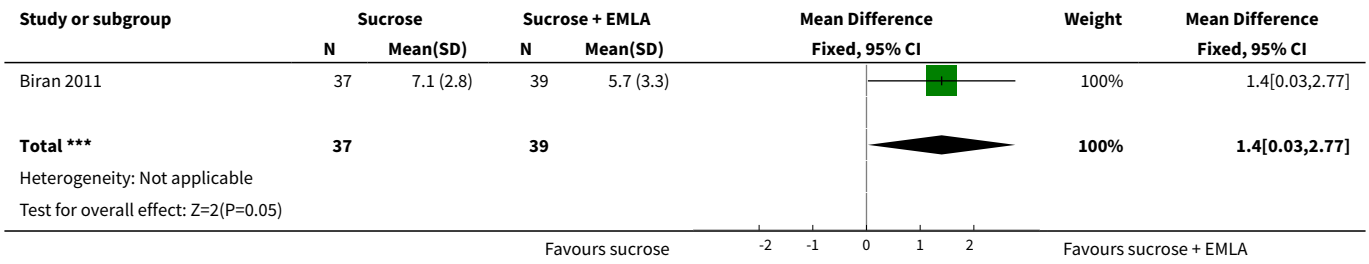
Study or subgroup	Sucrose N	Sucrose Mean(SD)	Sucrose + EMLA N	Sucrose + EMLA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Biran 2011	37	7.7 (2.9)	39	7.1 (3)		100%	0.6[-0.73,1.93]
Total ***	**37**		**39**			**100%**	**0.6[-0.73,1.93]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.89(P=0.38)							



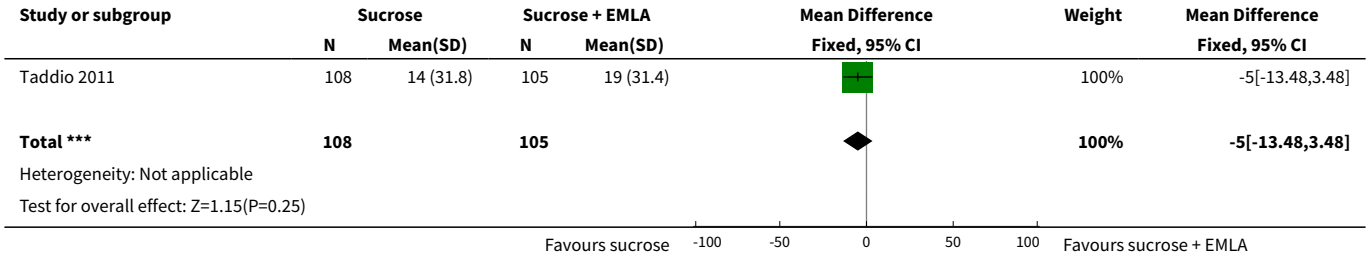
Analysis 20.3. Comparison 20 Venipuncture: sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/Liposomal lidocaine cream on the skin, Outcome 3 DAN score during venipuncture.

Study or subgroup	Sucrose N	Sucrose Mean(SD)	Sucrose + EMLA N	Sucrose + EMLA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
20.3.1 Preterm infants							
Biran 2011	37	7.7 (2.1)	39	6.4 (2.5)		100%	1.3[0.26,2.34]
Subtotal ***	**37**		**39**			**100%**	**1.3[0.26,2.34]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.46(P=0.01)							
Total ***	**37**		**39**			**100%**	**1.3[0.26,2.34]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.46(P=0.01)							

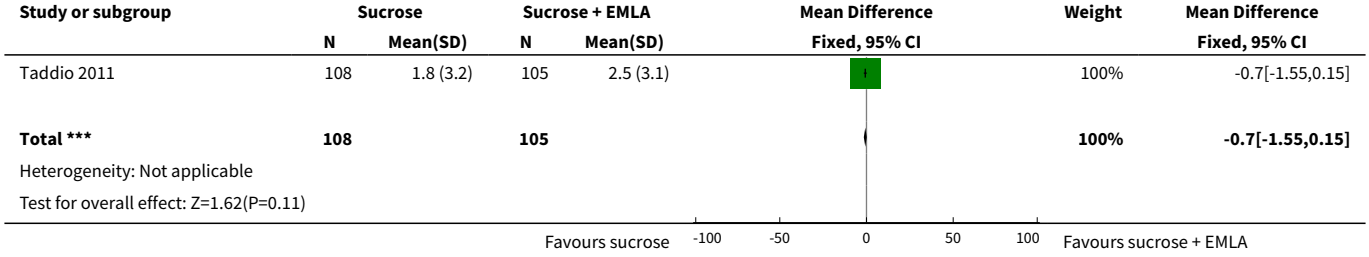
Analysis 20.4. Comparison 20 Venipuncture: sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/Liposomal lidocaine cream on the skin, Outcome 4 DAN score during recovery period.



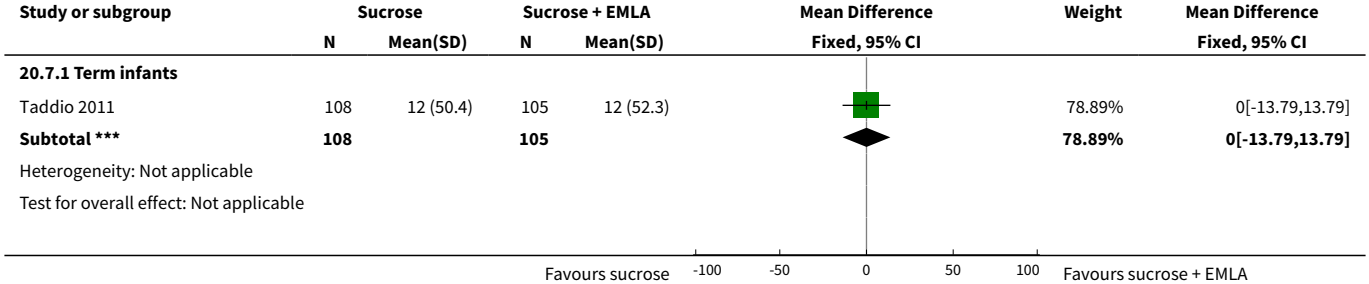
Analysis 20.5. Comparison 20 Venipuncture: sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/Liposomal lidocaine cream on the skin, Outcome 5 Facial grimacing score.

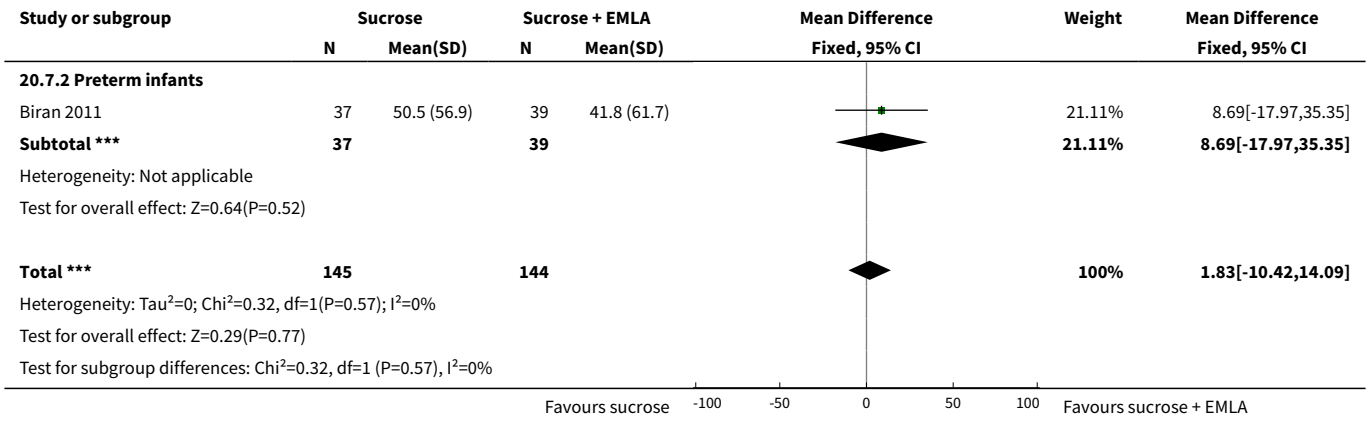


Analysis 20.6. Comparison 20 Venipuncture: sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/Liposomal lidocaine cream on the skin, Outcome 6 Observer-rated pain (VAS) (cm).

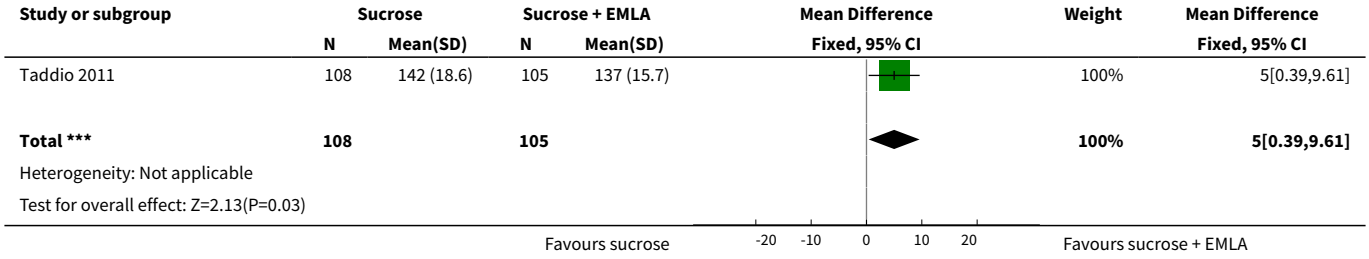


Analysis 20.7. Comparison 20 Venipuncture: sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/Liposomal lidocaine cream on the skin, Outcome 7 Mean crying times during all procedures (s).

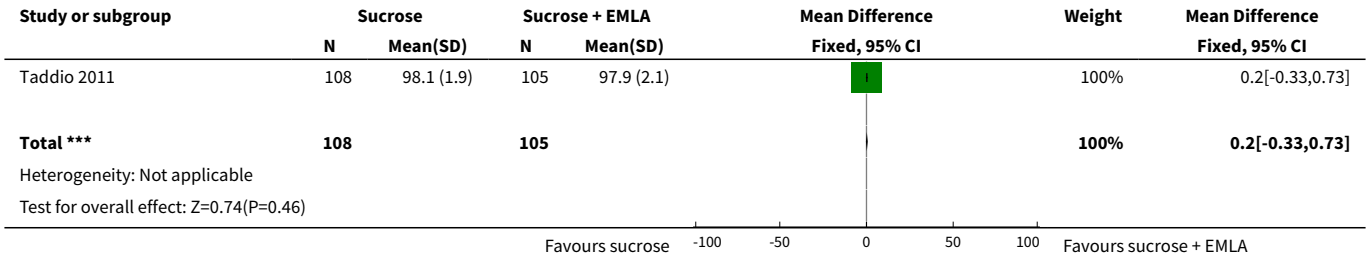




Analysis 20.8. Comparison 20 Venipuncture: sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/Liposomal lidocaine cream on the skin, Outcome 8 Heart rate (beats/min).



Analysis 20.9. Comparison 20 Venipuncture: sucrose (24% to 30%) versus sucrose (24% to 30%) + EMLA/Liposomal lidocaine cream on the skin, Outcome 9 Oxygen saturation %.



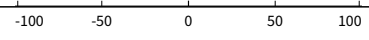
Comparison 21. Venipuncture: sucrose (24%) versus liposomal lidocaine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Facial grimacing score	1	216	Mean Difference (IV, Fixed, 95% CI)	-28.0 [-36.48, -19.52]
2 Observer-rated pain (VAS) (cm)	1	216	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.25, 0.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Cry duration (s)	1	216	Mean Difference (IV, Fixed, 95% CI)	-39.0 [-52.43, -25.57]
4 Heart rate (beats/min)	1	216	Mean Difference (IV, Fixed, 95% CI)	3.0 [-1.95, 7.95]
5 Oxygen saturation (%)	1	216	Mean Difference (IV, Fixed, 95% CI)	0.5 [-0.03, 1.03]

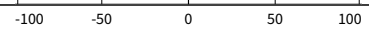
Analysis 21.1. Comparison 21 Venipuncture: sucrose (24%) versus liposomal lidocaine, Outcome 1 Facial grimacing score.

Study or subgroup	Sucrose N	Sucrose Mean(SD)	Liposomal lidocaine N	Liposomal lidocaine Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Taddio 2011	108	14 (31.8)	108	42 (31.8)		100%	-28[-36.48,-19.52]
Total ***	**108**		**108**			**100%**	**-28[-36.48,-19.52]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6.47(P<0.0001)							



Analysis 21.2. Comparison 21 Venipuncture: sucrose (24%) versus liposomal lidocaine, Outcome 2 Observer-rated pain (VAS) (cm).

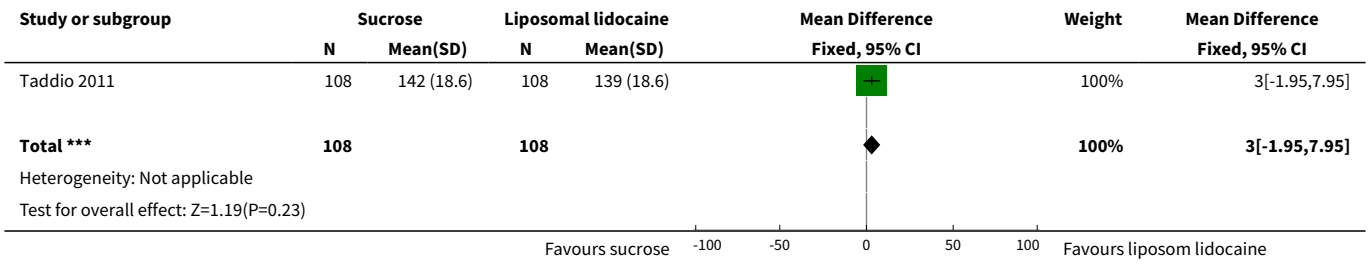
Study or subgroup	Sucrose N	Sucrose Mean(SD)	Liposomal lidocaine N	Liposomal lidocaine Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Taddio 2011	108	1.8 (3.2)	108	2.2 (3.2)		100%	-0.4[-1.25,0.45]
Total ***	**108**		**108**			**100%**	**-0.4[-1.25,0.45]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.92(P=0.36)							



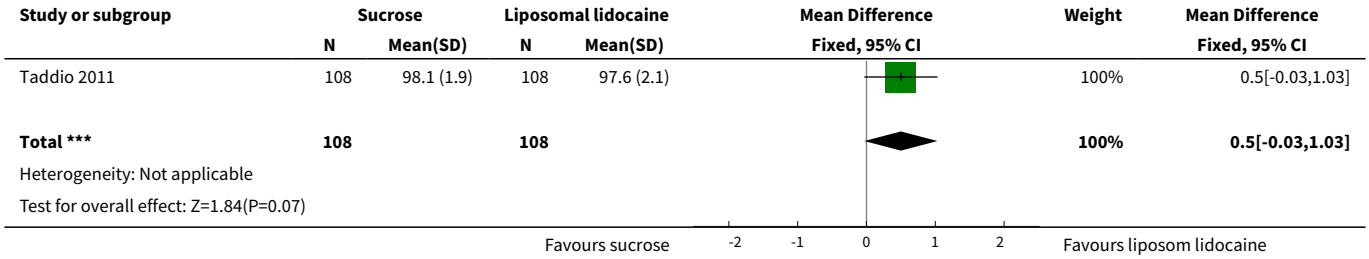
Analysis 21.3. Comparison 21 Venipuncture: sucrose (24%) versus liposomal lidocaine, Outcome 3 Cry duration (s).

Study or subgroup	Sucrose N	Sucrose Mean(SD)	Liposomal lidocaine N	Liposomal lidocaine Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Taddio 2011	108	12 (50.4)	108	51 (50.4)		100%	-39[-52.43,-25.57]
Total ***	**108**		**108**			**100%**	**-39[-52.43,-25.57]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.69(P<0.0001)							

Analysis 21.4. Comparison 21 Venipuncture: sucrose (24%) versus liposomal lidocaine, Outcome 4 Heart rate (beats/min).



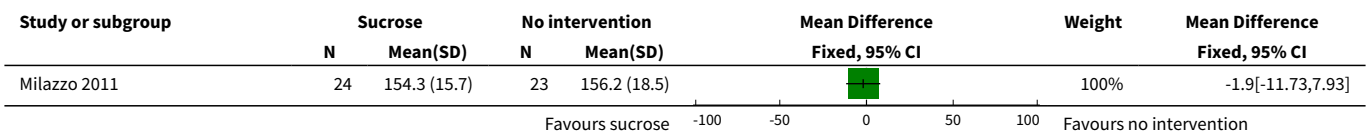
Analysis 21.5. Comparison 21 Venipuncture: sucrose (24%) versus liposomal lidocaine, Outcome 5 Oxygen saturation (%).

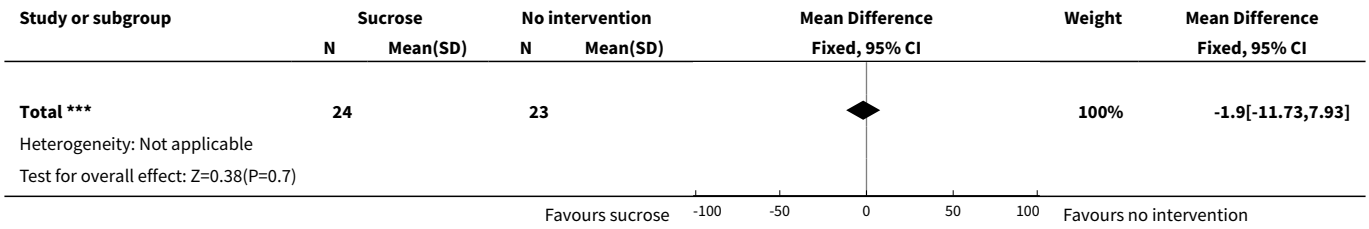


Comparison 22. Arterial puncture in preterm infants: sucrose (24%) versus no intervention

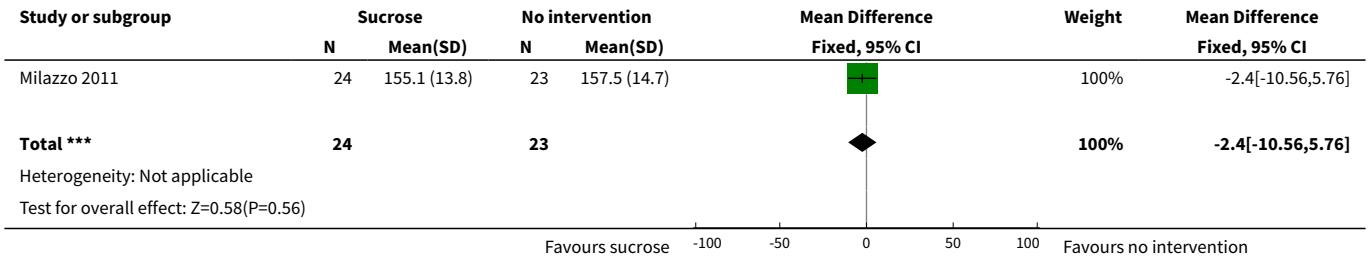
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Heart rate (beats/min) after needle insertion	1	47	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-11.73, 7.93]
2 Heart rate (beats/min) 1 min after procedure completed	1	47	Mean Difference (IV, Fixed, 95% CI)	-2.40 [-10.56, 5.76]
3 Oxygen saturation in blood (%) after needle insertion	1	47	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-4.65, 2.65]
4 Oxygen saturation in blood (%) 1 min after procedure	1	47	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-5.95, 0.15]

Analysis 22.1. Comparison 22 Arterial puncture in preterm infants: sucrose (24%) versus no intervention, Outcome 1 Heart rate (beats/min) after needle insertion.

