Blood sampling in infants (reducing pain and morbidity)

Search date July 2007

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ABSTRACT

INTRODUCTION: Preterm or ill neonates may undergo 1 to 21 heel punctures or venepunctures per day. These punctures are likely to be painful. Heel punctures comprise 61% to 87% and venepunctures comprise 8% to 13% of the invasive procedures performed on ill infants. Analgesics are rarely given specifically for blood sampling procedures, but 5% to 19% of infants receive analgesia for other indications. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of interventions to reduce pain-related distress and morbidity during venepuncture in preterm or term babies aged under 12 months in a neonatal unit? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2007 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 16 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: oral sweet solutions; pacifiers; and topical anaesthetics (lidocaine–prilocaine cream, tetracaine).

QUESTIONS

What are the effects of interventions to reduce pain-related distress and morbidity during venepuncture in preterm or term babies under 12 months in a neonatal unit? 3

INTERVENTIONS

VENEPUNCTURE

Likely to be beneficial

Oral sweet solutions 3

Pacifiers 10

Topical anaesthetics (lidocaine–prilocaine cream, tetracaine) 12

To be covered in future updates

Interventions in children in hospital over 1 year old

Key points

- Blood samples are usually taken from infants via heel punctures or venepuncture.

  Both procedures are likely to be painful, especially in younger infants, but analgesia is rarely given.

  Infants who have already experienced pain during heel punctures seem more likely to show signs of pain during later blood sampling than infants not experiencing such pain initially.

- High concentrations of oral sugar solutions are likely to reduce pain, either given together with a pacifier, or directly into the mouth before blood sampling.

  Oral 24% to 30% sucrose and 25% to 30% glucose solutions reduce signs of pain, especially crying, compared with water or no treatment in term and preterm infants. Oral 30% dextrose solution may also be effective.

  Lower concentrations of sugar solutions (10–12%) do not seem to be effective at reducing pain.

  Long-term use of oral sugar solutions has theoretical risks of hyperglycaemia and necrotising enterocolitis.

- Pacifiers without sugar solutions may also reduce pain responses compared with no treatment.

  Transient choking and oxygen desaturation may occur with the use of pacifiers, or after giving oral sugar solutions directly into the mouth.

- Topical anaesthetics may reduce pain responses to blood sampling compared with placebo.

  Topical lidocaine–prilocaine cream and tetracaine gel or patches reduced signs of pain in most studies of term and preterm infants.

  Adverse effects tend to be minor and transient, but systemic absorption may occur in young infants, which increases the risk of methaemoglobinaemia.

  We do not know whether oral sugars are more or less effective than topical anaesthetics in reducing pain from blood sampling.

DEFINITION

Methods of sampling blood in infants include heel puncture, venepuncture, and arterial puncture. **Venepuncture** involves aspirating blood through a needle from a peripheral vein. Heel puncture involves lancing the lateral aspect of the infant's heel, squeezing the heel, and collecting the pooled capillary blood. Heel puncture and arterial blood sampling are not discussed in this review. For this review, we included premature and term infants up to 12 months in a hospital setting.

INCIDENCE/ PREVALENCE

Preterm or ill neonates may undergo from 1 to 21 heel punctures or venepunctures per day. [1] [2] These punctures are likely to be painful. Heel punctures comprise 61% to 87% and venepunctures comprise 8% to 13% of the invasive procedures performed on ill infants. Analgesics are rarely given specifically for blood sampling procedures, but 5% to 19% of infants receive analgesia for other indications. [1] [2] In one study, comfort measures were provided during 63% of venepunctures and 75% of heel punctures. [2]

AETIOLOGY/ RISK FACTORS

Blood sampling in infants can be difficult to perform, particularly in preterm or ill infants. Young infants may have increased sensitivity and prolonged response to pain compared with older age groups. [3] Factors that may affect the infant's pain responses include corrected gestational age, previous pain experience, and procedural technique.

PROGNOSIS

Pain caused by blood sampling is associated with acute behavioural and physiological deterioration. [3] Experience of pain during heel puncture seems to heighten pain responses during subsequent blood sampling. [4] Other adverse effects of blood sampling include bleeding, bruising, haematoma, and infection.

