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[Intervention Review]

Sweet-tasting solutions for needle-related procedural pain in infants one month to one year of age

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ABSTRACT

Background

Administration of oral sucrose or glucose with and without non-nutritive sucking is frequently used as a non-pharmacological intervention for needle-related procedural pain relief in infants.

Objectives

To determine the effectiveness of sweet-tasting solutions for needle-related procedural pain in infants one month to one year of age compared with no treatment, placebo, other sweet-tasting solutions, or pharmacological or other non-pharmacological pain-relieving methods.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012); MEDLINE via Ovid (1966 to 2012); CINAHL via OVID (1982 to 2012). The World Health Organization International Clinical Trials Registry Platform was also searched for any ongoing trials. Clinical trial registries, conference proceedings and references for randomised controlled trials (RCTs) were also searched. An updated search was run to capture any new publications before finalising the review in April 2012 and no new included studies were identified. Two review authors (MK & JF) independently abstracted data and assessed quality using a standard form. Authors have been contacted for missing data.

Selection criteria

Randomised-controlled trials using a sweet-tasting solution to treat pain in healthy term infants (gestational age 37 weeks and over), between one month and 12 months of age who required needle-related procedures. These procedures included but were not limited to: subcutaneous or intramuscular injections, venepuncture, and heel lance. Studies in which the painful procedure was circumcision, lumbar puncture or supra-pubic bladder aspiration were not included as they are more severe and painful than needle-related procedures. Control conditions included no treatment or placebo (water) or any other identical intervention (same appearance and consistency) without active ingredient, another sweet-tasting solution, a pharmacological pain-relieving method (e.g. paracetamol, topical anaesthetic cream), non-pharmacological pain-relieving method (e.g. distraction method, non-nutritive sucking).

Data collection and analysis

Assessment of trial quality, data extraction and synthesis of data were performed using standard methods of the Cochrane Pain, Palliative and Supportive Care Group. We report mean differences (MD) with 95% confidence intervals (CI) using fixed-effect models as appropriate

for continuous outcome measures. We planned to report risk ratio (RR) and risk difference (RD) for dichotomous outcomes. The Chi² test and I² statistic were used to assess between-study heterogeneity.

Main results

Sixty-five (65) studies were identified for possible inclusion in this review. Fourteen published RCTs with a total of 1551 participants met the inclusion criteria. Duration of cry was significantly reduced in infants who were administered a sweet-tasting solution [MD -13.47 (95% CI -16.80 to -10.15)], $P < 0.00001$ compared with water. However, there was considerable heterogeneity between the studies ($I^2 = 94\%$) that we were unable to explain. Meta-analysis was not able to be undertaken for any of the other outcome measures, except for cry duration, because of differences in study design. However, most of the individual studies that measured pain found sucrose to significantly reduce pain compared with the control group. One study compared sucrose and Lidocaine-prilocaine cream and no significant difference was found between the two treatments for the outcomes pain and cry duration. Due to the differences between the studies, we were unable to identify the optimal concentration, volume or method of administration of sweet-tasting solutions in infants aged one to 12 months. Further large RCTs are needed.

Authors' conclusions

There is insufficient evidence to confidently judge the effectiveness of sweet-tasting solutions in reducing needle-related pain in infants (one month to 12 months of age). The treatments do, however, appear promising. Data from a series of individual trials are promising, as are the results from a subset meta-analysis of studies measuring duration of crying. Further well controlled RCTs are warranted in this population to determine the optimal concentration, volume, method of administration, and possible adverse effects.

PLAIN LANGUAGE SUMMARY

Sweet-tasting solutions for needle-related pain in infants up to one year of age

The use of needles that break the skin and cause pain is a common practice around the world with babies aged between one month and 12 months ([Appendix 4](#)). In this review we were interested in whether giving babies sugar-based solutions to taste when the needle breaks the skin will help reduce their pain. We found 14 separate studies that had asked this question. However, the differences between the studies were often too great to let us combine their findings. Overall, the studies show that different types of sugar-based solutions were effective but we were not able to confidently assert that there is strong evidence for this treatment in reducing pain. We did find some evidence that babies may not cry for as long if given sugar-based solutions. This review is broadly in agreement with two other reviews, one asking this question in younger children, and one in older children. There is a need for better studies in this field.