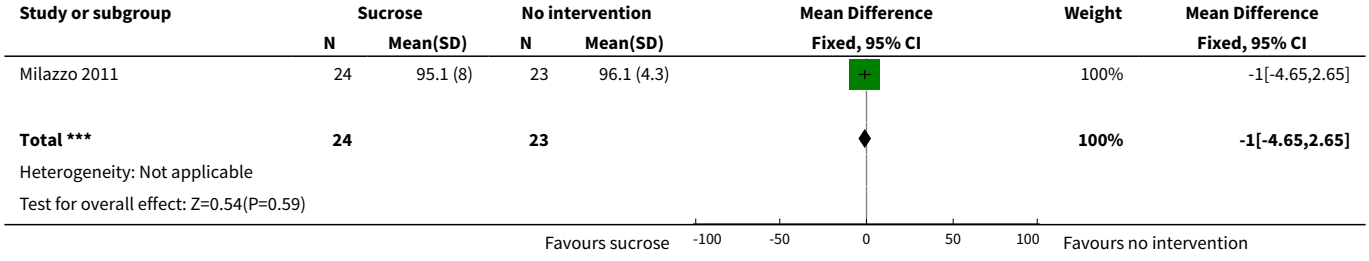




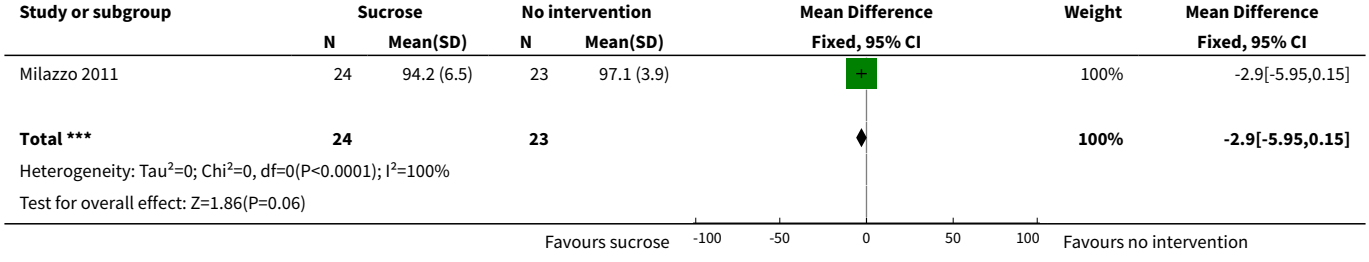
Analysis 22.2. Comparison 22 Arterial puncture in preterm infants: sucrose (24%) versus no intervention, Outcome 2 Heart rate (beats/min) 1 min after procedure completed.



Analysis 22.3. Comparison 22 Arterial puncture in preterm infants: sucrose (24%) versus no intervention, Outcome 3 Oxygen saturation in blood (%) after needle insertion.



Analysis 22.4. Comparison 22 Arterial puncture in preterm infants: sucrose (24%) versus no intervention, Outcome 4 Oxygen saturation in blood (%) 1 min after procedure.

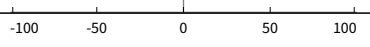


Comparison 23. Intramuscular injection (term infants): sucrose (20% to 25%) versus water or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NIPS 1 min to 2 min after IM injection	1	60	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-2.93, -1.67]
2 PIPP during IM injection (term infants)	1	232	Mean Difference (IV, Fixed, 95% CI)	-1.05 [-1.98, -0.12]
2.1 Infants of non-diabetic mothers	1	115	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-2.38, 0.18]
2.2 Infants of diabetic mothers	1	117	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.35, 0.35]
3 Duration of cry (s)	1	110	Mean Difference (IV, Fixed, 95% CI)	-163.83 [-192.58, -135.08]

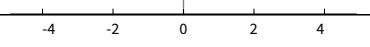
Analysis 23.1. Comparison 23 Intramuscular injection (term infants): sucrose (20% to 25%) versus water or no intervention, Outcome 1 NIPS 1 min to 2 min after IM injection.

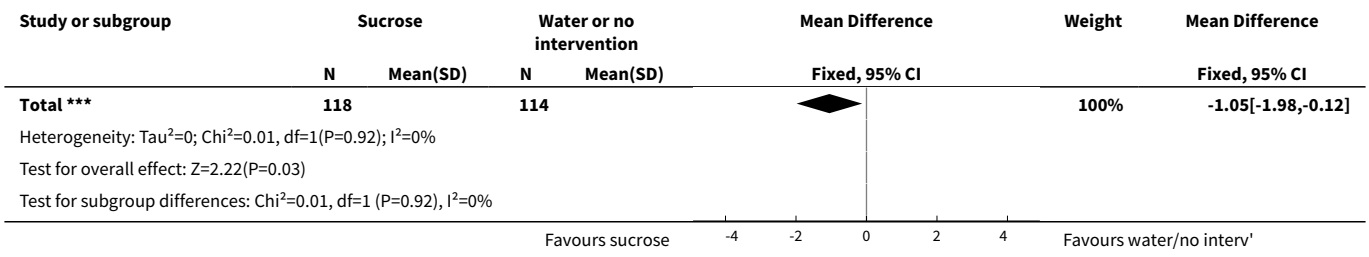
Study or subgroup	Sucrose		Water or no intervention		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Suhrabi 2014	30	2.9 (1.4)	30	5.2 (1)		100%	-2.3[-2.93,-1.67]
Total ***	**30**		**30**			**100%**	**-2.3[-2.93,-1.67]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.12(P<0.0001)							



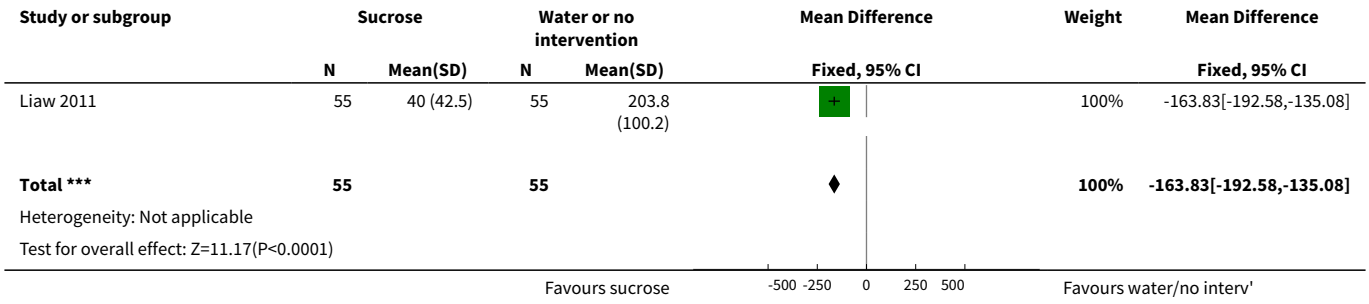
Analysis 23.2. Comparison 23 Intramuscular injection (term infants): sucrose (20% to 25%) versus water or no intervention, Outcome 2 PIPP during IM injection (term infants).

Study or subgroup	Sucrose		Water or no intervention		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
23.2.1 Infants of non-diabetic mothers							
Taddio 2008	59	7.4 (3.8)	56	8.5 (3.2)		52.57%	-1.1[-2.38,0.18]
Subtotal ***	**59**		**56**			**52.57%**	**-1.1[-2.38,0.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.68(P=0.09)							
23.2.2 Infants of diabetic mothers							
Taddio 2008	59	6.2 (3.8)	58	7.2 (3.6)		47.43%	-1[-2.35,0.35]
Subtotal ***	**59**		**58**			**47.43%**	**-1[-2.35,0.35]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.45(P=0.15)							





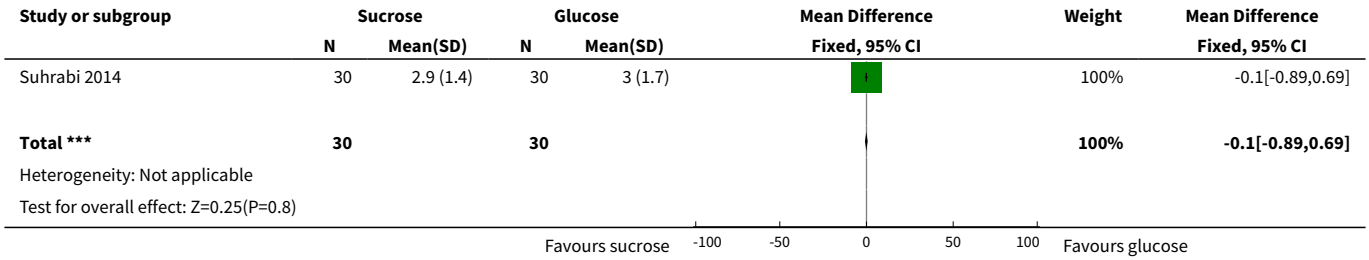
Analysis 23.3. Comparison 23 Intramuscular injection (term infants): sucrose (20% to 25%) versus water or no intervention, Outcome 3 Duration of cry (s).



Comparison 24. Intramuscular injection (term infants): sucrose (25%) versus glucose (25%)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NIPS 1 min to 2 min after immunization	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.89, 0.69]

Analysis 24.1. Comparison 24 Intramuscular injection (term infants): sucrose (25%) versus glucose (25%), Outcome 1 NIPS 1 min to 2 min after immunization.



Comparison 25. Intramuscular injection (term infants): sucrose (25%) versus sucrose (25%) + warmth

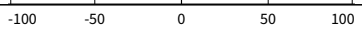
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Crying time (s)	1	29	Mean Difference (IV, Fixed, 95% CI)	15.2 [11.52, 18.88]
2 Grimacing time	1	29	Mean Difference (IV, Fixed, 95% CI)	16.20 [12.35, 20.05]

Analysis 25.1. Comparison 25 Intramuscular injection (term infants): sucrose (25%) versus sucrose (25%) + warmth, Outcome 1 Crying time (s).

Study or subgroup	Sucrose N	Sucrose Mean(SD)	Sucrose + warmth N	Sucrose + warmth Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Gray 2015	15	28 (6.9)	14	12.8 (2.2)		100%	15.2[11.52,18.88]
Total ***	**15**		**14**			**100%**	**15.2[11.52,18.88]**
Heterogeneity: Not applicable							
Test for overall effect: Z=8.1(P<0.0001)							

Analysis 25.2. Comparison 25 Intramuscular injection (term infants): sucrose (25%) versus sucrose (25%) + warmth, Outcome 2 Grimacing time.

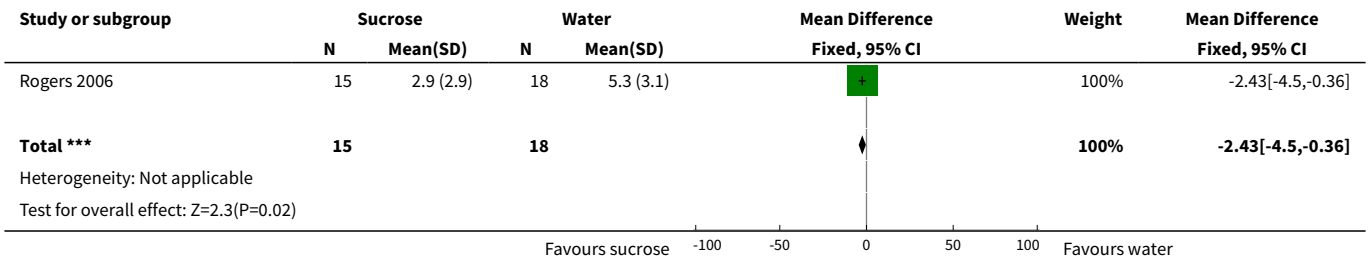
Study or subgroup	Sucrose N	Sucrose Mean(SD)	Sucrose + warmth N	Sucrose + warmth Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Gray 2015	15	31.1 (7.2)	14	14.9 (2.4)		100%	16.2[12.35,20.05]
Total ***	**15**		**14**			**100%**	**16.2[12.35,20.05]**
Heterogeneity: Not applicable							
Test for overall effect: Z=8.24(P<0.0001)							



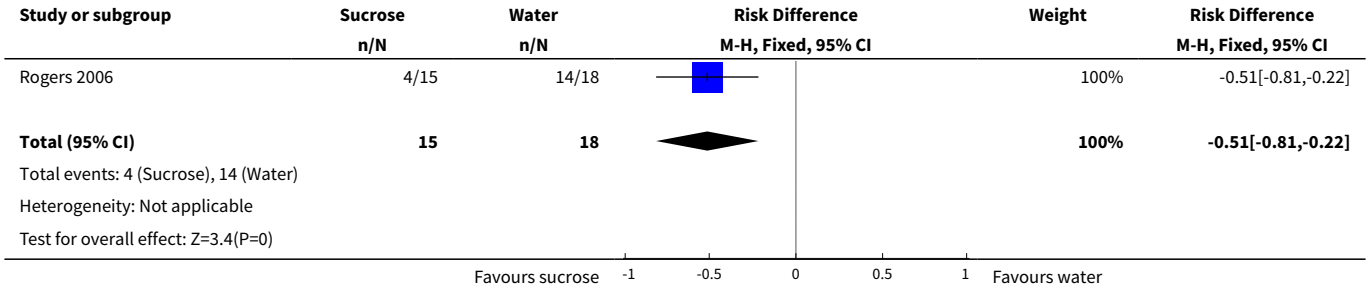
Comparison 26. Bladder catheterization: sucrose (24%) versus sterile water

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in DAN score	1	33	Mean Difference (IV, Fixed, 95% CI)	-2.43 [-4.50, -0.36]
2 Infants crying at maximal catheter insertion	1	33	Risk Difference (M-H, Fixed, 95% CI)	-0.51 [-0.81, -0.22]

Analysis 26.1. Comparison 26 Bladder catheterization: sucrose (24%) versus sterile water, Outcome 1 Change in DAN score.



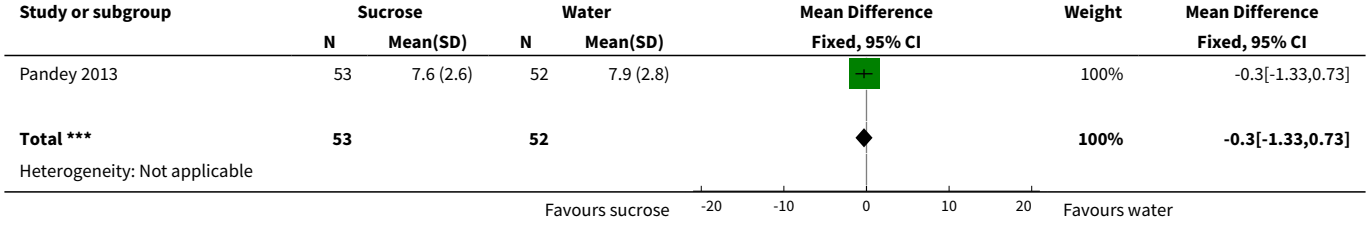
Analysis 26.2. Comparison 26 Bladder catheterization: sucrose (24%) versus sterile water, Outcome 2 Infants crying at maximal catheter insertion.

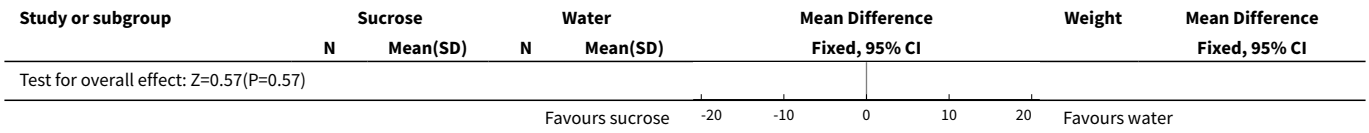


Comparison 27. Orogastric tube insertion in preterm infants: sucrose (24%) versus distilled water

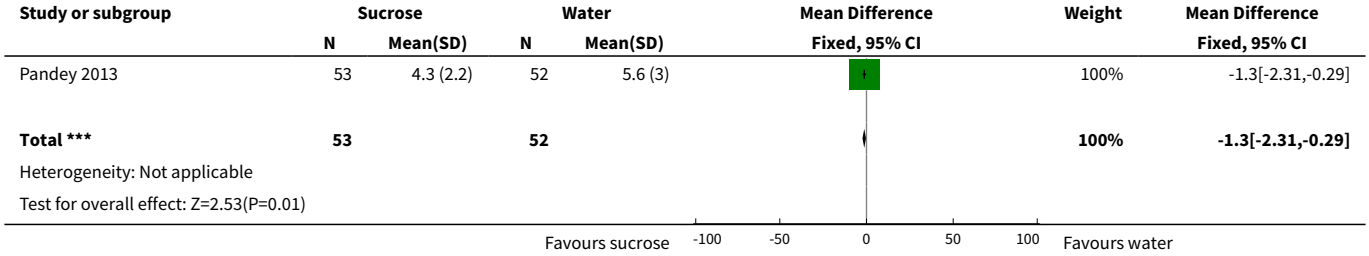
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PIPP score intra procedure	1	105	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.33, 0.73]
2 PIPP score 30 s post procedure	1	105	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-2.31, -0.29]
3 PIPP score 1 min post procedure	1	105	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.40, 0.40]

Analysis 27.1. Comparison 27 Orogastric tube insertion in preterm infants: sucrose (24%) versus distilled water, Outcome 1 PIPP score intra procedure.

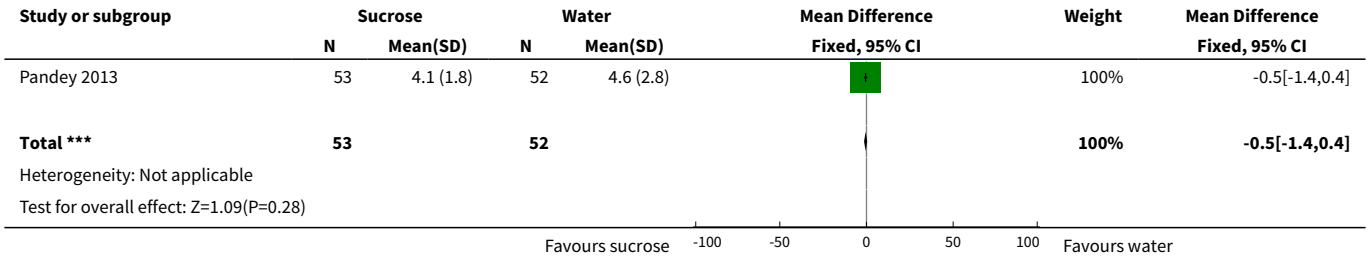




Analysis 27.2. Comparison 27 Orogastric tube insertion in preterm infants: sucrose (24%) versus distilled water, Outcome 2 PIPP score 30 s post procedure.



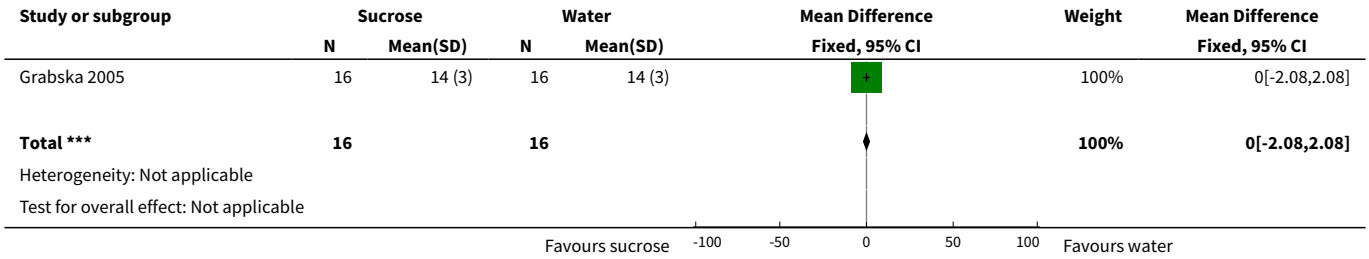
Analysis 27.3. Comparison 27 Orogastric tube insertion in preterm infants: sucrose (24%) versus distilled water, Outcome 3 PIPP score 1 min post procedure.