AIMS OF INTERVENTION

To obtain an adequate blood sample by venepuncture, with minimal pain-related stress and morbidity for the infant and minimal adverse effects of treatments.

OUTCOMES

The assessment of pain is difficult in preverbal children. We found no easily administered, widely accepted assessment of pain in infants. Where available, we have analysed the proportion of infants crying, or the duration of crying. Other pain-related responses measured in the studies included facial expressions (the number of specific expressions, or the duration of those expressions), heart rate, and transcutaneous oxygen saturation levels. Studies used composite scales composed of behavioural and cardiorespiratory signs of pain-related distress, only some of which have been validated, such as the Premature Infant Pain Profile scale. We did not pool differences in pain-related responses or for different pain scales. Pain assessment methods varied in the RCTs, and a validated scale was not always used. Some measurements (e.g., facial expression) are difficult to score objectively. In many RCTs, blinding was not possible (e.g., where pacifiers were used).

METHODS

Clinical Evidence search and appraisal July 2007, and additional hand searches by contributors. The following databases were used to identify studies for this review: Medline 1966 to July 2007, Embase 1980 to July 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials, Issue 2, 2007. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as “open”, “open label”, or not at least single-blinded where blinding was possible (blinding not possible where pacifiers were used). In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 17). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions to reduce pain-related distress and morbidity during venepuncture in preterm or term babies under 12 months in a neonatal unit?**

OPTION ORAL SWEET SOLUTIONS

- For GRADE evaluation of interventions for Blood sampling in infants (reducing pain and morbidity), see table, p 17 .
- High concentrations of oral sugar solutions are likely to reduce pain, either given together with a pacifier, or directly into the mouth before blood sampling. Oral 24% to 30% sucrose and 25% to 30% glucose solutions reduce signs of pain, especially crying, compared with water or no treatment in term and preterm infants. Oral 30% dextrose solution may also be effective. Lower concentrations of sugar solutions (10–12%) do not seem effective at reducing pain. Long-term use of oral sugar solutions has theoretical risks of hyperglycaemia and necrotising enterocolitis.

Benefits and harms

Oral sucrose versus oral water:

We found one systematic review (search date 2004; 3 RCTs). [5] The systematic review did not perform a meta-analysis, so the RCTs [6] [7] [8] are reported here separately. The first RCT compared 12% sucrose and 24% sucrose versus water. [6] The second RCT compared 25% sucrose versus water. [7] The third RCT compared six treatments: 2 mL of water, 2 mL of 30% sucrose, 2 mL of 30% glucose, 2 mL of 30% sucrose plus a pacifier, a pacifier alone, and no treatment. [8]

Response to pain

Oral sucrose compared with oral water Oral sucrose (24–30%) seems more effective at reducing crying time and pain scores as assessed using the Douleur Aiguë du Nouveau-né (DAN) scale (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crying					
[6] RCT **3-armed trial**	28 preterm infants undergoing venepuncture In review [5] The remaining arm evaluated 12% sucrose	**Mean duration of first cry** 19 seconds with 24% sucrose 73 seconds with water 20 infants in this comparison	P <0.05	○○○	24% sucrose
[6] RCT **3-armed trial**	28 preterm infants undergoing venepuncture In review [5] The remaining arm evaluated 24% sucrose	**Mean duration of first cry** 63 seconds with 12% sucrose 73 seconds with water 20 infants in this comparison	Reported as not significant P value not reported	⟷	Not significant
[7] RCT	39 preterm neonates undergoing venepuncture In review [5]	**Mean duration or first cry** 19 seconds with 25% sucrose 52 seconds with water	Mean difference: 34 seconds 95% CI 16 seconds to 51 seconds P <0.001	○○○	25% sucrose
[7] RCT	39 preterm neonates undergoing venepuncture In review [5]	**Mean total duration of crying** 32 seconds with 25% sucrose 73 seconds with water	Mean difference: 41 seconds 95% CI 19 seconds to 62 seconds P = 0.001	○○○	25% sucrose
Composite scales: Douleur Aiguë du Nouveau-né [DAN]					
[8] RCT **6-armed trial**	150 term newborn infants undergoing venepuncture	**Median DAN scores** 5 with 30% sucrose 7 with water	Median difference: 2 95% CI 0 to 4 P = 0.01	○○○	30% sucrose