BACKGROUND

An infant is a child in the earliest period of life up to 12 months of age, while a neonate is a newborn infant who is less than four weeks old (Peter 2006). For many years, procedural pain and distress in both neonates during the first 28 days of their lives and older infants (up to one year of life) have been under-studied and under-treated (Cohen 2006). Several reasons have been proposed for this, such as a belief that neonates and infants do not fully experience pain as adults do (Derbyshire 1999), concern regarding the risks associated with using analgesics (Hatch 1987) and the inability of infants to verbalise their pain. Recent evidence suggests that neonates and older infants do feel pain (Derbyshire 2006). Increasing attention has been directed towards pain and distress-reducing strategies during painful procedures such as immunisations because of possible short- and long-term adverse effects. As a consequence, there has been increasing interest in the use of pharmacological agents such as local anaesthetic creams (Taddio 1998) and non-pharmacological pain-reducing interventions such as non-nutritive sucking on a pacifier (Carbajal 1999) and music and distraction interventions (Cohen 2006) to decrease pain during and after invasive procedures in neonates and infants.

Description of the condition

Worldwide, routine medical procedures are common in infancy and acute procedural pain remains one of the most common adverse stimuli experienced by infants less than one month of age (Finley 2001; Main 2000; Uman 2006). Immunisation injections constitute a necessary preventive health measure and infants receive up to 15 injections within the first 18 months of life (WHO 2005). However, the provision of the protection conferred by these vaccinations is associated with pain and distress.

In addition to the short-term distress that painful procedures can cause, it has been suggested that frequent, painful procedures may have an accumulative effect (Anand 2000a; Mitchell 2002; Reis 1996; Reis 2003; Schechter 2007). Evidence shows that children who experience moderate pain, such as with immunisation, during infancy may have significant long-term physiological, psychological and behavioural sequelae such as decreased immune system functioning (Page 2004), increased sensitivity to pain (AAP 2001; Lewis 1992; Page 2004; Reis 1997; Reis 2003; Taddio 1995), increased avoidance behaviour (AAP 2001; Lewis 1992; Page 2004; Reis 1997; Reis 2003; Taddio 1995), social hypervigilance (AAP 2001; Lewis 1992; Page 2004; Reis 1997; Reis 2003; Taddio 1995) and higher levels of anxiety before a painful procedure (Crombez 1999). Infants also tend to be less co-operative during the procedure (Taddio 1995). Early exposure to a painful procedure and its associated distress has also been linked in adulthood to fear of medical events and clinical settings, avoidance of health care (Pate 1996) and increased sensitivity to painful medical procedures (MacLaren 2007; Pate 1996; Taddio 1995).

Topical anaesthetic creams, such as lignocaine with prilocaine cream (EMLA), have been shown to be effective in relieving pain during some medical procedures including circumcision (Koren 1993). It has been argued that these creams are not as effective for deep tissue pain, such as that caused by intramuscular injections (Cohen 1999; Jain 2000; Larsson 1995; Rushforth 1995). Topical local anaesthetic creams need to be applied 30 to 60 minutes before a procedure. Therefore, this option is not seen as a quick-acting, effective strategy for use with infants (Jain 2000).

In recent years, much attention has been devoted to a variety of strategies for reducing procedural pain in infants (MacLaren 2007) such as breastfeeding (Efe 2007; Golianu 2007; Shah 2007), non-nutritive sucking on a pacifier (Blass 1999; Carbajal 1999; Golianu 2007), distraction interventions (Cohen 2006) and, most recently and increasingly, the oral administration of sweet-tasting solutions during needle-related painful procedures (Barr 1995; Blass 1995; Carbajal 1999; Gibbins 2002; Golianu 2007; Isik 2000; Jatana 2003). Breastfeeding is considered a simple way to manage needle-related procedural pain (Shah 2007) because of its comforting effect but it is not always possible (Cohen 2000; Frank 1995; Sweet 1998). The use of non-nutritive sucking for procedural pain (Aarts 1999; Schubiger 1997) is not always possible as it may not be acceptable to mothers who are exclusively breastfeeding and also contravenes the World Health Organization's recommendations for successful breastfeeding (Sadeeh 1996). Sucking on a pacifier has been associated with breastfeeding problems and early weaning (Schubiger 1997; Vallenias 1998). Conversely, a Cochrane systematic review (Jaafar 2012) found that pacifier use in full-term breastfeeding infants after birth or after the establishment of lactation did not significantly affect the prevalence or duration of exclusive or partial breastfeeding up to the age of four months. A study by Cohen 2000 found distraction interventions in infants (for example, rattles and dolls) to be more effective before and after a painful procedure than during the painful procedure itself.