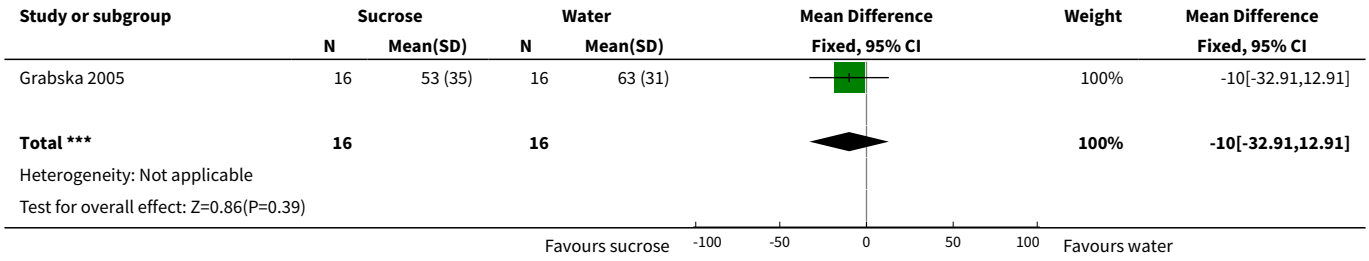
Comparison 28. ROP examination: sucrose (24%) by syringe + swaddled + pacifier versus water by syringe + swaddled + pacifier

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PIPP during examination	1	32	Mean Difference (IV, Fixed, 95% CI)	0.0 [-2.08, 2.08]
2 Crying time (%)	1	32	Mean Difference (IV, Fixed, 95% CI)	-10.0 [-32.91, 12.91]
3 Heart rate (beats/min)	1	32	Mean Difference (IV, Fixed, 95% CI)	-6.0 [-19.33, 7.33]
4 Mean blood pressure (mmHg)	1	32	Mean Difference (IV, Fixed, 95% CI)	-5.00 [-18.48, 4.48]
5 Respiratory rate (breaths/min)	1	32	Mean Difference (IV, Fixed, 95% CI)	2.0 [-5.07, 9.07]
6 Oxygen saturation (%)	1	32	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-5.86, -0.14]

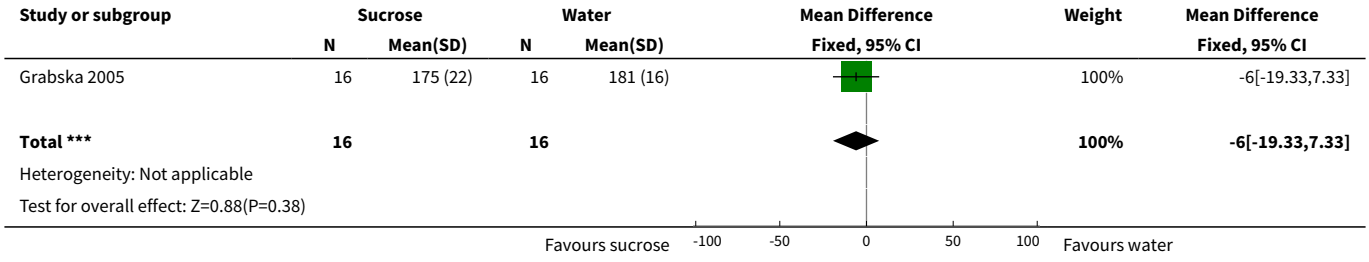
Analysis 28.1. Comparison 28 ROP examination: sucrose (24%) by syringe + swaddled + pacifier versus water by syringe + swaddled + pacifier, Outcome 1 PIPP during examination.



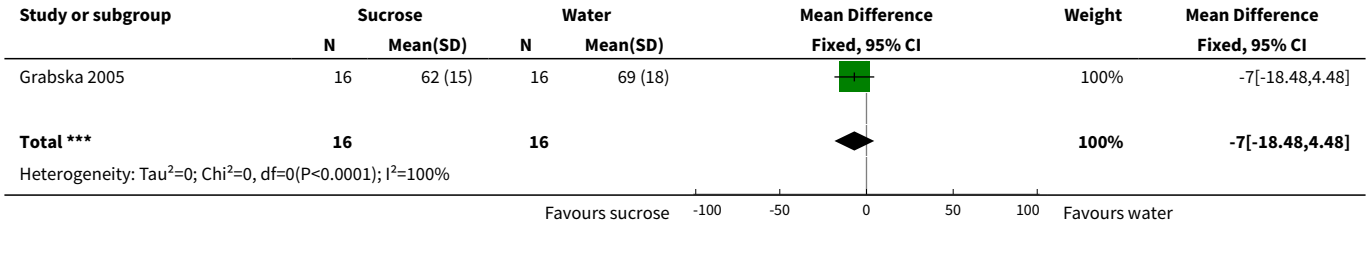
Analysis 28.2. Comparison 28 ROP examination: sucrose (24%) by syringe + swaddled + pacifier versus water by syringe + swaddled + pacifier, Outcome 2 Crying time (%).

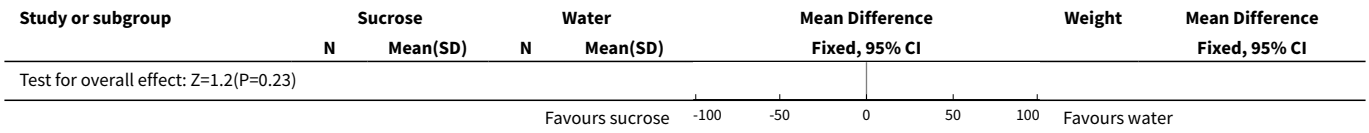


Analysis 28.3. Comparison 28 ROP examination: sucrose (24%) by syringe + swaddled + pacifier versus water by syringe + swaddled + pacifier, Outcome 3 Heart rate (beats/min).

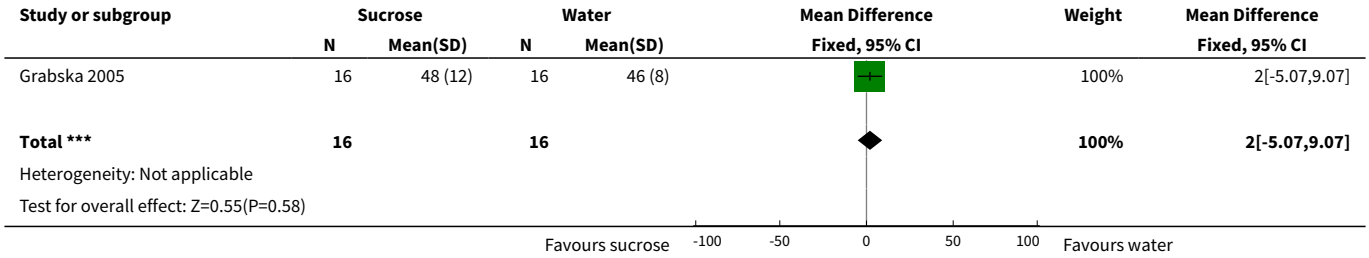


Analysis 28.4. Comparison 28 ROP examination: sucrose (24%) by syringe + swaddled + pacifier versus water by syringe + swaddled + pacifier, Outcome 4 Mean blood pressure (mmHg).

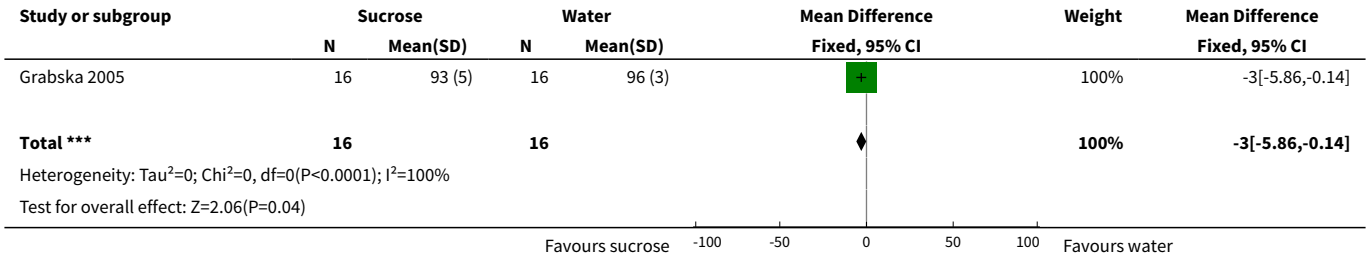




Analysis 28.5. Comparison 28 ROP examination: sucrose (24%) by syringe + swaddled + pacifier versus water by syringe + swaddled + pacifier, Outcome 5 Respiratory rate (breaths/min).



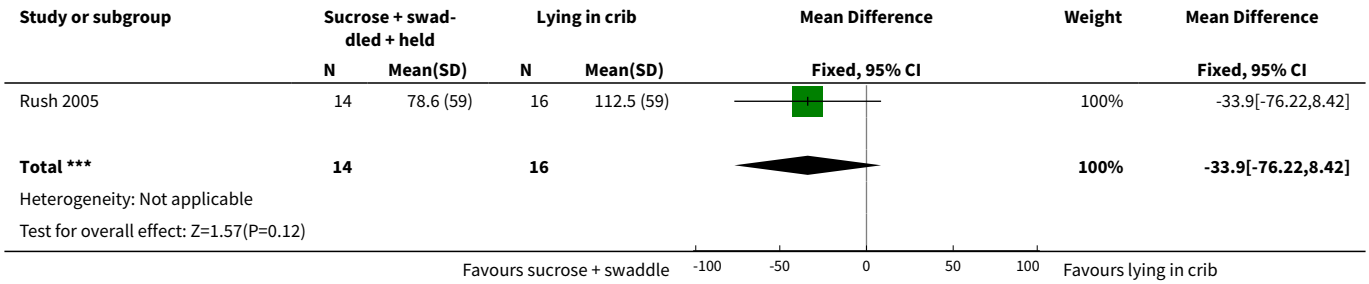
Analysis 28.6. Comparison 28 ROP examination: sucrose (24%) by syringe + swaddled + pacifier versus water by syringe + swaddled + pacifier, Outcome 6 Oxygen saturation (%).



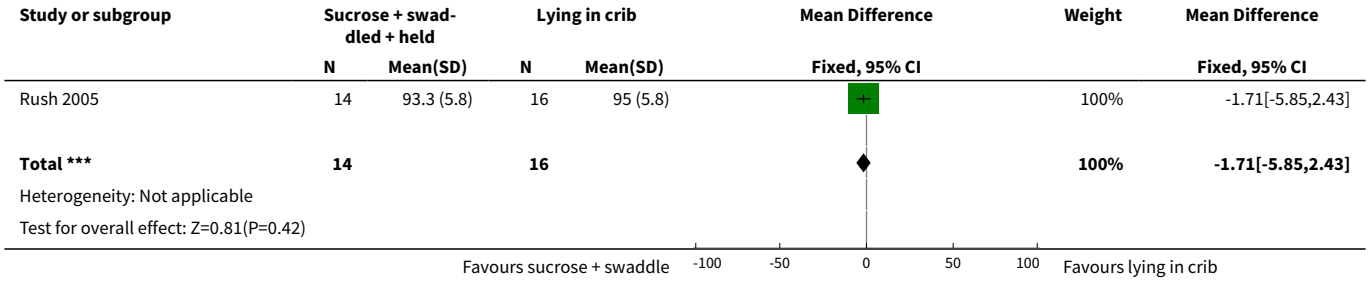
Comparison 29. ROP examination: sucrose (24%) + swaddled + held versus lying in the crib

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total crying time	1	30	Mean Difference (IV, Fixed, 95% CI)	-33.90 [-76.22, 8.42]
2 Oxygen saturation (%) during examination	1	30	Mean Difference (IV, Fixed, 95% CI)	-1.71 [-5.85, 2.43]

Analysis 29.1. Comparison 29 ROP examination: sucrose (24%) + swaddled + held versus lying in the crib, Outcome 1 Total crying time.



Analysis 29.2. Comparison 29 ROP examination: sucrose (24%) + swaddled + held versus lying in the crib, Outcome 2 Oxygen saturation (%) during examination.

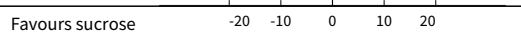


Comparison 30. ROP examination: sucrose (24% to 33%) (sucrose or sucrose + NNS) versus control (water or water + NNS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PIPP score during eye examination	3	134	Mean Difference (IV, Fixed, 95% CI)	-2.15 [-2.86, -1.43]
1.1 Sucrose via syringe versus control (sterile water via syringe)	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.54, 0.54]
1.2 Sucrose + pacifier versus control (sterile water + pacifier)	3	114	Mean Difference (IV, Fixed, 95% CI)	-2.47 [-3.27, -1.66]
2 Crying time (s) during eye examination	1	64	Mean Difference (IV, Fixed, 95% CI)	-21.10 [-33.10, -9.10]

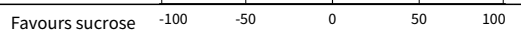
Analysis 30.1. Comparison 30 ROP examination: sucrose (24% to 33%) (sucrose or sucrose + NNS) versus control (water or water + NNS), Outcome 1 PIPP score during eye examination.

Study or subgroup	Sucrose N	Sucrose Mean(SD)	Water N	Water Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
30.1.1 Sucrose via syringe versus control (sterile water via syringe)							
Boyle 2006	10	14.3 (1.6)	10	15.3 (1.9)		21.65%	-1[-2.54,0.54]
Subtotal ***	**10**		**10**			**21.65%**	**-1[-2.54,0.54]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.27(P=0.2)							
30.1.2 Sucrose + pacifier versus control (sterile water + pacifier)							
Boyle 2006	11	12.1 (3.4)	9	12.3 (2.9)		6.73%	-0.2[-2.96,2.56]
Dilli 2014	32	13.7 (2.1)	32	16.4 (1.8)		55.88%	-2.7[-3.66,-1.74]
Mitchell 2004	15	8.8 (2.7)	15	11.4 (2.3)		15.74%	-2.6[-4.41,-0.79]
Subtotal ***	**58**		**56**			**78.35%**	**-2.47[-3.27,-1.66]**
Heterogeneity: Tau^2=0; Chi^2=2.84, df=2(P=0.24); I^2=29.49%							
Test for overall effect: Z=5.97(P<0.0001)							
Total ***	**68**		**66**			**100%**	**-2.15[-2.86,-1.43]**
Heterogeneity: Tau^2=0; Chi^2=5.56, df=3(P=0.13); I^2=46.07%							
Test for overall effect: Z=5.88(P<0.0001)							
Test for subgroup differences: Chi^2=2.73, df=1 (P=0.1), I^2=63.32%							



Analysis 30.2. Comparison 30 ROP examination: sucrose (24% to 33%) (sucrose or sucrose + NNS) versus control (water or water + NNS), Outcome 2 Crying time (s) during eye examination.

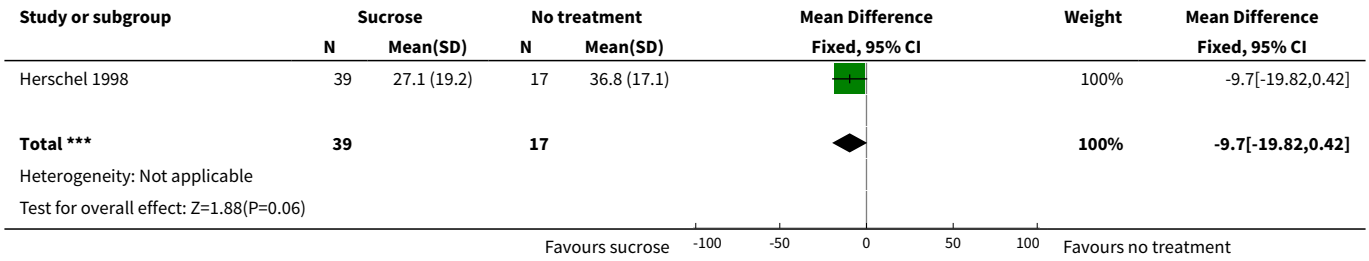
Study or subgroup	Sucrose N	Sucrose Mean(SD)	Water N	Water Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dilli 2014	32	58.7 (16.6)	32	79.8 (30.4)		100%	-21.1[-33.1,-9.1]
Total ***	**32**		**32**			**100%**	**-21.1[-33.1,-9.1]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.45(P=0)							



Comparison 31. Circumcision: sucrose 50% solution on a premature nipple containing a 2 x 2 cm sterile gauze pad moistened by the fluid versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline in heart rate (beats/min)	1	56	Mean Difference (IV, Fixed, 95% CI)	-9.70 [-19.82, 0.42]

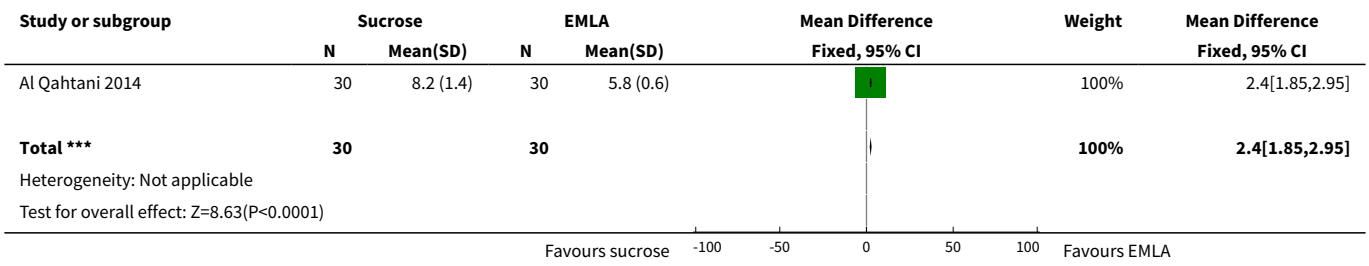
Analysis 31.1. Comparison 31 Circumcision: sucrose 50% solution on a premature nipple containing a 2 x 2 cm sterile gauze pad moistened by the fluid versus no treatment, Outcome 1 Change from baseline in heart rate (beats/min).



Comparison 32. Circumcision: sucrose (24%) versus EMLA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 N-PASS score during circumcision	1	60	Mean Difference (IV, Fixed, 95% CI)	2.40 [1.85, 2.95]
2 N-PASS score after 5 min	1	60	Mean Difference (IV, Fixed, 95% CI)	1.4 [0.74, 2.06]
3 Heart rate (beats/min) during circumcision	1	60	Mean Difference (IV, Fixed, 95% CI)	6.0 [0.19, 11.81]
4 Respiratory rate (cycles/min) during circumcision	1	60	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-4.00, 0.20]
5 Oxygen saturation (%) during circumcision	1	60	Mean Difference (IV, Fixed, 95% CI)	-2.70 [-3.70, -1.70]

Analysis 32.1. Comparison 32 Circumcision: sucrose (24%) versus EMLA, Outcome 1 N-PASS score during circumcision.

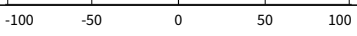


Analysis 32.2. Comparison 32 Circumcision: sucrose (24%) versus EMLA, Outcome 2 N-PASS score after 5 min.

Study or subgroup	Sucrose N	Sucrose Mean(SD)	EMLA N	EMLA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Al Qahtani 2014	30	4.5 (1.4)	30	3.1 (1.2)		100%	1.4[0.74,2.06]
Total ***	**30**		**30**			**100%**	**1.4[0.74,2.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.16(P<0.0001)							

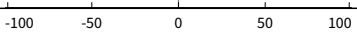
Analysis 32.3. Comparison 32 Circumcision: sucrose (24%) versus EMLA, Outcome 3 Heart rate (beats/min) during circumcision.

Study or subgroup	Sucrose N	Sucrose Mean(SD)	EMLA N	EMLA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Al Qahtani 2014	30	205 (12.8)	30	199 (10)		100%	6[0.19,11.81]
Total ***	**30**		**30**			**100%**	**6[0.19,11.81]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.02(P=0.04)							



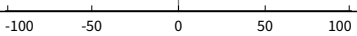
Analysis 32.4. Comparison 32 Circumcision: sucrose (24%) versus EMLA, Outcome 4 Respiratory rate (cycles/min) during circumcision.

Study or subgroup	Sucrose N	Sucrose Mean(SD)	EMLA N	EMLA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Al Qahtani 2014	30	53.9 (4.1)	30	55.8 (4.2)		100%	-1.9[-4,0.2]
Total ***	**30**		**30**			**100%**	**-1.9[-4,0.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.77(P=0.08)							



Analysis 32.5. Comparison 32 Circumcision: sucrose (24%) versus EMLA, Outcome 5 Oxygen saturation (%) during circumcision.