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [5] The remaining arms evaluated 30% glucose, 30% sucrose plus a pacifier, a pacifier alone, and no treatment	50 infants in this comparison			

Adverse effects

No data from the following reference on this outcome. [5] [6] [7] [8]

Oral sucrose plus pacifiers versus pacifiers alone:

We found one systematic review, [5] which identified one RCT. [8] It compared six treatments: 2 mL of water, 2 mL of 30% sucrose, 2 mL of 30% glucose, 2 mL of 30% sucrose plus a pacifier, a pacifier alone, and no treatment. [8]

Response to pain

Oral sucrose plus pacifier compared with pacifier alone 30% oral sucrose plus a pacifier is no more effective at reducing pain scores as assessed using the DAN scale (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Composite scales: Douleur Aiguë du Nouveau-né [DAN]					
[8] RCT **6-armed trial**	150 term newborn infants undergoing venepuncture In review [5] The remaining arms evaluated water, 30% sucrose, glucose, and no treatment	**Median DAN scores** 1 with 30% sucrose plus pacifier 2 with pacifier alone 50 infants in this comparison	Median difference: 1 95% CI 0 to 2 P = 0.06	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [5] [8]

Oral glucose versus water or no glucose:

We found four RCTs comparing 1 to 2 mL oral 10% to 30% glucose versus water. [8] [9] [10] [11] The first RCT compared six treatments: 2 mL of water, 2 mL of 30% sucrose, 2 mL of 30% glucose, 2 mL of 30% sucrose plus a pacifier, a pacifier alone, and no treatment. [8] The second RCT compared 30% glucose with no treatment. [9] The third RCT compared 25% glucose and 10% glucose with water. [10] The fourth RCT compared two different volumes of 30% glucose solution (2 mL and 0.4 mL) versus water. [11]

Response to pain

Oral glucose compared with water or no glucose 30% glucose is more effective at reducing pain responses as assessed using the Premature Infant Pain Profile (PIPP) and at reducing the duration of crying (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crying					
[9] RCT	120 term newborn infants, 60 of whom had venepuncture and were analysed separately Subgroup analysis	**Mean crying time** 12 seconds with 30% glucose 27 seconds with no treatment	Reported as not significant P value not reported	⟷	Not significant
[10] RCT **3-armed trial**	60 preterm infants undergoing venepuncture The remaining arm evaluated 10% glucose	**Mean duration of crying** 41 seconds with 25% glucose 86 seconds with water	P = 0.04	○○○	25% glucose
[10] RCT **3-armed trial**	60 preterm infants undergoing venepuncture The remaining arm evaluated 25% glucose	**Mean duration of crying** 69 seconds with 10% glucose 86 seconds with water	P = 0.23	⟷	Not significant
[11] RCT **3-armed trial**	58 clinically stable infants, at least 30 weeks gestation at birth, undergoing venepuncture The remaining arm evaluated 0.4 ml glucose	**Mean duration of first cry** 0 seconds with glucose 2 mL 13 seconds with water 38 infants in this comparison	P <0.05	○○○	glucose 2 mL
[11] RCT **3-armed trial**	58 clinically stable infants, at least 30 weeks' gestation at birth, undergoing venepuncture The remaining arm evaluated 0.4 ml glucose	**Proportion of infants who cried** 0% with glucose 2 mL 11% with water Absolute numbers not reported 38 infants in this comparison	P <0.05	○○○	glucose 2 mL
[11] RCT **3-armed trial**	58 clinically stable infants, at least 30 weeks gestation at birth, undergoing venepuncture The remaining arm evaluated 0.4 ml glucose	**Mean time to first cry** 300 seconds with glucose 2 mL 2 seconds with water 38 infants in this comparison	P <0.05	○○○	glucose 2 mL
[11] RCT **3-armed trial**	58 clinically stable infants, at least 30 weeks' gestation at birth, undergoing venepuncture The remaining arm evaluated 2 ml glucose	**Median duration of first cry** 18 seconds with glucose 0.4 mL 13 seconds with water 40 infants in this comparison	Reported as not significant P value not reported	⟷	Not significant
[11] RCT **3-armed trial**	58 clinically stable infants, at least 30 weeks' gestation at birth, undergoing venepuncture	**Proportion of infants that cried** 9% with 0.4 mL glucose 11% with water	Reported P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated 2 ml glucose	Absolute numbers not reported 40 infants in this comparison			
[11] RCT **3-armed trial**	58 clinically stable infants, at least 30 weeks gestation at birth, undergoing venepuncture The remaining arm evaluated 2 ml glucose	**Mean time to first cry** 2 seconds with 0.4 mL glucose 2 seconds with water 40 infants in this comparison	Reported as not significant P value not reported	⟷	Not significant
Composite scales: Douleur Aiguë du Nouveau-né (DAN) , Premature Infant Pain Profile (PIPP)					
[8] RCT **6-armed trial**	150 term newborn infants undergoing venepuncture The remaining arms evaluated 30% sucrose, 30% sucrose plus a pacifier, a pacifier alone, and no treatment	**Median DAN scores** 5 with 30% glucose 7 with water 50 infants in this comparison	Median difference: 2 95% CI 1 to 4 P = 0.005	○○○	30% glucose
[9] RCT	120 term newborn infants, 60 of whom had venepuncture and were analysed separately Subgroup analysis	**Mean PIPP score** 3 with 30% glucose 6 with no glucose	P = 0.02	○○○	30% glucose
[11] RCT **3-armed trial**	58 clinically stable infants, at least 30 weeks' gestation at birth, undergoing venepuncture The remaining arm evaluated 0.4 ml glucose	**Median PIPP score** 5.5 with with glucose 2 mL 11 with water	P = 0.01	○○○	glucose 2 ml
[11] RCT **3-armed trial**	58 clinically stable infants, at least 30 weeks' gestation at birth, undergoing venepuncture The remaining arm evaluated 2 ml glucose	**Median PIPP score** 7 with with glucose 0.4 mL 11 with water 40 infants in this comparison	Reported as not significant P value not reported	⟷	Not significant
Other pain-related responses					
[11] RCT **3-armed trial**	58 clinically stable infants, at least 30 weeks' gestation at birth, undergoing venepuncture	**Oxygen consumption (mL/kg)** 1.1 with glucose 2 mL 1.7 with glucose 0.4 mL 1.5 with water	Reported as not significant P value not reported	⟷	Not significant
[11] RCT **3-armed trial**	58 clinically stable infants, at least 30 weeks' gestation at birth, undergoing venepuncture	**Heart rate increase (beats per minute)** 17 with glucose 2 mL 19 with glucose 0.4 mL 23 with water	P = 0.61 among groups	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [8] [9] [10] [11]