Description of the intervention

Sweet-tasting oral solutions administered before painful procedures such as heel lancing and venepuncture have been found to have pain-relieving effects in infants (Blass 1995; Erikson 2004; Stevens 2004). They are increasingly being recommended as a strategy for pain management (Stevens 2004). Sucrose, a disaccharide, is derived from the condensation of the monosaccharides (simple sugars) glucose and fructose (Eliasson 2006). Sucrose and glucose are the most commonly used non-artificial sweet-tasting solutions (Gradin 2005; Kracke 2005), with fructose used less commonly (Akcem 2004). Sucrose is crystalline, water-soluble and forms a thick, sweet-tasting solution with a sticky feeling (Eliasson 2006). Glucose and fructose solutions are less thick and appear similar to water (Eliasson 2006).

There is a range of different concentrations of solutions recommended for administration (Stevens 2004). There is also a range of recommendations in relation to intervals between doses and the frequency of administration (Blass 1995). The pain-relieving effect of sucrose, for example, is reported to last about five minutes with the most intense effect at two minutes (Stevens 2004). The sweet solutions can be administered orally using a range of methods such as a syringe, dropper or pacifier (Carbajal 1999; Stevens 2004).

Preparations that contain fructose, such as sucrose (glucose and fructose), may have a deleterious effect in infants with fructose intolerance (Bucher 2000). In addition, concerns could be raised to some adverse effects in relation to sweet-tasting solutions usage such as tooth decay and obesity.

How the intervention might work

Orally administered sweet-tasting solutions have a clearly demonstrated pain-reducing effect. However, their exact mechanism of action remains largely unresolved (Gradin 2005).

It has been suggested that all sweet-tasting solutions have the same mode of action and analgesic effect (Blass 1991). One of the most common explanations is that the analgesic effect of sweet solutions works via the opioid receptors (Blass 1991; Gibbins 2002; Kracke 2005; Pomonis 2000). It has been theorised that sweet-tasting solutions trigger the release of endogenous opioids and the released beta-endorphins result in an action similar to that of an opioid (Blass 1991; Blass 1995; Carbajal 1999; Skogsdal 1997) in reducing the transmission of a pain signal to the central nervous system (Blass 1994). However, a study by Taddio 2003 did not find a significant difference in the serum beta-endorphin concentrations of preterm infants before and after a single dose of sucrose. Another study in infants found that the intravenous injection of an opioid antagonist (naloxone) did not diminish the analgesic effect of orally administered glucose given before blood sampling, casting doubt on an association between the glucose effect and activation of endogenous opioids (Gradin 2005).

A Cochrane review by Stevens 2004 included more than 20 randomised controlled trials (RCTs) to evaluate sucrose for heel stick or venepuncture in term and preterm neonates up to 28 days of age and indicated that sucrose was safe and effective in the management of pain from single procedures.

It has been hypothesised that a sweet solution's effectiveness may be the result of direct contact between the solution and the taste receptors in the mouth leading to a feeling of comfort (Barr 1999; Skogsdal 1997). It has also been suggested that sweet-tasting solutions administered via a pacifier may have a greater pain and comforting effect than sweet-tasting solutions administered via a syringe (Greenberg 2002; Reis 2003; Shah 2007).

Why it is important to do this review

While a Cochrane review has been conducted (Stevens 2004) to determine the effectiveness of sucrose during the neonatal period, less is known about the effectiveness of sweet-tasting solutions in older infants. Conflicting evidence regarding the efficacy of sweet-tasting solutions during different types of painful procedures still exists. Moreover, some findings were that a sweet solution given two minutes before the painful stimulus was only effective during the recovery phase of the procedure (Bilgen 2001; Bucher 2000; Harrison 2003). A recent Cochrane review was unable to determine the effectiveness of sucrose in infants over one year of age up to 16 years of age because of insufficient evidence (Harrison 2011). The purpose of this Cochrane systematic review was to evaluate the effectiveness of sweet-tasting solutions in the reduction of needle-related pain in infants one month to one year old.

OBJECTIVES

To determine the effectiveness of sweet-tasting solutions for needle-related procedural pain in infants one month to one year of age compared with no treatment, placebo, other sweet-tasting solutions, or pharmacological or other non-pharmacological pain-relieving methods.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) using a sweet-tasting solution to treat pain were included. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. Studies reporting treatment of consecutive pain episodes were accepted if outcomes for the first or each episode were reported separately. Cross-over studies were eligible if there was adequate outcome reporting between treatments.

Types of participants

Term healthy infants between one month and 12 months of age requiring a needle-related procedure. These procedures included, but were not limited to: subcutaneous or intramuscular injections, venepuncture, and heel lance. Studies in which the painful procedure was circumcision, lumbar puncture or supra-pubic bladder aspiration were not included.