Study or subgroup	Sucrose N	Sucrose Mean(SD)	EMLA N	EMLA Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Al Qahtani 2014	30	94 (2.3)	30	96.7 (1.6)		100%	-2.7[-3.7,-1.7]
Total ***	**30**		**30**			**100%**	**-2.7[-3.7,-1.7]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.3(P<0.0001)							

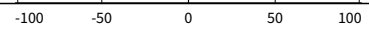


Comparison 33. Circumcision: sucrose (24%) versus EMLA + sucrose (24%)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 N-PASS score during circumcision	1	60	Mean Difference (IV, Fixed, 95% CI)	3.00 [2.42, 3.58]
2 N-PASS score after 5 min	1	60	Mean Difference (IV, Fixed, 95% CI)	1.20 [0.49, 1.91]
3 Heart rate (beats/min) during circumcision	1	60	Mean Difference (IV, Fixed, 95% CI)	12.0 [6.62, 17.38]
4 Respiratory rate (cycles/min)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.60 [-1.77, 2.97]
5 Oxygen saturation (%) during circumcision	1	60	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-4.39, -2.41]

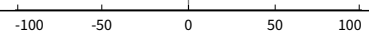
Analysis 33.1. Comparison 33 Circumcision: sucrose (24%) versus EMLA + sucrose (24%), Outcome 1 N-PASS score during circumcision.

Study or subgroup	Sucrose N	Sucrose Mean(SD)	EMLA + sucrose N	EMLA + sucrose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Al Qahtani 2014	30	8.2 (1.4)	30	5.2 (0.8)		100%	3[2.42,3.58]
Total ***	**30**		**30**			**100%**	**3[2.42,3.58]**
Heterogeneity: Not applicable							
Test for overall effect: Z=10.19(P<0.0001)							

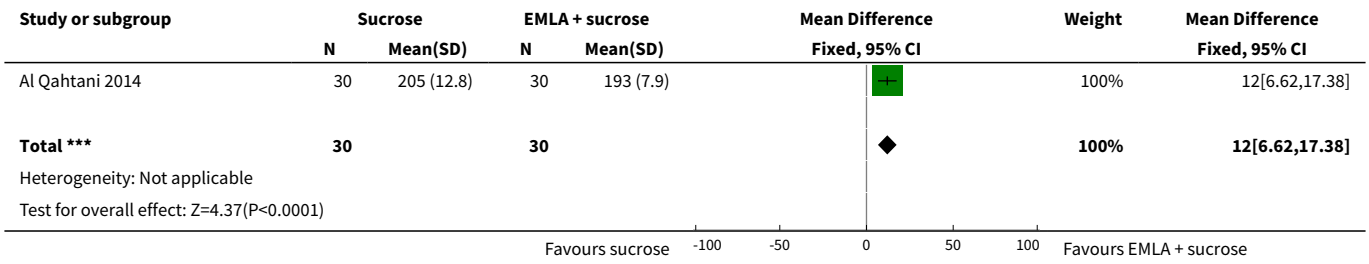


Analysis 33.2. Comparison 33 Circumcision: sucrose (24%) versus EMLA + sucrose (24%), Outcome 2 N-PASS score after 5 min.

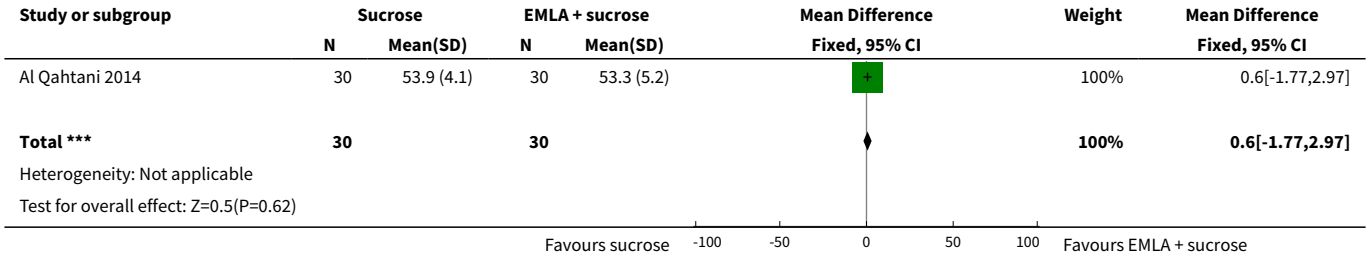
Study or subgroup	Sucrose N	Sucrose Mean(SD)	EMLA + sucrose N	EMLA + sucrose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Al Qahtani 2014	30	4.5 (1.4)	30	3.3 (1.4)		100%	1.2[0.49,1.91]
Total ***	**30**		**30**			**100%**	**1.2[0.49,1.91]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.32(P=0)							



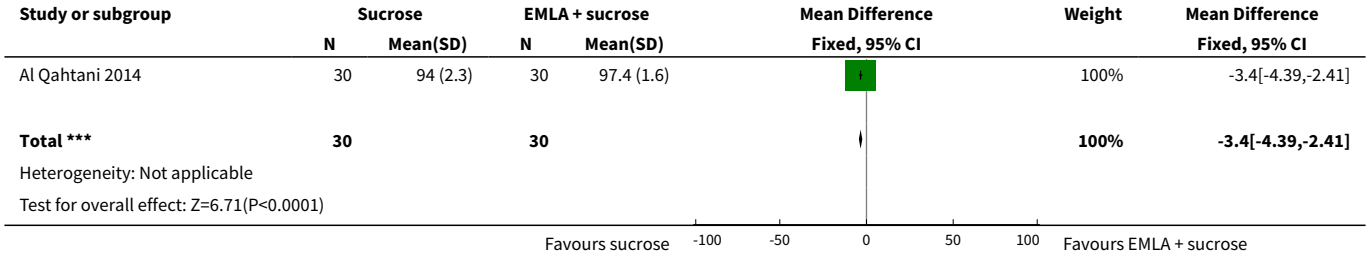
Analysis 33.3. Comparison 33 Circumcision: sucrose (24%) versus EMLA + sucrose (24%), Outcome 3 Heart rate (beats/min) during circumcision.



Analysis 33.4. Comparison 33 Circumcision: sucrose (24%) versus EMLA + sucrose (24%), Outcome 4 Respiratory rate (cycles/min).



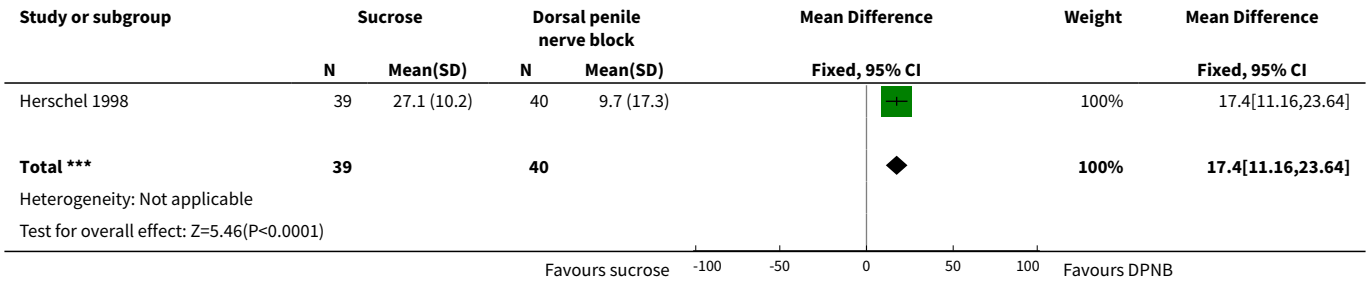
Analysis 33.5. Comparison 33 Circumcision: sucrose (24%) versus EMLA + sucrose (24%), Outcome 5 Oxygen saturation (%) during circumcision.



Comparison 34. Circumcision: sucrose solution (50%) on a premature nipple containing a 2 x 2 cm sterile gauze pad moistened by the fluid versus dorsal penile nerve block (DPNB)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in heart rate (beats/min) from baseline	1	79	Mean Difference (IV, Fixed, 95% CI)	17.40 [11.16, 23.64]

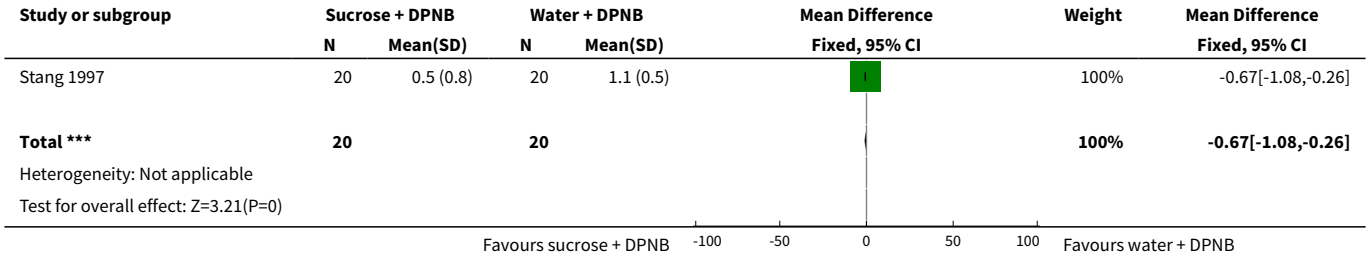
Analysis 34.1. Comparison 34 Circumcision: sucrose solution (50%) on a premature nipple containing a 2 x 2 cm sterile gauze pad moistened by the fluid versus dorsal penile nerve block (DPNB), Outcome 1 Change in heart rate (beats/min) from baseline.



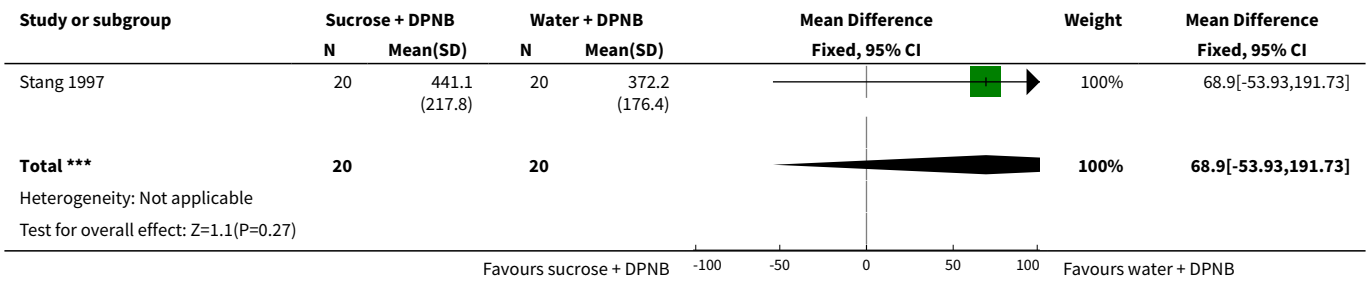
Comparison 35. Circumcision: pacifier dipped in sucrose (24%) + DPNB versus pacifier dipped in water + DPNB

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean Behavioral Distress Scale scores during circumcision	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.08, -0.26]
2 Mean plasma cortisol levels n mol/dL	1	40	Mean Difference (IV, Fixed, 95% CI)	68.90 [-53.93, 191.73]

Analysis 35.1. Comparison 35 Circumcision: pacifier dipped in sucrose (24%) + DPNB versus pacifier dipped in water + DPNB, Outcome 1 Mean Behavioral Distress Scale scores during circumcision.



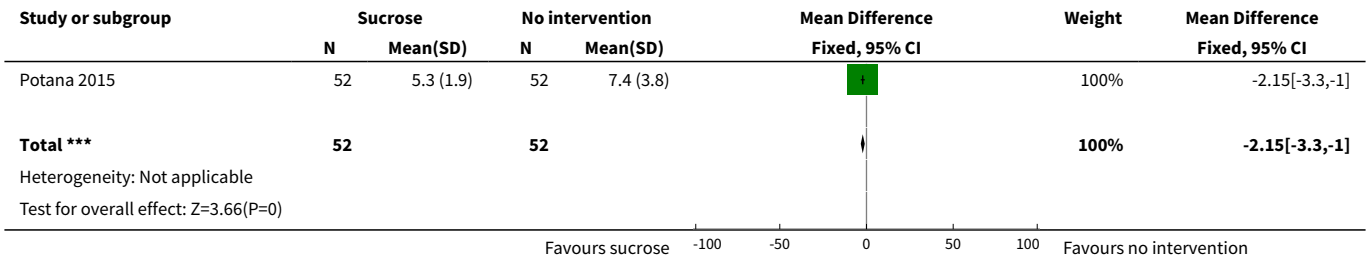
Analysis 35.2. Comparison 35 Circumcision: pacifier dipped in sucrose (24%) + DPNB versus pacifier dipped in water + DPNB, Outcome 2 Mean plasma cortisol levels n mol/dL.



Comparison 36. Echocardiography (term and preterm infants): sucrose (24%) versus no medication/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PIPP	1	104	Mean Difference (IV, Fixed, 95% CI)	-2.15 [-3.30, 1.00]

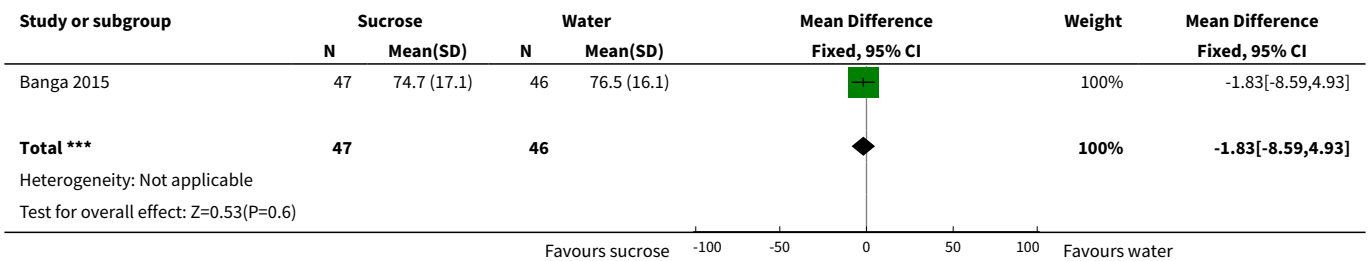
Analysis 36.1. Comparison 36 Echocardiography (term and preterm infants): sucrose (24%) versus no medication/placebo, Outcome 1 PIPP.



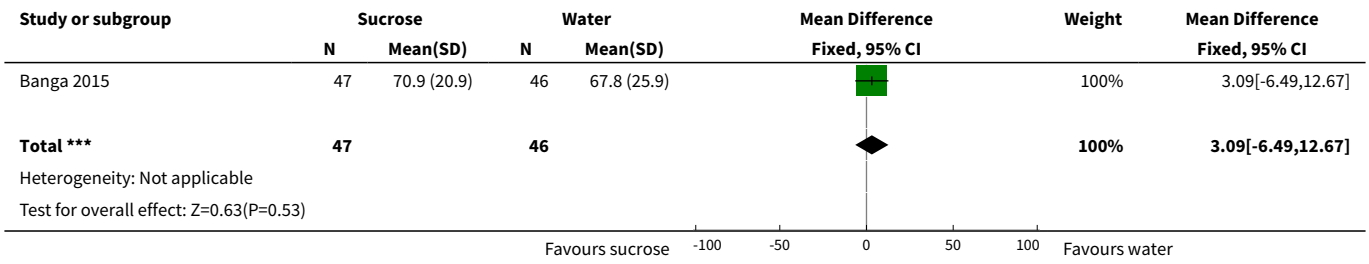
Comparison 37. Potentially painful procedures over seven days: sucrose (24%) versus water

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 'Motor development and vigor' (MDV) domain of NAPI tool	1	93	Mean Difference (IV, Fixed, 95% CI)	-1.83 [-8.59, 4.93]
2 'Alertness and orientation' (AO) domain of NAPI	1	93	Mean Difference (IV, Fixed, 95% CI)	3.09 [-6.49, 12.67]

Analysis 37.1. Comparison 37 Potentially painful procedures over seven days: sucrose (24%) versus water, Outcome 1 'Motor development and vigor' (MDV) domain of NAPI tool.



Analysis 37.2. Comparison 37 Potentially painful procedures over seven days: sucrose (24%) versus water, Outcome 2 'Alertness and orientation' (AO) domain of NAPI.



ADDITIONAL TABLES

Table 1. Trials assessing pain during heel lances

Study	Partici-pants	Procedure	Interventions	Outcomes	Metrics used	Results
Abbasoglu 2015	42 term newborns, undergo-ing heel lancing between postnatal days 3 to 8 as part of neonatal screening	Heel lance	1. Laser acupuncture: 0.3 J of energy was applied to the Yintang point using a Laser PRE-MIO-30 unit for 30 s 2. Sucrose: 0.5 mL 24% solu-tion was giv-en orally via syringe 2 min before heel lancing	NIPS Crying time	Mean and SD	The NIPS score was significantly low-er in the sucrose group 3.66 ± 1.01 vs 4.52 ± 0.87 in the laser group (P = 0.006) The crying time was significantly low-er in the sucrose group 46.66 s ± 37.82 vs 97.95 s ± 34.23 in the laser group (P = 0.000) Data included in RevMan-analyses
Al-tun-Köroğlu 2010	75 full-term infants	Heel lance	1. 3 mL hind milk (n = 25) 2. 3 mL 12.5% sucrose solu-tion (n = 25) 3. 3 mL distilled water (n = 25) The volume of 3mL was provid-ed in 3 doses (1 mL prior to, 1 mL immediately be-fore, and 1mL after the proce-dure)	NFCS, cry-ing 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 for all measures Maximum HR in hind milk group was significantly lower than distilled wa-ter group (184 beats/min vs. 196 beats/min, P = 0.031) Significant reduction in average NFCS score. 1st min NFCS score and 5th min NFCS score in the hind milk

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

						group compared to the distilled water group (P = 0.006, P = 0.017 and P = 0.021, respectively) No data included in RevMan-analyses
Asmerom 2013	131 preterm infants ≤ 36.5 weeks' gestation who: 1. weighed ≥ 800 g; 2. had a central catheter in place; and 3. required a heel lance	Heel lance	1. Sucrose (24%) with NNS (n = 44): 2 mL for neonates > 2 kg, 1.5 mL for neonates 1.5 kg-2 kg, and 0.5 mL for neonates < 1.5 kg 2. Placebo + NNS (n = 45) 3. 42 infants received no heel lance no sucrose or placebo	PIPP after 2 min, plasma hypoxanthine, uric acid, xanthine, allantoin HR, oxygen saturation	Mean and lowest and highest values	Oral sucrose given before a single heel lance significantly decreased behavioural markers of pain Sucrose increased markers of ATP use, as evidenced by significant increases over time in plasma hypoxanthine and uric acid concentrations We received the PIPP scores as means and SD from Dr D Angeles and the data were included in RevMan-analyses
Blass 1997	72 term infants, 22 h to 40 h old	Heel lance	2 mL of one of the following solutions: 1. water 2. 12% sucrose 3. protein mixture 4. 7% lactose 5. dilute fat (coconut and soy oil) 6. concentrated fat 7. fat and lactose mixture RSF (water, protein, lactose, fat) 8. 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) No data could be used in RevMan-analyses
Blass 1999	40 term newborn infants, 34 h to 55 h old	Heel lance	Prior to heel lance: 1. 2 mL 12% sucrose over 2 min via syringe (n = 10) 2. 2 mL water via syringe over 2 min (n = 10)	% time crying 3 min after heel lance Mean change in HR % time grimacing	Mean percentage Mean change (beats/min) Graphically reported	2 mL 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)*

			3. Pacifier dipped every 30 s in 12% sucrose solution for 2 min(n = 10) 4. Pacifier dipped in water every 30 s for 2 min (n = 10)			Mean HR increased significantly from treatment to heel lance in infants receiving water alone (mean increase of 17 beats/min, P = 0.002) and water with pacifier (mean increase of 20 beats/min, P = 0.005). Mean increase in HR also increased for the 12% sucrose and pacifier group (mean difference of 7.4 beats/min, P = 0.05) but not for infants receiving 12% sucrose alone (mean difference of 5.9 beats/min, P = 0.142) 12% sucrose reduced grimacing compared to water (P = 0.0003). 12% sucrose with pacifier reduced grimacing compared to water (P = 0.001) and pacifier alone (P = 0.04) No data could be used in RevMan-analyses
Bucher 1995	16 preterm infants, 27 to 34 weeks' GA, PNA approximately 42 days	Heel lance	1. 2 mL 50% sucrose via syringe into the mouth 2 min before heel lance 2. 2 mL distilled water via syringe into the mouth 2 min before heel lance (n = 16, cross-over design)	% time crying Recovery time until crying stopped Increase in HR Recovery time for HR $TcPO_2$ (max increase - kPa); $TcPO_2$ (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),	Median, IQR	Cry duration (% of total duration of intervention) significantly reduced in 2 mL 50% (1.0 g) sucrose group (71.5%) compared to control group (93.5%, P = 0.002) Median increase in HR (beats/min) after heel lance was significantly reduced in the 2 mL 50% (1.0 g) sucrose group (35 beats/min) compared to water (51 beats/min), P = 0.005 No significant differences between groups with respect to measures for $TcPO_2$ (P = 0.05) and $TcPCO_2$ (P = 0.21) Decrease in cerebral blood volume was not significant between sucrose and placebo groups Data were not presented for effects of sucrose or water prior to cross over. No data could be used in RevMan-analyses