Oral sucrose versus topical anaesthetics:

We found one systematic review (search date 2004), which did not perform a meta-analysis. [12] It identified one RCT comparing lidocaine–prilocaine cream versus 24% sucrose versus lidocaine–prilocaine cream plus sucrose versus water. [6]

Response to pain

Oral sucrose compared with topical anaesthetics We don't know whether oral sucrose is more effective than lidocaine–prilocaine cream at reducing crying time (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crying					
[6] RCT **4-armed trial**	55 venepunctures in 51 term neonates In review [12] The remaining arms evaluated lidocaine–prilocaine cream plus sucrose, and water	**Crying** with 24% sucrose with lidocaine–prilocaine cream Absolute results reported graphically Less crying with 24% sucrose	Significance not assessed		

Oral glucose versus topical anaesthetics:

We found one systematic review (search date 2004; 1 RCT). [12] The RCT identified by the review compared 30% oral glucose plus topical placebo versus topical lidocaine–prilocaine anaesthetic cream plus oral water. [13]

Response to pain

Oral glucose compared with topical anaesthetics 30% oral glucose is more effective at reducing pain as assessed using the PIPP scale (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crying					
[13] RCT	201 term infants undergoing venepuncture In review [12]	**Median duration of crying , first 3 minutes** 1 second with 30% oral glucose plus topical placebo 18 seconds with topical lidocaine–prilocaine anaesthetic cream plus oral water	P = 0.001	○○○	30% oral glucose
Composite scales: Premature Infant Pain Profile [PIPP]					
[13] RCT	201 term infants undergoing venepuncture In review [12]	**Mean PIPP scores** 4.6 with 30% oral glucose plus topical placebo 5.7 with topical lidocaine–prilocaine anaesthetic cream plus oral water	P = 0.03	○○○	30% oral glucose