Types of interventions

- Sweet-tasting solution versus no treatment or placebo (water or an identical intervention, same appearance and consistency, without active ingredient, e.g. glucose).
- Sweet-tasting solution versus another sweet-tasting solution.
- Sweet-tasting solution versus a pharmacological pain-relieving method (e.g. paracetamol, topical anaesthetic cream).
- Sweet-tasting solution versus a non-pharmacological pain-relieving method (e.g. distraction method, non-nutritive sucking).

Types of outcome measures

Primary outcomes

Pain assessed by a validated pain or comfort scale.

- Pain scales include the Riley Infant Pain Scale (RIPS), Neonatal Facial Coding System (NFCS), Infant Body Coding System (IBCS), E'chelle Douleur Inconfort Nouveau-Ne' (EDIN), Modified Behavioral Pain Scale (MBPS), Neonatal Infant Pain Scale (NIPS), Children's Hospital of Eastern Ontario Pain Scale (CHEOPS).
- Comfort scales including the Comfort Scale.

Secondary outcomes

- Duration of first cry (beginning of the procedure until the end of procedure). Proportion of time crying (per cent crying time from start of the procedure until the end of procedure).
- Duration of total crying time upon commencement of procedure (seconds).
- Duration of total crying time following the procedure (seconds).
- Parent stress or satisfaction using a validated scale.
- Desaturation (< 80%). Baseline heart rate (post injection heart rate difference).
- Pain assessed by a validated pain or comfort scale at subsequent procedures.
- Pain assessed by crying at subsequent procedure measured as above (seconds).

- Failure to complete subsequent procedures.
- Measurement of infant development using a validated scale.
- Developmental follow-up, by targeting infants when undergoing painful minor procedures and having sweet solutions as pain relief up to 24 months.
- Adverse events, if any (e.g. bleeding, bruising, choking, vomiting).

Search methods for identification of studies

The systematic review followed the standard search strategy methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We attempted to identify all relevant studies regardless of language or publication status. Randomised controlled trials (RCTs) were included; non-randomised controlled trials were excluded. Publications in abstract form only were not included in the review but were listed in excluded studies. Meta-analysis references were searched and used to evaluate the reviewed studies and to include those that were related to the search criteria.

Electronic searches

Two review authors independently performed the electronic database searches of: Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012); MEDLINE via Ovid (1966 to April 2012); CINAHL via OVID (1982 to April 2012). The World Health Organization International Clinical Trials Registry Platform was searched for ongoing trials.

Text word fields and, where applicable, database subject heading fields (for example, MeSH) were searched using the following terms: procedural pain management, and infant* or term neonate*, Needles or needle*, and blood sample* or immuni* or inculat* or vaccin* or inject* or finger prick* or "heel prick*" or "heel lance*" or heel-lance* or "heel puncture*" or heel-puncture* or "heel stick" or suture* or (laceration* adj3 repair*).mp. etc. Truncation symbols were used, when appropriate, to capture variations in spelling and the endings of the search terms.

In order to expand the search to include all sweet solutions, in addition to sucrose, the following search terms were used: exp sucrose/ (sucrose or glucose or sugar or ((sweet* or pleasant* or nice*) adj6 (solution* or taste or tasting)).mp. or sugar solutions or lactose or fructose or lycerine or glycerine, or dextrose, or saccharose or saccharide or aspartame, etc. expand the results.

The terms included in the electronic search strategy are included in [Appendix 1](#).

Searching other resources

We also searched symposia, proceedings of pain conferences such as the proceedings of the World Congress on Pain, in infants, previous reviews, cross references, abstracts, relevant bibliographies, expert informants and journal handsearching.

Data collection and analysis

Selection of studies

The selection of studies was performed independently by two review authors as follows.

1. Search results were merged using reference management software and duplicate records of the same reports removed.
2. Titles and abstracts were examined to remove irrelevant reports.
3. The full text of the potentially relevant reports were retrieved.
4. Multiple reports of the same study were linked together.
5. Full-text reports were examined for compliance of the studies with eligibility criteria.
6. Correspondence occurred with trial investigators, when appropriate, to clarify study eligibility.
7. At all stages, reasons for inclusion and exclusion of articles were noted.
8. Disagreements were resolved through consensus when needed.
9. Final decisions were made on study inclusion and proceeded to data collection.
10. All discrepancies were resolved through a consensus process.