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

				recovery time for respirations Cerebral near-infrared spectroscopy (cerebral oxyhaemoglobin, deoxyhaemoglobin, total blood volume)		
Cignacco 2012	71 preterm infants between 24 weeks 0/7 and 32 weeks 0/7 PMA	Repeated heel lances	1. Sucrose group (n = 24): 20% oral sucrose (0.2 mL/kg), ~2 min before the heel lance. If the infant seemed to be in pain during the heel lance phase, up to 2 additional doses of sucrose were administered and noted in the study chart 2. Sucrose + FT group (n = 23): FT was started at the beginning of the baseline phase and sucrose was given 2 min before the heel lance 3. FT group (n = 24): FT was started at the beginning of the baseline phase, and the infant was 'tucked' through all 3 phases	Bernese Pain Scale for Neonates. Data collection occurred during: 1. baseline (before any manipulation) 2. heel lance (skin preparation, heel stick, and haemostasis after blood was drawn) 3. recovery (3 min after the heel lance) The BPSN contains 9 items: 3 physiologic (HR, respiratory rate, and oxygen saturation) and 6 behavioral	Mean, SD	Sucrose with and without FT had pain-relieving effects even in preterm infants of GA ≤ 32 weeks having repeated pain exposures. These interventions remained effective during repeated heel sticks across time. FT was not as effective Data included in RevMan-analyses

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

				(grimacing, body movements, crying, skin colour, sleeping patterns, consolation) items. 3 phases (baseline, heel stick, recovery) of 5 heel stick procedures were videotaped for each infant		
Codipietro 2008	101 term infants Mean PMA: 1. sucrose group: 39.3 weeks 2. breastfeeding group: 39.4 weeks	Heel lance	1. 1 mL 25% sucrose via syringe (n = 50) 2. Breastfeeding prior to heel lance (n = 51)	Duration of first cry (s), % crying time in first 2 min, and % crying time during blood sampling HR (beats/min) increase from baselines at 30 s following commencement of procedure Oxygen saturation decrease PIPP during blood sampling, 2 min after heel lance	Median, range	Median duration (s) of first cry: breastfeeding group; 3 (range 0 to 120) compared to sucrose group; 21 (range 0 to 120), P = 0.004 % crying during first 2 min: breastfeeding group 4 (range 0 to 100) compared to sucrose; 45 (range 0 to 100) (P < 0.0001) % crying during sampling: breastfeeding group; 8 (range 0 to 100) compared to sucrose 56.5 (range 0 to 100) (P = 0.0003) Median increase in HR (beats/min) from baseline to 30 s after start of heel lance was significantly lower in breastfeeding group; 13 (range -12 to 54) compared to sucrose group; 22 (range -32 to 65) (P = 0.005) Median decrease in oxygen saturation (%) from baseline to 30 s after start of heel lance was significantly greater in sucrose group; -3 (range -30 to 1) compared to breastfeeding group; -1 (range -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 Data could not be used in RevMan analyses
Gibbins 2002	190 preterm and term infants, mean GA	Heel lance	2 min prior to heel lance: 1. Sucrose + NNS group: 0.5 mL	PIPP scores at 30 and 60 s after heel lance	Reported means, SD	Statistically significant difference in mean PIPP scores at both 30 s (P < 0.001) and 60 s (P < 0.001) after heel lance in favour of sucrose group and sucrose + NNS group. Post hoc Tukey

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

	33.7 weeks, < 7 days PNA		24% sucrose via syringe to the anterior surface of the tongue followed by pacifier (n = 64) 2. Sucrose group: 0.5 mL 24% sucrose without pacifier (n = 62) 3. Water + NNS group: 0.5 mL sterile water with pacifier (n = 64)	Incidence of adverse events		tests showed infants who received sucrose + pacifier had significantly lower PIPP scores 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), or water + NNS (mean 10.19, SD 2.67, P < 0.001). At 60 s after heel lance, PIPP scores were significantly lower for sucrose + NNS group (mean 8.78, SD 4.03) compared to the sucrose alone group (mean 11.20, SD 3.25, P = 0.005) and water + NNS group (mean 11.20, SD 3.47, P = 0.007). No significant differences in PIPP scores found between sucrose alone group or water + NNS group at both follow-up times 3 neonates in the sucrose alone group desaturated during the study period. No adverse events occurred with neonates randomized to the sucrose + NNS group Data used in RevMan-analyses
Gormally 2001	94 term newborns, mean GA 39.4 weeks, 2nd or 3rd day of life	Heel lance	1. Water group: no holding and sterile water given by pipette (n = 21) 2. Sucrose group: no holding and 0.25 mL 24% sucrose solution given by pipette (n = 22) 3. Holding + water group: holding and sterile water given by pipette (n = 20) 4. Holding + sucrose group: holding and 0.25 mL 24% sucrose solution by pipette (n = 22) All solutions given 3 times at 30-s intervals	% 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 intervention, 1, 2, 3 min after heel lance Pain concatenation scores for facial activity before intervention, 1, 2, 3 min after heel lance	Not reported	Crying decreased over time (P < 0.001) but no significant interaction noted for time with holding, taste or holding and taste. Effect of taste on crying was significant (P < 0.05) in favour of sucrose group. Effect of holding not statistically significant (P = 0.09)). No statistically significant interaction between taste and holding to reduce crying (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 (P < 0.004), indicating synergistic effect that was also dependent on pre-intervention HR (P < 0.004). No significant main effects noted for vagal tone; as with HR, effect of vagal tone was dependent on pre-intervention vagal tone for both holding and taste interventions (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 (P < 0.001). Only the effect of holding reduced pain scores (P <0.02). No difference as to whether

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

						infant received sucrose (taste main effect P = 0.68) No data could be used in RevMan-analyses
Greenberg 2002	84 term newborns, approximately 17 to 19 h old	Heel lance	1. Sugar-coated pacifier (n = 21) 2. Water-moistened pacifier (n = 21) 3. Sucrose group: 2 mL 12% sucrose (n = 21) 4. Control group: routine care (n = 21)	Duration of cry from procedure phase to 3 min post-procedure Vagal tone and vagal tone index Salivary cortisol levels	Mean and SE reported for time crying (s)	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 = 0.006). Lower vagal tone during heel lance in the sugar-coated pacifier 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) Mean duration of cry used in RevMan-analyses
Guala 2001	140 term, 38 to 41 weeks' GA	Heel lance	1. Nothing (n = 20) 2. Water (n = 20) 3. 5% glucose (n = 20) 4. 33% glucose (n = 20) 5. 50% glucose (n = 20) 6. 33% sucrose (n = 20) 7. 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) Data used in RevMan-analyses
Haouari 1995	60 term infants, 37 to 42 weeks' gestation, 1 to 6 days of age	Heel lance	2 min prior to heel lance: 1. 2 mL 12.5% sucrose (n = 15) 2. 2 mL 25% sucrose (n = 15) 3. 2 mL 50% sucrose (n = 15) 4. 2 mL sterile water (n = 15) All solutions were given by syringe on the	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 50% sucrose group compared with water (P = 0.02). Significant reduction in median time crying at end of first min (P < 0.02) in 50% sucrose group (35 s; range 14 to 60) compared with water (60 s; range 50 to 60). In second min, duration of cry was significantly less in 50% sucrose group (0 s; range 0 to 25) and in 25% 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

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

			tongue over < 1 min			A significant trend towards a reduction in crying time with greater concentrations of sucrose (P = 0.007). There was a similar trend in the reduction of the duration of first cry with increasing concentrations of sucrose (P = 0.004) Significant decrease in % change in HR 3 min after heel lancing (P = 0.02) in the 50% sucrose group (mean 0.1%, SEM 3.3) compared to water group (mean 17.5%, SEM 6.0) We transcribed SEMs to SDs and included data in RevMan-analyses
Harrison 2003	99 sick hospitalised infants Mean GA (SD): 1. sucrose group: 36.7 weeks (3.3) 2. control group: 36.8 weeks (3.7) (author provided data on a subset of infants from a larger study (n = 128) that fulfilled our inclusion criteria)	Heel lance	1. 1 mL water (n = 46) 2. 1 mL 25% sucrose (n = 53) For infants weighing ≤ 1500 g the dose was reduced to 0.5 mL	Duration of cry until 5-s pause, incidence and duration of crying time during the heel lance and squeeze and during the 3-min recovery period HR at baseline, heel lance, during heel lance and 1, 2, 3 min post heel lance Oxygen saturation (%) 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,	Mean, SD (collected from authors)	Mean (SD) length of first cry (s) was higher in the water group (70.5 (83.6)) compared to the sucrose group (46.8 (63.1)). The sucrose group cried 57.1% of the procedure time compared to 58.8% in the water group. The mean (SD) 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) beats/min in the sucrose group and 159.5 (19.2) beats/min in the water group. HR at 30 s from the beginning of the procedure was 175.4 (22.2) and 172.8 (23.6) beats/min in the sucrose and water groups, respectively. The HR in both groups decreased after the procedure to 152.1 (22.5) beats/min in the sucrose group and 154.2 (29.1) beats/min in the water group 2 min post heel lance Results of oxygen saturation (%) were similar between the 2 groups Mean (SD) facial scores were significantly 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 Data included in RevMan-analyses

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

				during heel lance and 1, 2, 3 min post heel lance		
Isik 2000a	113 healthy term newborns GA 37 to 42 weeks, median PNA 2 days, range 2 to 5 days	Heel lance	Solution syringed into the anterior third of the tongue for 1 min prior to heel lance: 1. 2 mL 30% sucrose (n = 28) 2. 2 mL 10% glucose (n = 29) 3. 2 mL 30% glucose (n = 28) 4. 2 mL distilled water (n = 28)	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 and SEM	Infants who received 30% 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 = 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 Data used in RevMan-analyses
Johnston 1997	85 preterm infants, 25 to 34 weeks' GA, 2 to 10 days of age	Heel lance	Solutions via syringe into the mouth just prior to heel lance: 1. 0.05 mL 24% sucrose (n = 27) 2. 0.05 mL 24% sucrose and simulated rocking 15 min prior to heel lance (n = 14) 3. 0.05 mL sterile water and simulated rocking 15 min prior to heel lance (n = 24) 4. 0.05 mL sterile water	HR at baseline and 3 x 30-s blocks Behavioural facial actions (NFCS) at baseline and 3 x 30-s blocks	Means and SD not reported	Although HR increased across all phases of procedure (P < 0.04), there were no significant differences noted between groups (P = 0.566) Decrease in % facial action in 24% sucrose alone group and combined 24% sucrose and rocking group compared to water group (P < 0.02) No data could be used in RevMan-analyses
Johnston 1999	48 preterm neonates mean GA 31 weeks, range 25 to 34 weeks, within 10	Heel lance	1. 0.05 mL 24% sucrose as a single dose, followed by 2 doses of sterile water (n = 15)	PIPP scores in 5 x 30 s blocks	Reported means, SD in graph form	Statistically significant difference between groups (P < 0.0001) for mean PIPP scores. Post hoc analysis found significantly lower PIPP scores with repeated doses of 24% sucrose compared to placebo groups across all blocks of time (P < 0.05). PIPP scores for repeated doses of 24% sucrose

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

	days of birth		2. 3 doses 0.05 mL 24% sucrose (n = 17) 3. 3 doses 0.05 mL sterile water (n = 16) given by syringe to anterior surface of the tongue at: 2 min prior to heel lance, just prior to lancing and 2 min after lancing			were significantly lower compared to single doses of 24% sucrose (8.25 vs. 6.25) only at last block of time (P < 0.05). PIPP scores for single doses of 4% sucrose compared to placebo showed trend towards statistical significance in favour of 24% sucrose (P = 0.07) Data obtained from the author on 31 infants that could be used in RevMan-analyses
Leng 2013	560 term neonates: GA: 37 to 42 weeks; birthweight: 2500 g-4000 g; age 3 to 28 days	Heel lance	1. Boiled water 2. 10% glucose 3. 25% glucose 4. 50% glucose 5. 12% sucrose 6. 24% sucrose 7. 30% sucrose	Increase in HR (beats/min) Decrease in oxygen saturation (%) Pain levels (test not specified)	Reported means and full ranges, not IQRs	The average HR increase 3, 5 and 10 min after procedure in the 25% and 50% glucose groups, 12% and 24% and 30% sucrose groups was significantly lower than those in the placebo group (P < 0.01 or 0.05). The average HR increase 3 min after procedure in the sucrose groups was lower than that in the glucose groups (P < 0.01). At 3 min after heel lance neonates who received 30% sucrose had a significantly lower average HR increase than those who received 12% and 24% sucrose (both P < 0.05). The average oxygen saturation decrease 3, 5, 10 min after procedure was significantly lower than those in the placebo group (P < 0.01). The average oxygen saturation decrease 3 min after procedure in the sucrose groups was significantly lower than that in the glucose groups (P < 0.01). The average pain score 3, 5, 10 min after procedure was significantly lower than those in the placebo group (P < 0.01). The average pain score 3 min after procedure in the sucrose groups was significantly lower than that in the glucose groups (P < 0.01). We could not include in RevMan-analyses data for 30% sucrose vs. sterile water for increase in HR and decrease in oxygen saturation at 3 min after heel lance as data were reported as means and full ranges In addition results were reported late at 3, 5 and 10 min after heel lance
Leng 2015	671 term neonates:	Shallow (blood glucose test) and deep	1. Sucrose group: 2 mL 24% sucrose administered	Revised NFCS, increase in HR (%), de-	Factor analysis	A significant synergistic analgesic effect was observed between the sucrose + NNS and sucrose + swaddling groups in both the shallow (P = 0.015)

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

	GA 37 to 42 weeks at birth; PNA 3 to 28 days; birthweight 2500 g to 4000 g; Apgar score ≥ 8 at 5 min after birth; resting HR 120 to 140 beats/min; resting O_2 saturation ≥ 95%; required neonatal congenital metabolism disease screening or blood glucose test	(congenital metabolism disease screening) heel lance	to the infant's mouth by syringe 2 min before the heel lance procedure 2. Sucrose + NNS group: 2 mL 24% sucrose administered as above, then a standard silicone newborn pacifier was placed into the infant's mouth until the end of the process. 3. Sucrose + swaddling group: infants were swaddled with a cotton blanket, upper but not lower limb movements were restricted by the blanket, and then 2 mL 24% sucrose administered as above. The lower limbs were swaddled immediately after the heel lance procedure until the end of the process. 4. Sucrose + NNS + swaddling group: infants were swaddled with a cotton blanket, upper but not lower limb movements were restricted by the blanket, then 2 mL 24% sucrose administered as	crease in oxygen saturation (%)	mean and SD	and deep heel lance (P = 0.007) procedure. The sucrose + NNS + swaddling group exhibited the lowest pain score. For the deep heel lance procedure, the sucrose + NNS group had a significantly lower increase in HR % and decrease in oxygen saturation (%) than the sucrose group (P = 0.000, P = 0.001), while this difference was not observed in the shallow heel lance procedure. No difference was found between the sucrose and sucrose + swaddling groups, in terms of different physiological parameters NNS and swaddling had synergistic effects on pain relief when used with oral sucrose. For the deep heel lance procedure, oral sucrose combined with NNS and swaddling provided the best pain relief effect For the shallow heel lance procedure, addition of NNS and swaddling did not improve the effects Data included in RevMan-analyses

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

			above, then a standard silicone newborn pacifier was placed into the infant's mouth, the lower limbs were swaddled immediately after the heel lance procedure until the end of the process			
Liaw 2013	110 infants (PMA 26.4 to 37 weeks)	Heel lance	1. Sucrose intervention: 0.2 mL–2.0 mL 20% sucrose fed through a syringe 2 min before the heel-lance procedures depending on the infant's PMA (PMA 26–28 weeks: 0.2 mL; PMA 28.1–30 weeks: 0.5 mL; PMA 30.1–32 weeks: 1 mL; PMA 32.1–37 weeks: 1.5 mL; PMA > 37 weeks: 2.0 mL) 2. NNS intervention: NNS via a standard silicone newborn pacifier to stimulate sucking 1 min before touching the foot to initiate heel-lance procedures 3. FT intervention: infants were in a flexed posture and gently held by the interveners warm hands without strongly re-	Infants' behavioural states (quiet sleep, active sleep, transition state, active awake, quiet awake, fussing or crying)	Graph form, CI, rate ratio and SE	Infants receiving NNS + sucrose + FT or NNS + sucrose experienced 52.8% (P = 0.023) and 42.6% (P = 0.063) more quiet-sleep occurrences than those receiving routine care after adjusting for phase, baseline states, non-treatment sucking during baseline and recovery, positioning, and infants' characteristics. Infants receiving FT + sucrose, NNS + sucrose, NNS + sucrose + FT and NNS + FT experienced 77.3% (P < 0.001), 72.1% (P = 0.008), 51.5% (P = 0.017), and 33.0% (P = 0.105) fewer occurrences of fussing or crying, respectively, than those receiving routine care after adjusting for related factors No data could be used in RevMan-analyses

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

			straining the infant's head and body, one hand on the infant's head, and the other on the trunk. The 3 interventions outlined above were used in different combinations: NNS + FT (n = 22) FT + sucrose (n = 21) NNS + sucrose (n = 21) NNS + sucrose + FT (n = 23) Control: routine care (n = 23)			
Marin Gabriel 2013	Healthy, term neonates, GA 37 to 41 weeks	Heel lance	1. Sucrose group (n = 32 analyzed): 2 mL 24% sucrose (given with a sterile syringe into the mouth) 2 min before heel lance 2. Sucrose + SSC group (n = 35 analyzed): sucrose as above, SSC as below 3. SSC group (n = 31? Written to authors as could be 32): infants were held prone between mothers' breast at least 5 min before heel lance. 4. Breastfeeding + SSC (n = 29 analyzed): Infants started breastfeeding 5 min	NIPS; HR; crying time (s); crying in blood sampling; number of heel lances (%)	Median and IQR	The breastfeeding + SSC group achieved a significant lower median NIPS score (value = 1) compared with other groups (value = 2, 4 and 4, respectively). The percentage of neonates with moderate to severe pain was lower in the breastfeeding + SSC group. Both the breastfeeding + SSC group and the sucrose + SSC group experienced a significantly lower percentage of crying compared with the SSC group No data used in RevMan-analyses

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

			before heel lance These interventions were used in different combinations (BF + SSC; Sucrose + SSC; SSC; Sucrose)			
Mathai 2006	104 term neonates, PNA > 24 h. Mean PNA: sucrose group: 48 h; distilled water group: 44 h	Heel lance	1. 2 mL 20% sucrose inserted in mouth via a dropper (n = 17) 2. 2 mL distilled water inserted in mouth via a dropper (n = 15) 3. Rocking (n = 17) 4. Massage (n = 17) 5. 2 mL expressed breast milk (n = 18) 6. NNS (n =20)	Time of first cry (s), total cry (s) HR before heel lance, 2 min after heel lance and 4 min after heel lance oxygen saturation (%) 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 min, 4 min after heel lance	Mean, SD	No significant difference between sucrose group and any other group for time of first cry NNS or 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 in oxygen sasturation (%) 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 or rocking significantly decreased the DAN scores at 2 and 4 min post heel lance, P < 0.05 Reported data that could be used in RevMan-analyses
Okan 2007	31 healthy, preterm newborns, mean GA 30.5 weeks, mean PMA 32.3 weeks	Heel lance	1. 2 mL 20% sucrose 2. 2 mL 20% glucose 3. 2 mL water The solutions were administered via syringe onto the anterior portion of the tongue Cross over study - Infants received all 3 interventions at different times	Duration of first cry and total crying time HR, oxygen saturation (%), RR (breaths/min) and NFCS scores at baseline, 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 Significantly higher HR in the water group (mean 175, SD 20.8) compared to the sucrose (mean 166, SD 17.6) and glucose groups (mean 165, SD 17.5) at 1 min following heel lance (P = 0.007). No significant differences between the sucrose and glucose groups The study found no significant results for respiratory rate or oxygen saturation between groups.