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[13] RCT	201 term infants undergoing venepuncture In review [12]	**Proportion of infants with pain defined as PIPP score over 6** 19% with 30% oral glucose plus topical placebo 42% with topical lidocaine–prilocaine anaesthetic cream plus oral water Absolute numbers not reported	P = 0.0007	○○○	30% oral glucose

Oral dextrose versus water:

We found one RCT comparing 30% dextrose versus water. [14]

Response to pain

Oral dextrose compared with water Oral dextrose is more effective at reducing crying time and reducing pain as assessed using the Neonatal Infant Pain Scale (NIPS) (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crying					
[14] RCT	52 neonates with birth weight of at least 2500 g, admitted to hospital with jaundice, undergoing venepuncture	**Median duration of crying** 45 seconds with 30% dextrose 191 seconds with water	P = 0.03	○○○	30% dextrose
Composite scales: Neonatal Infant Pain Scale (NIPS)					
[14] RCT	52 neonates with birth weight of at least 2500 g, admitted to hospital with jaundice, undergoing venepuncture	**Median NIPS score , 3 minutes after venepuncture** 13 with dextrose 21 with water	P = 0.03	○○○	30% dextrose

Adverse effects

No data from the following reference on this outcome. [14]

Other sweeteners:

We found no RCTs of other sweeteners for venepuncture.

Different concentrations of oral glucose versus each other:

We found one RCT comparing 25% glucose and 10% glucose. [10]

Response to pain

Different concentrations of oral glucose compared with each other 25% glucose is more effective than 10% glucose at reducing the duration of crying (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crying					
[10] RCT **3-armed trial**	60 preterm infants undergoing venepuncture The remaining arm evaluated water	**Mean duration of crying** 41 seconds with 25% glucose 69 seconds with 10% glucose	P = 0.03	○○○	25% glucose

Adverse effects

No data from the following reference on this outcome. [10]

Oral sucrose versus oral glucose:

We found one RCT comparing six treatments: 2 mL of water, 2 mL of 30% sucrose, 2 mL of 30% glucose, 2 mL of 30% sucrose plus a pacifier, a pacifier alone, and no treatment. [8]

Response to pain

Oral sucrose compared with oral glucose We don't know whether oral sucrose is more effective at reducing pain scores assessed using the DAN scale (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Composite scales: Douleur Aiguë du Nouveau-né (DAN)					
[8] RCT **6-armed trial**	150 term newborns undergoing venepuncture The remaining arms evaluated water, 30% sucrose plus a pacifier, a pacifier alone, and no treatment	**Median DAN scores** 5 with 30% sucrose 5 with 30% glucose 50 infants in this comparison	Significance not assessed for 30% sucrose *v* 30% glucose		

Adverse effects

No data from the following reference on this outcome. [8]

Further information on studies

[11] The results from oxygen consumption and heart rate during venepuncture, suggest that infants who received glucose did still feel a degree of stress, despite having lower pain scores.

Comment: Transient choking and oxygen desaturation have been reported with the administration of oral sweeteners (directly into the mouth and when given on a pacifier). [15] The safety of repeated oral

administration of sucrose or glucose has not been adequately investigated. Theoretical adverse effects include hyperglycaemia and necrotising enterocolitis.

OPTION PACIFIERS

- For GRADE evaluation of interventions for Blood sampling in infants (reducing pain and morbidity), see table, p 17 .
- Pacifiers without sugar solutions may also reduce pain responses compared with no treatment. Transient choking and oxygen desaturation may occur with the use of pacifiers, or after giving oral sugar solutions directly into the mouth.

Benefits and harms

Pacifiers versus oral water:

We found 1 RCT comparing six treatments: 2 mL of water, 2 mL of 30% sucrose, 2 mL of 30% glucose, 2 mL of 30% sucrose plus a pacifier, a pacifier alone, and no treatment. [8]

Response to pain

Pacifers compared with oral water Pacifers are more effective at reducing pain scores as assessed using the Douleur Aiguë du Nouveau-né (DAN) scale (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Composite scales: Douleur Aiguë du Nouveau-né (DAN)					
[8] RCT **6-armed trial**	150 term newborn infants undergoing venepuncture The remaining arms evaluated 30% sucrose, 30% glucose, 30% sucrose plus a pacifier, and no treatment	**Median DAN score** 2 with pacifiers 7 with water 50 infants in this comparison	Median difference: 5 95% CI 4 to 7 P <0.0001	○○○	pacifier

Adverse effects

No data from the following reference on this outcome. [8]

Pacifiers versus oral sucrose:

We found 1 RCT comparing six treatments: 2 mL of water, 2 mL of 30% sucrose, 2 mL of 30% glucose, 2 mL of 30% sucrose plus a pacifier, a pacifier alone, and no treatment. [8]

Response to pain

Pacifers compared with oral sucrose Pacifers are more effective than oral sucrose 30% at reducing pain scores as assessed using the DAN scale (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Composite scales: Douleur Aiguë du Nouveau-né (DAN)					
[8] RCT **6-armed trial**	150 term newborn infants undergoing venepuncture The remaining arms evaluated	**Median DAN score** 2 with pacifiers 5 with 30% sucrose 50 infants in this comparison	Median difference: 3 95% CI 1 to 5 P = 0.001	○○○	pacifier

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	water, 30% glucose, 30% sucrose plus a pacifier, and no treatment				

Adverse effects

No data from the following reference on this outcome. [8]

Pacifiers versus oral glucose:

We found 1 RCT comparing six treatments: 2 mL of water, 2 mL of 30% sucrose, 2 mL of 30% glucose, 2 mL of 30% sucrose plus a pacifier, a pacifier alone, and no treatment. [8]

Response to pain

Pacifiers compared with oral glucose Pacifers are more effective than oral glucose 30% at reducing pain scores as assessed using the DAN scale (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Composite scales: Douleur Aiguë du Nouveau-né (DAN), Premature Infant Pain Profile (PIPP)					
[8] RCT **6-armed trial**	150 term newborn infants undergoing venepuncture The remaining arms evaluated water, 30% sucrose, 30% sucrose plus a pacifier, and no treatment	**Median DAN score** 2 with pacifier 5 with 30% glucose 50 infants in this comparison	Median difference: 3 95% CI 2 to 5 P = 0.0001	○○○	pacifier

Adverse effects

No data from the following reference on this outcome. [8]

Pacifiers plus oral sucrose versus oral water:

We found 1 RCT comparing six treatments: 2 mL of water, 2 mL of 30% sucrose, 2 mL of 30% glucose, 2 mL of 30% sucrose plus a pacifier, a pacifier alone, and no treatment. [8]

Response to pain

Pacifiers plus oral sucrose compared with oral water Pacifiers plus oral sucrose 30% are more effective at reducing pain scores as assessed using the DAN scale (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Composite scales: Douleur Aiguë du Nouveau-né (DAN), Premature Infant Pain Profile [PIPP]					
[8] RCT **6-armed trial**	150 term newborn infants undergoing venepuncture The remaining arms evaluated 30% sucrose, 30% glucose, a pacifier alone, and no treatment	**Median DAN score** 1 with pacifier plus 30% sucrose 7 with water 50 infants in this comparison	Median difference: 6 95% CI 5 to 8 P <0.0001	○○○	pacifier plus 30% sucrose

Adverse effects

No data from the following reference on this outcome. [8]

Pacifiers versus oral sucrose plus pacifiers:

See benefits and harms of oral sweet solutions, p 3 .

See benefits and harms of oral sweet solutions:

See benefits and harms of topical anaesthetics, p 12 .

Further information on studies

Comment: The use of pacifiers has been associated with transient choking and oxygen desaturation.

OPTION TOPICAL ANAESTHETICS (LIDOCAINE–PRILOCAINE CREAM, TETRACAINE)

- For GRADE evaluation of interventions for Blood sampling in infants (reducing pain and morbidity), see table, p 17 .
- Topical anaesthetics may reduce pain responses to blood sampling compared with placebo. Topical lidocaine–prilocaine cream and tetracaine gel or patches reduced signs of pain in most studies of term and preterm infants. Adverse effects tend to be minor and transient, but systemic absorption may occur in young infants, which increases the risk of methaemoglobinaemia. We don't know whether oral sugars are more or less effective than topical anaesthetics in reducing pain from blood sampling.