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

			Data from the first treatment in each infant could not be derived			Significantly higher NFCS score in the placebo group in the 4th min following heel lance (mean 1.3, SD 2.0) and 5th min 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 min and P = 0.046 at 5th min). There were no significant differences between the sucrose and glucose groups Data could not be used in RevMan-analyses.
Örs 1999	102 healthy, term infants, GA 37 to 42 weeks, median PNA 1.6 days, range 1 to 15 days	Heel lance	1. 2 mL 25% sucrose (n = 35) 2. 2 mL human milk (n = 33) 3. 2 mL sterile water (n = 34) All solutions syringed onto anterior part of tongue for 1 min Heel prick performed 2 min after intervention	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 25% sucrose group (median 36, IQR 18 to 43) compared to human milk (median 62, IQR 29 to 107) and sterile water (median 52, IQR 32 to 158) (P = 0.0009). Recovery time for crying was significantly reduced in 25% 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 25% 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) No data were used in RevMan-analyses
Overgaard 1999	100 newborn term infants, mean PNA 6 days, range 4 to 9 days	Heel lance	1. 2 mL 50% sucrose solution via syringe into the mouth over 30 s 2 min prior to heel lance (n = 49) 2. 2 mL sterile water via syringe into the mouth over 30 s 2 min prior to heel lance (n = 47) In addition to the intervention to which the infants were assigned, parents were instructed to com-	Median crying time during heel lance, fraction of crying during sampling, crying time during first min after end of sampling, total crying time Change in HR at 0 and 1 min Oxygen saturation (%)	Median, 5th and 95th percentiles	Median duration of first cry in group receiving 50% 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 (2 to 183)) compared to placebo group (40 s (12 to 157)) (P = 0.07). Median fraction of crying during sampling in 50% sucrose group was significantly lower (43% (4 to 100)) compared to placebo group (83% (20 to 100)) (P = 0.004). Median crying time during first min after end of sampling in 50% 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 50% sucrose group was significantly lower (30 s (2 to 217)) com-

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

			fort the infant as much as possible	at 0 and 1 min NIPS scores 1 min after heel lance and 1 min after blood sampling		pared to placebo group (71 s (13 to 176)) (P = 0.007) No significant HR differences between groups (P = 0.6) No significant differences between groups with respect to changes in oxygen saturation (%) (P = 0.9) Median NIPS scores 1 min after heel lance were lower in 50% 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 50% sucrose group (0 (0 to 7)) compared to placebo group (2 (0 to 7)) (P = 0.05) As means were not reported we could not include the results in RevMan-analyses
Ramenghi 1996a	15 preterm infants, GA 32 to 34 weeks, > 24 h of age	Heel lance	1. 1 mL 25% sucrose 2. 1 mL sterile water The solutions were administered via syringe into the baby's mouth for 1 min Cross-over study	Duration of first cry and % time crying 5 min after lance HR (at -2, 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 Quality/intensity of sucking		
Ramenghi 1996b	60 term infants, GA 37 to 42 weeks, 2 to 5 days old	Heel lance	1. 2 mL 25% (0.5 g) sucrose (n = 15) 2. 2 mL 50% (1.0 g) sucrose (n = 15) 3. Calpol (n = 15) 4. Single-dose sterile water (n = 15)	Duration of first cry after lance, % time crying over 3 min after heel lance % change in HR over 5 min (at -2, 0, 1, 3 and	Median, IQR	Significant decrease in duration of first cry and % crying during 3 min after heel lance in the 25% sucrose, 50% sucrose and Calpol groups (P = 0.02) (data in graph form only) Significant increase in HR for 3 min after heel lance in water group compared with 50% sucrose group and Calpol group (P = 0.009) Pain score (0 to 5) was significantly higher in water group (score = 2,

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

				5 min from heel lance) Behavioural scores (4 facial expressions and the presence of crying) -2, -1, 0, 1, 2, 3 and 5 min		range 1 to 5) than in other 3 groups: 50% sucrose group (score = 0, range 0 to 3); 25% sucrose group (score = 0, range 0 to 2); Calpol group (score = 0, range 0 to 1) (P = 0.05) No data were used in RevMan-analyses
Ramenghi 1999	30 preterm infants, GA 32 to 36 weeks, PNA > 24 h	Heel lance	1. 25% sucrose solution (volume not reported) 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 2. Sterile water given 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, n =15) The cross-over concerned mode of delivery of the solution - intraorally or via NG tube. Infants stayed in their original group assigned to receive either sucrose or sterile water	% 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 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 via 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 received 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 Cross-over design: data from the first assignment prior to cross-over were presented. These data were not used in RevMan-analyses
Rushforth 1993	52 term infants, GA 37 to 42 weeks, 2 to	Heel lance	1. 2 mL 7.5% sucrose administered by a dropper in-	% crying during sampling and 3 min	Medians only	No significant differences in median % time crying between group receiving 7.5% sucrose (74.3%) compared to group receiving water (73.2%).

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

	7 days of age		to the mouth over a 1-min period prior to heel lance (n = 26) 2. 2 mL sterile water administered by dropper into the mouth over a 1-min period prior to heel lance (n = 26)	after sampling		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) No data could be used in RevMan-analyses
Simonse 2012	71 preterm infants GA 32 to 36 + 6/7 weeks at birth undergoing heel lance with an automated piercing device.	Heel lance	1. 1-2 mL 24% sucrose orally before heel lance (n = 24 were analyzed), combined with NNS 2. Breastfed in mother's arms (n = 23) 3. Bottle-fed breast milk and held in the arms of an experienced nurse (n = 23) All 46 infants (in groups 2 and 3) were analyzed	PIPP score; COMFORT-neo Score, HR and oxygen saturation (%)	Mean and 95% CI	There was no significant difference in mean PIPP score between neonates receiving breast milk (6.1) and those receiving sucrose (5.5), with a mean difference of 0.6 (95% confidence interval -1.6 to 2.8; P = .58). No data were provided for HR and oxygen saturation 95% CI were transformed to SD and used in RevMan-analyses
Slater 2010	44 term infants, GA 37 to 43 weeks, < 8 days old	Heel lance	1. 0.5 mL 24% sucrose given via syringe (n = 20) 2. 0.5 mL 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, 95% CI, mean weight	Only mean baseline HR given: 24% sucrose 132. 6 beats/min (124.3 to 140.9); sterile water 131.8 (122.2 to 141.5) (P = 0.90) Only mean baseline oxygen saturation (%) given: 24% sucrose 99.4 (98.8 to 100.1); sterile water 97.4 (95.0 to 99.8) (P = 0.13) PIPP score during insertion: baseline PIPP score: 24% sucrose 1.3 (0.8 to 1.7), sterile water 1.3 (0.8 to 1.8) (P = 0.91); PIPP during procedure: 24% sucrose 5.8 (3.7 to 7.8), 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

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

						withdrawal activity (P = 0.56); significant difference in facial non-responders for 24% sucrose 35%, for sterile water 0% (P < 0.0001) Results presented as mean and 95% CIs Data used in RevMan-analyses
Stevens 1999	122 preterm neonates, GA 27 to 31 weeks, ≤ 28 days of age	Heel lance	1. Prone positioning 30 min prior to heel lance 2. Pacifier dipped in sterile water and placed into the mouth 2 min prior to heel lance 3. Pacifier dipped in 24% sucrose and placed into the mouth 2 min prior to heel lance 4. Control: Containment in SnuggleUp device (n = 122) NB: all infants were contained in SnuggleUp device for all interventions Each infant received all 4 interventions in random order (serving as his/her own control); there was 1 control group and 3 intervention groups	PIPP scores at 30 s and 60 s	Reported means, SD	Main effect of treatment for mean PIPP scores (P < 0.0001). Post hoc analysis revealed significant reduction in PIPP scores 30 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) (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) (P = 0.003). Trend towards lower PIPP scores with sucrose and pacifier group compared to water and pacifier group (P < 0.05) The first author provided data for 61 infants for PIPP at 30 s after heel lance and for 45 infants at 60 s after heel lance for infants before cross-over
Stevens 2005a	66 preterm infants, GA 26 to 30 weeks, PNA < 72 h	Heel lance	1. Standard care (i.e. positioning and swaddling) (n = 21) 2. Standard care as above + 0.1 mL sterile water via syringe into	PIPP at days 7, 14, 21 and 28 at routine heel lance Adverse effects	Not reported	Significant main effect of group (there was a significant difference in a particular group) (P = 0.03) with differences occurring between the sucrose + pacifier group and the standard care group (at 60 s P = 0.01). Mean PIPP scores were generally higher in the standard care group

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

			the mouth immediately followed by a pacifier 2 min prior to painful procedure (n = 23) 3. Standard care as above + 0.1 mL 24% sucrose via syringe 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	Neurobiological risk status		Adverse effects: no group differences for adverse events, clinical outcomes or neurobiological risk status No data used in RevMan-analyses
Storm 2002	48 preterm infants, median GA of 32 weeks, median PNA of 14 days	Heel lance	1. 2 mL 15% sucrose (n = 12) 2. 1 mL 25% sucrose (n =12) 3. Milk via NG tube (n = 12) 4. Milk via NG tube + 1 mL 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 25% sucrose (P < 0.05) and food (milk) + 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) No data could be included in RevMan-analyses
Thakkar 2016	180 full-term neonates, birthweight > 2000 g and age > 24 h	Heel lance	1. 2 mL 30% sucrose (n = 45) 2. 2 mL 30% sucrose + NNS (n = 45) 3. NNS (n = 45) 4. No intervention (n = 45)	PIPP Total crying time Adverse events	Median, IQR	Median (IQR) PIPP score was 3 (2 to 4) in the sucrose + NNS group compared with 7 (6.5 to 8) in the sucrose only group, 9 (7 to 11) in the NNS group and 13 (10.5 to 15) in the no intervention group. The sucrose + NNS group had a significant decrease in the median PIPP score compared with other groups (P = 0.000). Median PIPP score

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

						decreased significantly with any intervention compared with no intervention (P = 0.000) A total of 5 episodes of adverse events were reported No data were used in RevMan-analyses
Tutag Lehr 2015	56 term infants ≤ 7 days old: appropriate for gestational age	Heel lance	1. 2.0 mL 24% sucrose orally (n = 29) 2. Sterile water orally (n = 27)	Primary outcome – mean skin blood flow (SBF); NIPS Skin blood flow (SBF), perfusion units (PU) measured by Laser Doppler Imager (LDI) during heel lance HR, RR (breaths per minute), oxygen saturation (%)	Mean, SE, median, IQR	Mean SBF and median NIPS scores immediately post heel lance were lower in sucrose-treated infants (167.9 PU ± 15.5 vs. 205.4 PU ± 16.0, P = 0.09; NIPS 1 (IQR 0-4) vs. NIPS 3 (IQR 0-6), P = 0.02) although no significant difference in mean SBF. During heel lance NIPS score was predictive of SBF. An increase of 1 in NIPS score was associated with 11 PU increase in SBF (R = 0.21; P = 0.09) for sucrose and 16 PU increase for placebo-treated infants (R = 0.20; P = 0.014). Increased SBF assessed by LDI is a pain response among term neonates following routine heel lance that was not completely attenuated by oral sucrose administration. Increased SBF is associated with NIPS scores. Sucrose analgesic efficacy evidenced by decreased NIPS scores for the sucrose group. Association of SBF with NIPS scores suggests LDI is potentially useful for assessing newborn procedural pain SEs were transformed to SDs and were used in RevMan-analyses for skin blood flow For heart rate, respiratory rate and oxygen saturation results were presented as means and SDs and were used in RevMan-analyses
Unc-eta-Barranechea 2008	150 term infants	Heel lance	1. Facilitated tucking 2. NNS + water 3. NNS + 2 mL 24% sucrose	Mean crying time between groups Modified NFCS	Mean, SD	Statistically significant differences in crying time between facilitated tucking and 2 intervention groups (P < 0.001). No significant difference between NNS + water and NNS + 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) Data used in RevMan-analyses

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

Yilmaz 2010	120 infants, GA 37 to 42 weeks Mean GA (SD): 1. Control group (n = 30): 39.67 (0.80) 2. Mother's milk group (n = 30): 39.10 (1.03) 3. Sucrose group (n = 30): 39.10 (0.71) 4. Pacifier group (n = 30): 39.20 (0.93)	Heel lance	1. Control group: infants lay in their mothers' lap; no interventions were made before the painful procedure 2. Mother's milk group: 2 mL mother's milk administered 2 min before the procedure by using an oral syringe and avoiding contact of the syringe with the mouth and lips 3. Sucrose group: 2 mL 20% sucrose via a syringe as above, 2 min before the procedure 4. 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 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) Outcome data were presented according to different procedure times and no data could be included in RevMan-analyses

Abbreviations
CI = confidence interval
BF = Breastfeeeding
BPSN = Bernese Pain Scale for Neonates
COMFORTneo = COOMFORT neo scale
DAN = Douleur Aiguë du Nouveau-né Scale
GA = gestational age
HR = heart rate
IQR = interquartile range(s)
min = minute(s)
NFCS = Neonatal Facial Coding System
NG = nasogastric
NIPS = Neonatal Infant Pain Scale
NNS = non-nutritive sucking
PIPP = Premature Infant Pain Profile
PMA = postmenstrual age
PNA = postnatal age
RR = respiratory rate
RSF = Ross Special Formula
SSC = skin-to-skin contact
SD = standard deviation
SE = standard error

SEM = standard error of the mean
SpO_2 = oxygen saturation
$TcPO_2$ = transcutaneous oxygen pressure
SSC = skin to skin contact

Table 2. Trials assessing pain during venipunctures

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Abad 1996	28 preterm, 29 to 36 weeks' PMA infants, PNA 1 to 26 days	Venipuncture	2 min prior to venipuncture: 1. 2 mL 12% sucrose via syringe (n = 8) 2. 2 mL 24% sucrose via syringe (n = 8) 3. 2 mL spring water via syringe (n = 12)	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 24% sucrose group (19.1 s) compared to 12% sucrose (63.1 s) and water (72.9 s) 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 12% sucrose had lower HR compared to the 24% sucrose group or water group at all 3 time points (pre solution, P = 0.048; 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) For time crying no SDs were reported by the authors Differences in oxygen saturation, respiratory rate and HR between 24% sucrose and water were reported only at 5 min after venipuncture and therefore the findings were not included in RevMan-analyses
Acharya 2004	39 preterm neonates, mean 30.5 weeks' PMA, mean PNA 27.2 days	Venipuncture	4 min prior to venipuncture: 1. 2 mL 25% (0.5 g) sucrose administered by syringe into front of infant's mouth over 2 min 2. water Cross-over trial	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	Mean (SD) Mean (95% CI)	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 (56.2)) (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)

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

				procedure, procedure and postprocedure phase of venipuncture Mean SpO_2 (%) at pre procedure, procedure and postprocedure NFCS changes across 3 phases of venipuncture		Mean change in HR from pre procedure to procedure was lower in the infants receiving sucrose compared to water (estimated treatment effect = 7.5, P = 0.003). Mean change in HR from pre procedure to postprocedure 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 preprocedure 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 procedure and postprocedure phase (estimated treatment effect = 2.39, P < 0.001) Data prior to cross-over for the two groups were not presented so we could not include the data in RevMan-analyses
Basnet 2010	50 term infants between 12 h to 8 days old 1. Non-sucrose group: 59.92 h old 2. Sucrose group: 68.76 h old	Venipuncture	1. No treatment group (n = 25) 2. Sucrose group (n = 25): 2 mL 30% sucrose administered 2 min before the procedure Method of administration (i.e. pacifier/syringe) was not reported	Duration of cry, DAN scale, number of infants crying. HR and SpO_2 were measured before, during and after the procedure	Mean and SD 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 significantly different between groups (P = 0.65) HR increased during procedure (P = 0.008) followed by decrease postprocedure (P = 0.001) in no treatment group; no significant changes in sucrose group (P = 0.39). Decrease in SpO_2 in the no treatment group (P = 0.001) during the procedure; no significant changes in sucrose group (P = 0.3) Significantly lower DAN scores in the 30% sucrose group (score of 3 (1.5 to 5.5) compared to the no treatment group (score of 7 (5 to 9.5) (P = 0.0001)

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

						Duration of cry could be used in RevMan-analyses
Biran 2011	76 preterm infants, mean (SD) PMA: 1. Sucrose group: 32.6 (2.33) weeks 2. Sucrose + EMLA group): 32.3 (2.01) weeks	Venipuncture	1. Sucrose group: 0.5 mL 30% sucrose solution orally and placebo cream (0.5 g) (n = 37) 2. Sucrose + EMLA group: 30% sucrose solution orally + EMLA (0.5 g) on the skin (n = 39) The sucrose solution was given 2 min before the procedure via syringe.	DAN scale, PIPP, crying time Adverse effects	Mean and SD	Mean (SD) DAN pain scores for the sucrose group and the sucrose + EMLA 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 recovery period. Significant time effect (P = 0.047) and treatment effect (P = 0.018) effect in favour of sucrose + EMLA group; no significant differences using PIPP No adverse effects after sucrose administration were observed Data used for meta-analysis
Carbajal 1999	150 term newborn infants, 3 or 4 days old	Venipuncture	1. No treatment (n = 25) 2. 2 mL sterile water via syringe over 30 s (n = 25) 3. 2 mL 30% glucose via syringe (n = 25) 4. 2 mL 30% sucrose via syringe (n = 25) 5. Pacifier alone (n = 25) 6. 2 mL 30% sucrose via syringe followed by sucking a pacifier (n = 25) Sucrose was administered over 30 s 2 min prior to the procedure	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); 30% sucrose (0.6 g) group 5 (2 to 8); pacifier alone group 2 (1 to 4); 30% sucrose with pacifier group 1 (1 to 2). All groups had significantly lower pain scores compared to sterile water group: 30% glucose (P = 0.005), 30% sucrose (P = 0.01), pacifier (P < 0.0001), 30% sucrose with pacifier (P < 0.0001). The pacifier alone group had significantly lower pain scores than infants receiving 30% glucose (P = 0.0001) or 30% sucrose (P = 0.001). Trend towards lower pain scores for infants receiving 30% sucrose with pacifier compared to pacifier alone (P < 0.06) No data were used in RevMan-analyses

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

Elserafy 2009	36 preterm infants, median (range): PMA 32 (27 to 36), mean (SD) PMA 32.4 (2.9) Note: two different mean PMAs reported in the article	Venipuncture	Infants randomly allocated to 6 different regimens: 1. 0.5 mL sterile water with pacifier 2. 0.5 mL sterile water without pacifier 3. 0.5 mL sucrose 24% with pacifier 4. 0.5 mL sucrose 24% without pacifier 5. pacifier alone 6. control group during a stay in intensive care of up to 15 days For the sucrose and water solutions, the tip of a 1 mL syringe without the needle was placed in the infant's mouth and the solution was instilled with gentle movements to stimulate sucking for 30 s. Each treatment was given 2 min prior to the procedure. Every infant participating in the study received each of 6 different regimens during a maximum stay of 15 days from admission or the end of the NICU stay	HR, SpO_2, PIPP, respiratory rate, blood pressure, glucose check Crying time was assessed at 0, 1, 3, 5, 10 min	Range, mean	PIPP score: significantly different between treatment groups P = 0.0005, over 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) The sucrose groups had significantly shorter crying times compared to the other groups (P = 0.001) This was a cross-over study and each infant got all the 6 different interventions No data that we could use in RevMan-analyses

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

Montoya 2009	111 preterm and term neonates (55 in treatment group and 56 in control group)	Venipuncture	5 min before venipuncture: 1. 1 mL 12% sucrose 2. Distilled water	Overall NIPS score	Means and SDs	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) Data used in RevMan-analyses (Article written in Spanish)
Taddio 2011	330 infants, mean PMA (SD) 39.5 (1.2): 1. Liposomal lidocaine group: mean PMA (SD) 39.6 (1) 2. Sucrose group: mean PMA (SD) 39.6 (1.3) 3. Sucrose liposomal lidocaine group: mean PMA (SD) 39.6 (1.3)	Venipuncture	1. Liposomal lidocaine + water group (n = 110): 1 g liposomal lidocaine 4% cream to the dorsum of the hand, occluded by a dressing (Tegaderm) for 30 to 40 min, and oral water 2. Sucrose + placebo group (n = 110): 2 mL 24% sucrose solution, administered by mouth using a syringe over 1 to 2 min, and placebo cream on back of hand 3. Sucrose + liposomal lidocaine group (n = 110): 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	Facial grimacing, cry duration (s), Observer-rated pain using a VAS (0 to 10 cm), HR (beats/min), oxygen saturation (%) Safety/adverse events	Means and 95% CI	The mean facial grimacing score differed among the randomised groups (P < 0.001). Post hoc analyses demonstrated a significantly lower score for the sucrose group compared with liposomal lidocaine group (MD 27; 95% CI -36 to -19; P < 0.001) and for the sucrose plus liposomal lidocaine group compared with the liposomal lidocaine group (MD 23; 95% CI -31 to -14; P < 0.001). No evidence of difference between the sucrose and sucrose + liposomal lidocaine groups (P = 0.3) Cry duration differed among groups (P < 0.001). Infants in the sucrose and sucrose + liposomal lidocaine groups cried less than infants in the liposomal lidocaine group (MD -38 s; 95% CI -52 to -25; P < 0.001; and MD 39 s; 95% CI - 52 to - 25; P < 0.001, respectively). There was no evidence of a difference in cry duration between the sucrose and sucrose + liposomal lidocaine group (MD 0 s; 95% CI -13 to 14; P = 0.95) No difference in VAS, HR or oxygen saturation (%) 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, oxygen saturation (%) and procedure duration were significantly higher in the liposomal lidocaine group compared to the control group. Cry duration

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

		cream) and oral solution (sucrose or placebo water) Non-randomised group of healthy neonates undergoing venipuncture were administered water	and procedure success rate did not differ beyond chance No significant adverse events reported We transcribed 95% CI to SDs and included results in RevMan-analyses

Abbreviations
CI = confidence interval
DAN = Douleur Aigue du Nouveau-ne
EMLA = eutectic mixture of local anaesthetics
HR = heart rate
IQR = interquartile range
MD = mean difference
NFCS = Neonatal Facial Coding System
NIPS = Neonatal Infant Pain Scale
PIPP = Premature Infant Pain Profile
PMA = postmenstrual age
PNA = postnatal age
SD = standard deviation
SEM = standard error of the mean

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: 1. Heel lance + water group: GA 40 weeks (range 38 to 42 weeks) 2. Heel lance + sucrose group: GA 39 weeks (range 37 to 41 weeks) 3. Venipuncture + water group: GA 39 weeks (range 37 to 41 weeks) 4. Venipuncture + sucrose group: GA 39 weeks (range 37 to 41 weeks)	Heel lance or venipuncture	2 min before procedure: 1. Heel lance + 0.1 mL sterile water on infant's tongue via syringe (n = 25) 2. Heel lance + 0.1 mL 50% sucrose on infant's tongue via syringe (n = 25) 3. Venipuncture + 0.1 mL sterile water on infant's tongue via syringe (n = 25) 4. Venipuncture + 0.1 mL 50% sucrose on infant's tongue via syringe (n = 25)	Duration of first cry (s), first crying time/total procedure time (%) and the ratio of crying: no crying NFCS score: 1. 1 min after oral administration of water/sucrose 2. disinfection of skin before heel lance or venipuncture 3. during skin puncture 4. during blood sampling 5. during compression to stop bleeding 6. during application of plaster, and 7. 1 min after application of plaster	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 < 0.001) 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 < 0.001) Sucrose did not significantly reduce NFCS scores during or after venipuncture We included data for sucrose vs water for heel lance and for venipuncture for duration of first cry

Abbreviations
GA = gestational age
IQR = interquartile range
NFCS = Neonatal Facial Coding System
SD = standard deviation

Table 4. Trials assessing pain during arterial puncture

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Milazzo 2011	47 neonates, GA 30 to 36 weeks, 48 h old	Arterial puncture	Sucrose group: 0.5 mL oral sucrose solution (Sweet-Ease, preservative-free, 24% sucrose solution 99044, Children's Medical Ventures, Norwell, Massachusetts) in a 1-mL syringe by the nurse caring for the infant (n = 24)	NIPS, HR, Oxygen saturation (%)	Mean, SD NIPS scores presented in graph form only	Sucrose group had significantly less crying than the control group, both during, and immediately after arterial puncture (P .006 and .022, respectively). No significant changes in other pain subscales, HR, or oxygen saturation were found during or after the arterial puncture (P = -0.05)

Table 4. Trials assessing pain during arterial puncture *(Continued)*

			Control group: no oral solution (n = 23)			Data for HR and oxygen saturation could be used in RevMan-analyses

Abbreviations
GA = gestational age
HR = heart rate
NIPS = Neonatal Infant Pain Scale
SD = standard deviation
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: 1. 2 weeks (n = 50) 2. 2 months (n = 44) 3. 4 months (n = 50) 4. 6 months (n = 46) 5. 9 months (n = 28) 6. 15 months (n = 30) 7. 18 months (n = 37) Only data for neonates at 2 weeks of age are included in this review	Subcutaneous injection	1. 2 mL 12% sucrose (0.24 g) 2. 2 mL sterile water 3. No treatment The solutions were given 2 min prior to the procedure	Cry duration (during and after procedure)	% time crying	The overall P value for % time crying was significant (F = 5.92, P < 0.005) for the 2-week-old age group. Pairwise comparisons of the % time spent crying of sucrose and water groups versus the no treatment group showed significant differences (P < 0.01 for both comparisons) This was the only age group (< 2 weeks) in which significant differences were observed between sucrose, water and no treatment groups Means and SDs were not reported. No data could be used in RevMan-analyses
Mucignat 2004	33 preterm neonates, mean (SD) GA at birth	Subcutaneous injections	1. NNS group: pacifier sucking (41 injections)	Duration of cry from needle introduction	Mean, SD	Crying time was significantly lower in the sucrose + EMLA + NNS group (P = 0.0002). The mean (SD) crying time in each group was as follows:

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

	30 weeks (6 days), GA at injection 32 weeks (6 days)	2. Sucrose + NNS group: 0.2 mL to 0.5 mL 30% sucrose with pacifier (86 injections) 3. EMLA + NNS group: local application of EMLA with pacifier (71 injections) 4. Sucrose + EMLA + NNS group: 0.2 mL to 0.5 mL sucrose with EMLA and pacifier (67 injections) Each infant was its own control	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			3.93 s (2.97) in the NNS group, 2.81 s (4.81) in the EMLA + NNS group, 2.32 s (7.51) in the sucrose + NNS group and 0.89 s (2.66) in the sucrose + EMLA + NNS 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 No data could be used in RevMan-analyses

Abbreviations
DAN = Douleur Aiguë du Nouveau-né Scale
EMLA = eutectic mixture of local anaesthetics
GA = gestational age
HR = heart rate
NFCS = Neonatal Facial Coding System
NNS = non-nutritive sucking
SD = standard deviation
SpO_2 = oxygen saturation

Table 6. Trials assessing pain during intramuscular injection (immunization for hepatitis B or vitamin K injection)

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Gray 2012	47 healthy full-term infants	Immunization for hepatitis B	1. Sucrose (n = 15) 2. Warmth (n = 14) 3. NNS with pacifier (n =15) 3 infants were subsequently excluded from data analysis (1 in the sucrose group and 2 in the warmth)	Cumulative crying time (s) Mean HR Mean respiratory sinus arrhythmia Cumulative distribution of grimace time	Graphs only	Infants in the warmth group cried significantly less than those in the sucrose or NNS groups after vaccination. HR patterns reflected this analgesia. Core temperature did not differ between study groups. "Providing natural warmth to newborn infants during a painful procedure decreases the crying and grimacing on par with the 'gold' standard treatments of sucrose or pacifier" (Gray 2012). No data could be used in RevMan-analyses

Table 6. Trials assessing pain during intramuscular injection (immunization for hepatitis B or vitamin K injection) *(Continued)*

Gray 2015	29 healthy, full-term newborns	Immunization for hepatitis B	1. Sucrose group: 0.24 g sucrose (1 mL 24% sucrose solution, SweetEase) (n = 15) 2. Sucrose + warmth group: sucrose as above and exposed to warmth (n = 14)	Duration (s)of grimace and cry	Means and SDs	The sucrose + warmth group cried significantly less 12.8 s (SD 2.2) vs. 28.0 s (SD 6.9) and grimaced less 14.9 s (SD 2.4) vs 31.1 s (SD 7.2) than the sucrose only group Data included in RevMan-analyses
Liaw 2011	165 healthy newborn infants PMA ≥ 36 weeks and birthweight ≥ 2200 g	Immunization for hepatitis B	1. 22% sucrose orally (n = 55) 2. Routine care (n = 55) 3. NNS (n = 55)	NFCS Cry duration HR RR	Cry duration (s) was reported as mean (SD) Other outcomes reported in graph form or in multiple regression models	Pain was significantly lower among infants in the NNS (P < 0.001) and sucrose (P < 0.001) groups than that in the routine care group after adjusting for time effects, infant sleep/wake state, number of prior painful experiences, and baseline pain scores. Infants in the NNS and sucrose groups had significantly lower mean HR and RR than the controls. Cry duration of infants receiving sucrose was significantly shorter than those in the NNS (P < 0.001) and routine care groups (P < 0.001) Data for cry duration included in RevMan-analyses
Suhrabi 2014	90 full-term neonates	Immunization for hepatitis B	1. Sucrose group (n = 30): 2 mL oral sucrose (25%) through a syringe in 30 s 2. Glucose group (n = 30): 2 mL oral glucose (25%) through a syringe in 30 s 3. Control group (n = 30): no intervention Solutions applied 2 min before hepatitis B vaccination	NIPS during 1-2 min after vaccination	Mean, SD	Comparison of pain severity, mean and SD of pain, showed greater intensity of pain in the glucose group than the sucrose group (3 ± 1.66 vs. 2.90 ± 1.44), but this difference was not significant statistically (P = 0.78). Pain intensity was higher in the control group than in the intervention groups (P < 0.001) NIPS during 1-2 min after vaccine injection were used in RevMan-analyses

Abbreviations
HR = heart rate
NFCS = Neonatal Facial Coding System
NIPS = Neonatal Infant Pain Scale

NNS = non-nutritive sucking
PMA = postmenstrual age
RR = respiratory rate
SD = standard deviation

Table 7. Trials assessing pain during bladder catheterization

Study	Participants	Procedures	Intervention	Outcomes	Metrics used	Results
Rogers 2006	83 infants ≤ 90 days of age requiring bladder catheterization. 3 infants were withdrawn after randomisation as a result of inappropriate enrolment or withdrawal of consent Subgroup analysis performed: infants 1 to 30, 31 to 60 and 61 to 90 days of age	Bladder catheterization	2 min before procedure: 1. 2 mL sterile water via syringe (n = 40) 2. 2 mL 24% sucrose (0.48 g) via syringe (n = 40)	% of subjects crying at maximal insertion Change in DAN scores	Change in mean (SD) for DAN score	Subgroup analysis of youngest infants (1 to 30 days) in sucrose group showed smaller changes in DAN score compared to water group (2.86 vs. 5.29; P = 0.035) Subgroup analysis of infants (1 to 30 days) showed infants in sucrose group were significantly less likely to cry during maximal catheter insertion compared to water group (28.6% vs. 78.6%; P = 0.008) Change in DAN score and number of infants crying at maximal catheter insertion used in meta-analysis

Abbreviations
DAN = Douleur Aiguë du Nouveau-né Scale
SD = standard deviation

Table 8. Trials assessing pain during naso- (NG) or orogastric (OG) intubations

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Kristoffersen 2011	24 preterm infants. PMA 28 to 32 weeks	NG tube insertion	6 interventions: 1. no treatment 2. 0.2mL sterile water only 3. 0.2mL 30% sucrose only 4. NNS (pacifier) only 5. NNS + plus sterile water 6. NNS + 30% sucrose The solutions were administered via syringe on the tip of the tongue immediately before tube insertion	PIPP scores	Median, range	Median PIPP score during the procedure was 9 and decreased gradually towards 4 after 5 min. The NNS + 30% sucrose intervention provided most effective pain reduction (P < 0.001 vs. no treatment). Highest pain score recorded in sterile water group Becasue of the cross-over design of the study no data could be used in RevMan-analyses

Table 8. Trials assessing pain during naso- (NG) or orogastric (OG) intubations *(Continued)*

			Cross-over design: each infant acted as his or her own control over a 3-week period during which the tube was changed 6 times			
McCullough 2008	20 infants, mean (SD) PMA 30.7 weeks (2.3)	NG tube insertion	2 min prior to procedure: 1. Water group: 0.5 mL to 2 mL sterile water 2. Sucrose group: 0.5 mL to 2 mL 24% sucrose Volume of solution was adjusted for current body weight: 1. > 2 kg = 2 mL 2. 1.5 to 2 kg = 1.5 mL 3. < 1.5 kg = 0.5 mL The infants were randomised several times to either sterile water or 24% sucrose. This was not done in a cross-over fashion 51 NG insertions (26 were in the sucrose group and 25 were in the water group) were performed in the 20 infants enrolled in the study	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 during NG tube insertion and after insertion	% 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 water group (14/25) Infants in the sucrose group had higher mean pre-treatment baseline HR than water group but showed no change in HR during NG tube insertion (mean change -0.7 beats/min). 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 group 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 To see if NFCS is specific for pain, authors analyzed 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 water group; P = 0.012) Data could not be used for RevMan-analyses as infants were randomised to the two different groups several times
Pandey 2013	120 clinically stable preterms (PMA < 37 weeks) within the	OG tube insertion	2 min before OGT insertion: 1. 1 mL lingual 24% sucrose administered. Total number ran-	The primary outcome was painful response assessed by PIPP, while the sec-	Mean, SD	The mean intraprocedure PIPP scores were significantly higher than the mean pre procedure PIPP scores, in the PMA groups of > 34 weeks, and 32 to 33 6/7 weeks, in both the water (7.25 vs. 3, and 8.14 vs. 3.14, respectively) and sucrose

Table 8. Trials assessing pain during naso- (NG) or orogastric (OG) intubations *(Continued)*

	first 7 postnatal days	domised: n = 60, final analysis n = 53 2. 1 mL lingual distilled water was administered Total number randomised: n = 60, final analysis n = 52	ondary outcomes were heart rate and SpO_2 changes. The pain response to the procedure according to the PIPP scale was evaluated at preprocedure, intra procedure, post 30 s, post 1 min and post 2 min. The secondary outcomes were the maximum heart rate and the minimum oxygen saturation recorded during the procedure.	arm (8.06 vs.3.21, and 7.18 vs. 4.18, respectively). The mean PIPP scores assessed at 30 s postprocedure in the sucrose group were significantly lower than the water group (4.32 vs. 5.6, P = 00.014). No significant adverse events were seen. Data could be used in RevMan-analyses for PIPP scores but not for heart rate and SpO_2 changes. No significant difference was observed between the baseline and maximum HR, and between baseline and lowest SpO_2, across the two study groups. However, there was a significant increase in mean HR from baseline in both the study groups during the procedure to 2 min postprocedure (19.44 beats/min in placebo group vs.22.5 beats/min in sucrose group) Data used in RevMan-analyses

Abbreviations
PMA = post menstrual age
HR = heart rate
NFCS = Neonatal Facial Coding Score
NG = nasogastric
NNS = non-nutritive sucking
OG = orogastric
PIPP = Premature Infant Pain Profile
SD = standard deviation
SpO_2 = oxygen saturation

Table 9. Trials assessing pain during retinopathy of prematurity (ROP) examinations

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Boyle 2006	40 preterm infants, median PMA 29 weeks (24 to 34 weeks): 1. Sterile water	Eye examination for ROP	2 min before start of eye examination: 1. Sterile water group (n = 10): 1 mL sterile water via a syringe into the mouth 2. Sucrose group (n = 10): 1 mL 33% sucrose via a syringe into the mouth	PIPP during examination of eye	Mean, SD, 95% CI	Mean (SD) PIPP scores were: 15.3 (1.9), 14.3 (1.6), 12.3 (2.9), and 12.1 (3.4) for groups the sterile water group, sucrose group, water + NNS group, and sucrose + NNS group, respectively

Table 9. Trials assessing pain during retinopathy of prematurity (ROP) examinations *(Continued)*

	group: median PMA 27 weeks (24 to 30 weeks), median PNA 45 days 2. Sucrose group: median PMA 29 weeks (25 to 34 weeks), median PNA 43 days 3. Water + NNS group: median PMA 30 weeks (27 to 31 weeks), median PNA 41 days 4. Sucrose + NNS group: median PMA 29 weeks (24 to 31 weeks), median PNA mean 42 days		3. Water + NNS group (n = 9): 1 mL sterile water via a syringe into the mouth and pacifier 4. Sucrose + NNS group (n = 11): 1 mL 33% sucrose via a syringe into the mouth and pacifier			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 (P = 0.321) Data used in RevMan-analyses
Dilli 2014	64 infants undergoing ROP eye examination. The groups had similar GA (28.5 ± 2.8 weeks), mean birthweight (1304 g ± 466 g) or corrected GA (35.4 ± 3.7 weeks) at examination	Eye examination for ROP	Topical anaesthetic (proxymetacaine; Alcaine(®) drop 0.5%: ALCON CANADA Inc., Mississauga, Canada) was applied 30 s before the eye examination in all infants 1. Sucrose + NNS group (n = 32): 0.5 mL/kg 24% sucrose with a pacifier 2. Water + NNS group (n = 32): received 0.5 mL/kg sterile water with a pacifier	Mean PIPP score during examination; secondary outcome measurements were frequency of tachycardia (> 180 beats/min), bradycardia (< 100 beats/min), desaturations (<	Mean, SD	The intervention group had a significantly lower mean PIPP score during examination of the first eye, following insertion of the speculum (sucrose + NNS group: 13.7 ± 2.1 vs. water + NNS group: 16.4 ± 1.8, P = 0.001). Data used in RevMan-analyses

Table 9. Trials assessing pain during retinopathy of prematurity (ROP) examinations *(Continued)*

				85% for > 10 s) and crying time.		
Gal 2005	23 neonates, PMA mean (SD) 26.4 weeks (1.5) PNA 28 to 93 days	Eye examination for ROP	1. 2 mL sterile water 2. 2 mL 24% sucrose Cross-over design Mydriatic eye drops (phenylephrine HCl 1%, cyclopentolate HCl 0.2%) and local anaesthetic eye drops (proxymetacaine HCl 0.5%; 2 drops) given to both groups prior to examination	SpO_2 desaturation by ≥ 10% pre-examination, at eye speculum insertion and postexamination PIPP scores at 5 and 1 min pre-examination, eye speculum insertion, and 1 and 5 min postexamination	Percentage of population Means, SD reported	No significant difference in SpO_2 desaturation by ≥ 10% pre-examination, at eye speculum insertion between water group and sucrose group PIPP score at the eye examination significantly lower in the sucrose group (mean 8.3, SD 4.5) compared to the water group (mean 10.5, SD 4.0), P = 0.01); however, this effect was not sustained at 1 and 5 min post examination Results for the two groups prior to cross-over were not reported. No data could be used in RevMan-analyses
Grabska 2005	32 preterm infants, mean PMA 28 weeks, mean PNA 50.8 days	Eye examination for ROP	1. Water group (n = 16): sterile water delivered either directly into the mouth or via a nipple 2 min prior to eye examination 2. Sucrose group (n = 16): 24% oral sucrose delivered either directly into the mouth or via a nipple 2 min prior to eye examination Doses were adjusted by weight: 1. < 1 kg = 0.5 mL (0.12 g) 2. 1 to 1.5 kg = 1.0 mL (0.24 g) 3. 1.5 to 2 kg = 1.5 mL (0.36 g) 4. > 2 kg = 2.0 mL (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 in-	% 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*	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 water groups in HR at any time point Significant reduction in SpO_2 in sucrose group after the study drug (mean 95%, SD 4%) compared to the water group (mean 97%, SD 3%) Significant reduction in SpO_2 in sucrose group 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 difference in RR and SpO_2 at 2 min post examination