Benefits and harms

Lidocaine–prilocaine cream versus placebo:

We found systematic review (search date 2004) [12] which found four RCTs, one of which met our inclusion criteria. [16]

Response to pain

Lidocaine–prilocaine cream compared with placebo We don't know whether lidocaine–prilocaine cream is more effective at reducing pain scores or duration of crying in infants undergoing venepuncture (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crying					
[16] RCT	60 healthy term neonates undergoing venepuncture In review [12]	**Proportion of infants who did not cry** 19/28 (68%) with lidocaine–prilocaine 14/28 (50%) with placebo	P = 0.12	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [16]

Tetracaine gel or patches versus placebo:

We found found four RCTs. [17] [18] [19] [20] The first RCT compared tetracaine gel, applied under occlusion for 1 hour, versus placebo. [17] The second RCT compared tetracaine patches versus placebo. [18] The third RCT compared tetracaine gel versus placebo, both applied 30 minutes prior to venepuncture under occlusive dressing. [19] The fourth RCT compared tetracaine gel versus placebo. [20] See comment for additional information about adverse effects.

Response to pain

Tetracaine gel compared with placebo Tetracaine is be more effective at reducing pain scores as assessed using the Neonatal Facial Coding System (NFCS) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crying					
[17] RCT	40 term and preterm newborn infants, gestational age 27–41 weeks, undergoing venepuncture	**Proportion who did not cry** 15/19 (79%) with tetracaine gel (applied under occlusion for 1 hour) 5/20 (25%) with placebo	P = 0.001	○○○	tetracaine
[19] RCT	137 stable premature infants, gestational age 29 to 37 weeks, undergoing venepuncture	**Median duration of crying , first minute after venepuncture** 5 seconds with tetracaine gel 0.5 seconds with placebo	P = 0.84	⟷	Not significant
[19] RCT	137 stable premature infants, gestational age 29 to 37 weeks, undergoing venepuncture	**Proportion of children who cried** 58% with tetracaine gel 50% with placebo Absolute numbers not reported	Significance not assessed		
Composite scales: Neonatal Facial Coding System (NFCS), Premature Infant Pain Profile (PIPP), other					
[17] RCT	40 term and preterm newborn infants, gestational age 27 to 41 weeks, undergoing venepuncture	**Median NFCS score** 3 with tetracaine gel (applied under occlusion for 1 hour) 16 with placebo	P = 0.001	○○○	tetracaine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[18] RCT	32 newborn infants undergoing venepuncture, gestational age 32 to 42 weeks	**Median NFCS pain scores** 0 with tetracaine patches 12.5 with placebo	P = 0.0002	○○○	tetracaine
[19] RCT	137 stable premature infants, gestational age 29 to 37 weeks, undergoing venepuncture	**Mean PIPP score** 7.7 with tetracaine gel 7.6 with placebo	P = 0.91	⟷	Not significant
[20]	40 neonates over 32 weeks' gestation undergoing venous cannulation	**Pain severity** with tetracaine gel with placebo Absolute results not reported 12-point pain scale, which included assessments of facial expression, cry, and heart rate (total scores from 0–2 = no pain, to 9–12 = severe pain)	P <0.01	○○○	tetracaine

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT	137 stable premature infants, gestational age 29 to 37 weeks, undergoing venepuncture	**Skin erythema** 7 infants with tetracaine gel 4 infants with placebo	P = 0.53	⟷	Not significant
[20] RCT	40 neonates over 32 weeks' gestation undergoing venous cannulation	**Erythematous rash** 1/20 (5%) with tetracaine gel with			

No data from the following reference on this outcome. [17] [18]

Topical anaesthetic versus oral sucrose:

See benefits and harms of oral sweet solutions, p 3 .

Topical anaesthetic versus oral glucose:

See benefits and harms of oral sweet solutions, p 3 .

Topical anaesthetic versus pacifiers:

We found no RCTs.

Further information on studies

[16] The RCT did not measure crying duration or pain score. [19] The RCT did not measure crying duration or pain score.