Table 9. Trials assessing pain during retinopathy of prematurity (ROP) examinations *(Continued)*

			stilled into the eyes just prior to the examination	*measures were taken at 1-min intervals and were means for each study period - study period times (in min) were not defined		No significant differences in PIPP scores between the sucrose and placebo groups before, during and after eye examinations Data for PIPP during examination used in RevMan-analyses
Mitchell 2004	30 preterm infants: 1. Water group: mean PMA 27.3 weeks, mean PNA 8.0 weeks 2. Sucrose group: mean PMA 26.5 weeks, mean PNA 8.5 weeks	Eye examination for ROP	1. Water + NNS group (n = 15): pacifier and 3 doses of 0.1 mL sterile water via syringe into the mouth 2. Sucrose + NNS group (n = 15): Pacifier and 3 doses of 0.1 mL 24% sucrose via syringe into the mouth 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 dose All infants received proxymetacaine 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 Data presented that could be used in RevMan-analyses
O'Sullivan 2010	40 preterm infants, corrected mean age: 1. Sucrose group = 33.0 ± 1.1 weeks 2. Water group = 33.1 ± 1.2 weeks	Eye examination for ROP	1. Sucrose + NNS group (n = 20): 0.2 mL sucrose with pacifier soaked in 24% sucrose solution 2. Water group (n = 20): 0.2 mL sterile water by mouth Infants were given mydriatic eye drops (cyclopentolate 0.2% and phenylephrine 1%) 60 min and 30 min prior to examination. Every neonate received local anaesthetic eye drops (tetracaine hydrochloride 1%) 30 s prior to examination. The interventions were given 2 min prior to the start of the eye examinations. The infants were swaddled in both groups	N-PASS, HR and SpO_2 at baseline, number of episodes of bradycardia and desaturation, adverse events	Median, range	Significantly lower N-PASS score at speculum insertion in sucrose compared to water group (6.5 vs. 5.0; P = 0.002); during procedure (9.5 vs. 7.5; P = 0.003). No significant differences between sucrose group and water group for episodes of desaturation, bradycardia, and adverse outcomes Data were not used in RevMan-analyses

Table 9. Trials assessing pain during retinopathy of prematurity (ROP) examinations *(Continued)*

Rush 2005	30 preterm infants < 32 weeks PMA: 1. Control group: mean PMA 28.88 weeks (range 25 to 31 weeks) 2. Sucrose group: mean PMA of 29.57 weeks (range 26 to 32 weeks)	Eye examination for ROP	Prior to examination: instillation of 0.5% proxymetacaine and 1% tropicamide, then 15 min later eye drop instillation of 0.5% tropicamide, 2.5% phenylephrine and 0.5% tropicamide 1. Control group (n = 16): no swaddling, no pacifier and no holding 2. Sucrose treatment group (n = 14): 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	Total crying time out of 5 min starting at the onset of the ROP examination HR 30 min before eye drop instillation and 5 min before ROP examination, during examination, and 5 min after the ROP examination SpO_2 and RR at 30 min before eye drop instillation, 5 min before the ROP exam, 3 measurements during the ROP exam, and 5 min after the ROP exam	Reported means and SEM Not reported SpO_2 means and SEM reported RR not reported	No significant differences in crying time between sucrose and water groups (P = 0.127) 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 Transcribed SEM to SD

CI = confidence interval
GA = gestational age
HR = heart rate
NNS = non-nutritive sucking
N-PASS = Neonatal Pain Agitation and Sedation Scale
PIPP = Premature Infant Pain Profile
PMA = postmenstrual age
PNA = postnatal age
ROP = retinopathy of prematurity
RR = respiratory rate
SD = standard deviation
SEM = standard error of the mean
SpO_2 = oxygen saturation

Table 10. Trials assessing pain during circumcision

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Al Qahtani 2014	90 full-term newborn males who underwent circumcision. PMA 38	Circumcision	1. EMLA group (n = 30): 1 g of a topical mixture of lidocaine (2.5%) and prilocaine (2.5%) cream was applied to the shaft of the	N-PASS used to assess the severity of pain and neonatal response to pain, 5 min before, during and 5 min af-	Mean, SD (Abstract says median)	N-PASS scores were significantly lower in EMLA + sucrose group (median EMLA + sucrose group = 5.2, EMLA group = 5.8, sucrose group = 8.5; P <

Table 10. Trials assessing pain during circumcision *(Continued)*

	weeks or more, 5-min Apgar score of 8 or higher, PNA of 12 h or more, birthweight > 2500 g and free from jaundice, anomalies of the penis and analgesia or sedation in the previous 48 h		penis with an occlusive dressing 1 h before the procedure 2. Sucrose group (n = 30): 2 mL oral sucrose (24% weight by volume) given through a dropper onto the tongue 2 min before the procedure 3. EMLA + sucrose group (n = 30): infants given both EMLA cream and oral sucrose as above	ter the circumcision for all newborns. The scale measures both physiologic (HR, RR, blood pressure and oxygen saturation) and behavioural (crying irritability, behaviour state, facial expression and extremities tone) responses to pain	(Tables state mean and SD)	0.001). The endogenous response to pain in terms of escalation of heart rate and reduction in O_2 saturation were minimal among EMLA + sucrose group (P < 0.0001) Duration of crying was comparable among all the groups Data used in RevMan-analyses
Herschel 1998	120 healthy male newborns, ≥ 38 weeks PMA	Circumcision	1. Control group (n = 40): no treatment 2. DPNB group (n = 40): 0.8 mL 1% lidocaine without epinephrine injected into dorsolateral penile root 3 min before procedure 3. Sucrose group (n = 39): pacifier dipped in 50% sucrose with a gauze pad moistened with sucrose inside the nipple 2 min before procedure	HR at baseline, restraint, skin preparation for procedure, lateral clamping, lysis of adhesions, 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	Mean, SD, mean differences and 95% CI	Mean change in HR from baseline through all follow-up times were significantly different between groups (P < 0.001) Mean (95% CIs) HR differences: 1. control vs. DPNB: 27.1 beats/min (17.6 to 36.6) 2. control vs. sucrose: 9.7 beats/min (0.1 to 19.3) 3. sucrose vs. DPNB: 17.4 beats/min (7.8 to 27.0) Sucrose had a 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: 1. Control: -2.5 (-15.8 to 3.12) 2. DPNB: -0.8 (-4.3 to 5.5) 3. Sucrose: 0.7 (-6.8 to 12.5) Differences between both the DPNB and sucrose groups compared to control were significant (P < 0.05)

Table 10. Trials assessing pain during circumcision *(Continued)*

						Control vs. sucrose: -3.3 (-5.0 to -1.6) was statistically significant (P < 0.001) Data used in RevMan-analyses
Kaufman 2002	57 term infants, mean age at time of procedure 30 h to 43 h	Circumcision	1. Gomco + water group (n = 14): Gomco method (of circumcision) and pacifier dipped in water 2. Gomco + sucrose group (n = 14): Gomco method and pacifier dipped in 24% sucrose 3. Mogen + water group (n = 15): Mogen method (of circumcision) and pacifier dipped in water 4. Mogen + sucrose group (n = 14): Mogen method and pacifier dipped in 24% sucrose All infants had EMLA cream applied 1 to 3 h before procedure	Time spent crying during procedure Time spent grimacing Procedure stages: 1. Table to restraint 2. Restraint to forceps 3. Forceps to excision 4. Excision to unrestraint 5. Unrestraint to 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 Mogen + water groups Overall, mean time grimacing was significantly reduced in infants treated with sucrose compared to infants treated with water (P = 0.0001) No data were presented that could be used in RevMan-analyses
Stang 1997	80 healthy, term, newborn male infants, mean PMA 39.5 weeks	Circumcision	1. DPNB + NNS group (n = 20): 0.8 mL lidocaine and 0.2 mL saline plus pacifier dipped in water and using new padded restraint chair 2. Buffered DPNB + NNS group (n = 20): 0.8 mL lidocaine and 0.2 mL sodium bicarbon-	Plasma cortisol level 30 min after beginning circumcision Behavioural arousal and behavioural distress scores were recorded at five scoring periods: 1. baseline 2. injection	Mean, SD	Plasma cortisol levels not significantly different between groups Data used in RevMan-analyses

Table 10. Trials assessing pain during circumcision *(Continued)*

			ate and pacifier dipped in water 3. DPNB + sucrose group (n = 20): 0.8 mL lidocaine and 0.2 mL saline and pacifier dipped in 24% sucrose 4. Control group (n = 20): DPNB (0.8 mL lidocaine and 0.2 mL saline) and pacifier dipped in water, rigid chair	3. immediate post injection (2 min) 4. delayed post injection (the next 2 min) 5. circumcision		

Abbreviations
CI = confidence interval
DPNB = dorsal penile nerve block
EMLA = eutectic mixture of local anaesthetics
HR = heart rate
N-PASS = Neonatal Pain Agitation and Sedation Scale
PMA = Post menstrual age
PNA = postnatal age
RR = respiratory rate
SD = standard deviation
SpO_2 = oxygen saturation

Table 11. Trials assessing pain during multiple procedures

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Banga 2015	106 infants between 32 and 37 weeks PMA Sucrose group: mean (SD) age (h) at enrolment 3.78 (2.92), mean (SD) birthweight (g) 1555.58 (242.79) Water group: mean (SD) age (h) at enrolment 3.16 (2.18), mean (SD) birthweight 1575.24 (241.89)	Repeated potentially painful procedures during the first 7 days after enrolment Mean (SD) number of procedures: 1. Sucrose group: 6.15 (1.55) 2. Water group: 6.15 (1.28) The authors did not describe which different potentially painful procedures were includ-	1. Sucrose group (n = 53): 0.5 mL sterile solution 24% sucrose (in 1 mL syringe) for every potentially painful procedure during the first 7 days after enrolment. Analyzed 47 (lost to follow-up 3, intervention discontinued 1, died 2) 2. Water group (n = 53): 0.5 mL double-distilled water (in 1 mL syringe) for every poten-	Primary outcome was score of motor development and vigor (MDV) and alertness and orientation (AO) domains of NAPI scale performed at 40 weeks PMA In addition, the highest HR and lowest SpO2 obtained during the procedure were recorded till 30 s after the prick, for newborns in both the groups (not reported)	Means, SDs, 95% CIs	A total of 93 newborns were analyzed. The baseline characteristics of the groups were comparable. No statistically significant difference was observed in the assessment at 40 weeks PMA, among the groups. Use of sucrose analgesia, for repeated painful procedures on newborns, does not lead to any significant difference in the short-term neurobehavioral outcome Data used in RevMan-analyses

Table 11. Trials assessing pain during multiple procedures *(Continued)*

		ed (we have written to the corresponding author (drbhanu04@gmail.com) to get a description of these procedures)	tially painful procedure during the first 7 days after enrolment Analyzed = 46 (lost to follow-up 5, intervention discontinued 0, died 2)			
Gaspardo 2008	33 preterm infants, median PMA 30 weeks	Venipuncture, arterial puncture, heel lance, intravenous cannulation, endotracheal tube introduction, endotracheal tube suctioning, gavage insertion for feeding, removal of electrode leads and tape	On day 1, no treatment was given to any neonate in order to collect baseline data. After that, on days 2 to 4 before every minor painful procedure infants received either: 1. Sucrose group (n = 17): 0.5 mL/kg 25% sucrose 2. Water group (n = 16): 0.5 mL/kg of sterile water	Pain was assessed over 4 days during morning blood collection (heel lance) Incidence of cry (% neonates crying), HR (% neonates with HR ≥ 160 beats per min), NFCS (% neonates with score ≥ 3), Activated Behavioural State (% neonates with score ≥ 4). The assessment was divided into five phases: Baseline Antisepsis, Puncture, Dressing, and Recovery. The neonates' facial activity (NFCS), behavioural state, and HR were evaluated	No means or standard deviations reported NFCS results reported in graph form only	The data analysis used cut-off scores for painful and distressful responses. There were significantly fewer sucrose group neonates with facial actions signalling pain than water group neonates in puncture phase and in antisepsis phase. There were significantly fewer sucrose group neonates crying during antisepsis phase, puncture phase, and dressing phase. There was no statistical difference between groups for physiological response. The efficacy of sucrose was maintained for pain relief in preterm neonates with no side effects Data could not be used in RevMan-analyses No side effects of using sucrose were detected
Johnston 2002	103 infants: 1. Sucrose group: mean PMA 28.18 (1.72)	Every time the infant was to undergo an invasive (e.g. heel lance, intravenous cannulation, arteri-	1. Sucrose group (n = 51): 0.1 mL 24% sucrose in sterile refrigerated syringe 2. Water group (n = 52): 0.1 mL water in ster-	Neurobehavioural development assessed by the sub scales of alertness and orientation and motor development	Beta, CI (multiple regression)	On the basis of analysis of covariance with PMA at birth and the number of invasive procedures as covariates, there were no group differences (between sucrose and water) for any of the secondary outcomes of Neuro-Biological Risk Scores (NBRS) at two weeks; postnatal age (P = 0.426) or at

Table 11. Trials assessing pain during multiple procedures *(Continued)*

	2. Water group: mean PMA 28.05 (2.06)	al puncture, injection) or non-invasive but presumably uncomfortable procedure (e.g. endotracheal tube suctioning, tape or lead removal, gavage insertion for feeding) the infant received sucrose or water	ile refrigerated syringe The solution was in a syringe and administered into the infant's mouth at the beginning of the procedure, 2 min into the procedure, and another 2 min into the procedure. If the procedure was > 15 min, up to another 3 0.1 mL doses were to be given 2 min apart	and vigour of the NAPI, SNAP and NBRS SNAP was measured for each 24-hour period during the study week and NBRS was measured at 2 weeks' PNA and at discharge		discharge (P = 0.965). In the sucrose group only, higher number of doses of sucrose predicted lower scores on motor development and vigor, and alertness and orientation at 36 weeks', lower motor development and vigor at 40 weeks', and higher NBRS at 2 weeks' postnatal age. Higher number of invasive procedures was predictive of higher NBRS both times in the water group. No significant differences found between the sucrose and water groups for Neurobehavioral Assessment of the Preterm Infant (NAPI). Data could not be used in RevMan-analyses
Taddio 2008	240 newborn infants born to non-diabetic and diabetic mothers, PMA ≥ 36 weeks	3 heel lances, venipuncture and intramuscular vitamin K injection Multiple painful stimuli	1. 2 mL 24% sucrose given to infants of non-diabetic mothers (n = 60) 2. 2 mL 24% sucrose given to infants of diabetic mothers (n = 60) 3. 2 mL sterile water given to infants of non-diabetic mothers (n = 60) 4. 2 mL sterile water given to infants of diabetic mothers (n = 60)	PIPP scores overall, during IM injection, during venipuncture and all 3 heel lances Safety	Mean, SD, 95% CI	Overall PIPP scores were significantly lower among newborns given sucrose (mean 6.8, SD 2.9) compared to water (mean 8.1, SD 2.5) (MD -1.3, 95% CI -2.0 to -0.6; P < 0.001) PIPP scores during IM injection did not differ between the sucrose and water group for non-diabetic (P = 0.10) or diabetic mothers (P = 0.15) PIPP scores during venipuncture were significantly lower among infants of non-diabetic mothers who received sucrose compared to water (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. water: 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 water did not have significantly different PIPP scores Results for different painful stimuli reported separately Data could be used in RevMan-analyses

Abbreviations

CI = confidence interval
PMA = gestational age
HR = heart rate
IM = intramuscular
MD = mean difference
NAPI = Neurobehavioral Assessment of the Preterm Infant
NBRS = Neuro-Biological Risk Score
NFCS = Neonatal Facial Coding System
PCA = postconceptional age
PIPP = Premature Infant Pain Profile
PMA = postmenstrual age
PNA = postnatal age
SD = standard deviation
SNAP = Score for Neonatal Acute Physiology
SpO_2 = oxygen saturation

Table 12. Trials assessing stress during echocardiography

Study	Participants	Procedure	Interventions	Outcomes	Metrics used	Results
Potana 2015	Neonates with established enteral feeding, not on any respiratory support and with PMA 32 to 42 weeks requiring echocardiography	Echocardiography	1. Sucrose group (n = 52): (Arbineo 24% w/v oral solution) 2 min prior to echocardiograph by a dropper. Dose: a. 1mL for 32 to 40 weeks b. 2mL for > 40 weeks 2. Control group (n = 52): no medication/no placebo	PIPP	Mean, SD	The mean (SD) PIPP score was significantly lower in the sucrose group 5.25 (1.92) vs 7.40 (3.78) in the control group 4 (7.6%) neonates spat up the sucrose solution after administration. No episodes of hyperglycaemia, necrotizing enterocolitis, or feed intolerance were reported after sucrose administration Data could be used in RevMan-analyses

Abbreviations
PIPP = Premature Infant Pain Profile
PMA = postmenstrual age
SD = standard deviation

APPENDICES

Appendix 1. Search terms used for searches of PubMed

Sucrose AND pain AND ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomised [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])).

WHAT'S NEW

Date	Event	Description
6 February 2017	Amended	Added external source of support

HISTORY

Protocol first published: Issue 2, 1998
Review first published: Issue 2, 1998

Date	Event	Description
31 March 2016	New citation required but conclusions have not changed	Authors' conclusions are not changed with the inclusion of additional studies.
15 March 2016	New search has been performed	This review was updated in 2016. An additional 20 studies were accepted for inclusion for a total of 74 studies. The total number of infants included in the review is now 7049. We converted 95% confidence intervals to standard deviations. We performed the comparisons based on the different concentrations of sucrose used and on the different control interventions. This resulted in a large number of comparisons and RevMan-analyses. Most comparisons and outcomes included a limited number of studies and infants. Although we included a total of 37 comparisons, we include 'Summary of findings' tables for primary outcomes (validated pain scales) and GRADE assessments based on the GRADE assessment tables that are available in RevMan.
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.
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.
3 February 2008	Amended	Converted to new review format.
20 April 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

For this update of the review the authors made these contribution:

Bonnie Stevens:

- writing the text of the background and discussion sections of the review;
- editing the text of the review.

Janet Yamada:

- literature search and identification of trials for inclusion;
- editing the text of the review.

Arne Ohlsson:

- literature search and identification of trials for inclusion;
- evaluation of methodological quality of included trials;
- abstraction of data;
- entering and verifying and data inRevMan;
- writing the text of the methods, results and reference sections of the review;
- completing the tables; characteristics of studies and additional tables;
- completing the summary of findings tables.

Sarah Haliburton:

- literature search and identification of trials for inclusion;
- evaluation of methodological quality of included trials;
- abstraction of data;
- verifying data and results in RevMan;
- checking for data accuracy in the results section;
- writing of text of review.

Allyson Shorkey:

- literature search and identification of trials for inclusion;
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- writing of text of review.

DECLARATIONS OF INTEREST

Bonnie Stevens - is an author of the following included trials: Gibbins 2002; Johnston 1997; Mitchell 2004; Stevens 1999; Stevens 2005a. For these trials two authors (SH, AS) did the data abstraction and RoB assessments. No other conflict of interest to declare

Janet Yamada - is an author of the following included trial: Stevens 2005a. For this trial two other authors (SH, AS) did the data abstraction and RoB assessments. No other conflict of interest to declare.

Arne Ohlsson - - is an author of the following included trial: Gibbins 2002. For this trial two other authors (SH, AS) did the data abstraction and RoB assessments. No other conflict of interest to declare.

Sarah Haliburton - No conflict of interest to declare

Allyson Shorkey - No conflict of interest to declare

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

- Canadian Institutes of Health Research (CIHR) Synthesis Grant: Knowledge Translation, Canada.

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

  Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C
- National Institute for Health Research, UK.

  Editorial support for Cochrane Neonatal has been funded with funds from a UK National Institute of Health Research Grant (NIHR) Cochrane Programme Grant (13/89/12). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the UK Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the update of the review in 2013, inclusion criteria were extended to all studies that used sucrose as an intervention for any acute painful procedure, including subcutaneous injections, circumcision, bladder catheterizations and eye examinations for retinopathy of prematurity, as well as repeated doses of sucrose. Long-term neurodevelopmental outcomes were added for that update. For this update in 2016 echocardiographic exam was added as a potentially stressful intervention.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Analgesics [*administration & dosage]; Infant, Premature; Pain [physiopathology] [*prevention & control]; Pain Measurement; Punctures [adverse effects]; Randomized Controlled Trials as Topic; Sucrose [*administration & dosage]

MeSH check words

Humans; Infant, Newborn