Comment: One cohort study (500 neonates) found that lidocaine–prilocaine cream was associated with skin problems in some infants. [21] These included transient erythema, and purpuric lesions where the cream was applied. Methaemoglobinaemia can occur after application, owing to the prilocaine constituent of lidocaine–prilocaine cream. In addition, the higher body surface area to weight ratio of infants increases systemic absorption of all topical preparations; this risk is greater in preterm infants because the skin barrier is immature. Levels of methaemoglobin over 25% to 30% can cause clinical symptoms of hypoxia. [22] One RCT (47 preterm and term infants) comparing methaemoglobin levels after lidocaine–prilocaine cream application versus placebo, found that the highest mean methaemoglobin levels (2.3%; range 0.6–6.2%) occurred after 15 days of repeated doses of lidocaine–prilocaine cream. [22]

GLOSSARY

Pacifier A device with a teat that a baby sucks on for comfort. Some pacifiers can deliver a liquid to the baby. Also known as a “dummy”, “soother”, or “plug” in some countries.

Low-quality evidence 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.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Premature Infant Pain Profile (PIPP) A 7-item composite scale that scores various behavioural and cardiorespiratory pain responses over 30 seconds after the painful response, each from 0 to 3 (with a maximum score of 21).

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Oral sweet solutions One RCT added comparing both 2 mL and 0.4 mL of glucose 30% versus water. [11] It found that 2 mL of glucose 30% reduced pain scores, the proportion of infants who cried, and duration of crying compared with water. However, it found no significant difference in pain score, number of infants who cried, or duration of crying between 0.4 mL glucose 30% and water. Categorisation unchanged (Likely to be beneficial).

Topical anaesthetics Two RCTs added comparing tetracaine versus placebo. [19] [20] The first RCT found that tetracaine reduced pain scores compared with placebo. [20] The second RCT found no significant difference in pain scores or duration of crying between tetracaine and placebo. However, the majority of infants in this RCT also received oral sucrose, which may affect the generalisability of the result. [19] Categorisation unchanged (Likely to be beneficial).

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Competing interests: OK declares that she has no competing interests.
We would like to acknowledge the previous contributors of this review, Dr Deborah Pritchard, Dr Linda Franck, and Dr Ruth Gilbert.

Disclaimer

GRADE **Evaluation of interventions for Blood sampling in infants (reducing pain and morbidity).**

Important outcomes									
			Response to pain						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions to reduce pain-related distress and morbidity during venepuncture in preterm or term babies under 12 months in a neonatal unit?									
3 (109) [6] [7] [8]	Response to pain	Oral sucrose versus oral water	4	–1	+1	–1	0	Moderate	Quality point deducted for sparse data. Consistency point added for dose response. Directness point deducted for uncertainty about method of assessing outcome
1 (50) [8]	Response to pain	Oral sucrose plus pacifiers versus pacifiers alone	4	–1	0	–1	0	Low	Quality points deducted for sparse data. Directness point deducted for uncertainty about method of assessing outcome
4 (228) [8] [9] [10] [11]	Response to pain	Oral glucose versus water or no glucose	4	0	0	–1	0	Moderate	Consistency point deducted for conflicting results using different measures of outcomes, but added for dose response. Directness points deducted for co-intervention in one RCT
1 (less than 51) [6]	Response to pain	Oral sucrose versus topical anaesthetics	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about method of assessing outcome
1 (201) [13]	Response to pain	Oral glucose versus topical anaesthetics	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about method of assessing outcome
1 (52) [14]	Response to pain	Oral dextrose versus water	2	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing outcome
1 (less than 60) [10]	Response to pain	Different concentrations of oral glucose versus each other	4	–1	1	–1	0	Moderate	Quality point deducted for sparse data. Directness point deducted for not using a validated method of assessing outcomes. Consistency point added for dose response
1 (50) [8]	Response to pain	Oral sucrose versus oral glucose	4	–2	0	–1	0	Unset	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about method of assessing outcome
1 (50) [8]	Response to pain	Pacifiers versus oral water	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing outcome
1 (50) [8]	Response to pain	Pacifiers versus oral sucrose	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing outcome
1 (50) [8]	Response to pain	Pacifiers versus oral glucose	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing outcome

Important outcomes			Response to pain						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (50) [8]	Response to pain	Pacifiers plus oral sucrose versus oral water	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing outcome
1 (60) [16]	Response to pain	Lidocaine–prilocaine cream versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about method of assessing outcome
4 (249) [17] [18] [19] [20]	Response to pain	Tetracaine gel or patches versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about method of assessing outcome

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.