Data extraction and management

Data were independently extracted from the included studies by two review authors using a pre-designed data collection form and entered electronically with appropriate version control. Each review author independently completed a comparison of extracted data. Any disagreements were discussed with a third review author and the decisions documented. Where there were missing data, we contacted the study authors using every means available (e-mail, formal letter, facsimile, phone call). All relevant data were entered into RevMan 5.1 by one review author (MK) and re-checked by second reviewer for accuracy (JF). The reliability of data extraction and data entry was examined throughout the process. When needed, a translator was asked to complete a data extraction form on behalf of the review author.

The data were extracted as follows.

- General study information such as title, authors, contact address, publication source, publication year.
- Characteristics of the study: design, study setting, inclusion and exclusion criteria, and quality criteria (e.g. randomisation method; allocation procedure; blinding of patients, caregivers and outcome assessors; withdrawals and dropouts; overall sample size; sample size per group; number of groups; painful procedure; number of interventions).
- Characteristics of the study population and baseline characteristics of the intervention and control groups (age, sex etc.) with numbers in each group.
- Characteristics of the interventions, such as treatment comparators, dose (volume), method of administration, frequency of administration, type of sweet solution, concentration of solution.
- Outcome measures (such as changes in pain behaviours or crying time).
- Results for the intention-to-treat population (where possible); outcome measures at the end of the placebo phase; any summary measures with standard deviations, confidence intervals and P values were given; dropout rate; and reasons for withdrawal.
- Adverse events.

Assessment of risk of bias in included studies

Two review authors (MK and JF) independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). To help protect against bias and misuse of statistical methods we consulted a statistician. Explicit judgements have been made about whether studies were at high risk of bias according to the criteria given in the Cochrane Handbook (Higgins 2011). With reference to (1) to (6) in the Handbook, the likely magnitude and direction of the bias have been assessed and whether considering them were likely to impact on the findings or not. We intended to explore the impact of the level of bias through undertaking sensitivity analyses (see [Sensitivity analysis](#)) if needed.

Measures of treatment effect

Data were analysed using the Cochrane statistical package RevMan 5.1 (Review Manager 2011) when appropriate. Data were then summarised in a meta-analysis if sufficiently homogeneous, both clinically and statistically.

Continuous data

For continuous data, results are presented as mean difference (MD) with 95% confidence interval (CI) determined for the individual studies. Since it was expected that some studies would be reporting mean change scores from baseline, while others would be reporting mean final scores, the MD was chosen as the measure of effect as change scores can be combined with final scores when using MD. We planned to undertake analyses separately for outcomes measured with different scales (as MD can only be used when all studies report the outcome using the same scale). If studies had measured the same outcome but used different scales, we would have used standardised mean difference (SMD).

Dichotomous data

If dichotomous data had been identified, we would have calculated risk ratios (RRs) and risk differences (RDs) with 95% CIs. If there was a statistically significant reduction in RD then the intention was to calculate the number needed to treat to benefit (NNTB) and associated 95% CI.

Unit of analysis issues

Only randomisation based on the individual patient was accepted.

Dealing with missing data

We intended that the primary analysis would be by intention-to-treat (ITT), reporting only available data (excluding where data were missing). For included studies, levels of attrition were noted. Missing data were obtained from the study authors whenever possible. Where data remained missing, we conducted sensitivity analyses to determine if results were sensitive to assumptions regarding losses using the imputation (both best and worst scenarios) method, and last observation carried forward (LOCF) to the final assessment for dichotomous and continuous outcome data respectively.

Assessment of heterogeneity

The I^2 statistic was used to measure heterogeneity among the studies in the relevant analysis. Where substantial heterogeneity was identified, it was then explored by pre-specified subgroup

analysis. The degree of heterogeneity was then graded as: 0% to 30% (might not be important); 31% to 50% (moderate heterogeneity); 51% to 75% (substantial heterogeneity); 76% to 100% (considerable heterogeneity).

Assessment of reporting biases

The standard methods of The Cochrane Collaboration were used to assess the methodological quality of the studies included in the review, addressing potential biases using a six-point 'Risk of bias' (RoB) scale (Higgins 2011). The following criteria were used: randomisation generation; concealment of allocation; blinding of intervention; incomplete outcome data reported; selective outcome reporting; other sources of bias. Possible answers to these questions were 'High risk', 'Low risk', 'Unclear risk'. Two review authors independently assessed the RoB of each study. Differences were resolved by discussion or through a third review author, if necessary. The review authors were not blinded to the study authors or institutions.

Data synthesis

Statistical analyses were carried out using the Review Manager software (Review Manager 2011). Studies using a single dose of a sweet-tasting solution were reported separately from studies in which subsequent or multiple doses of sweet-tasting solution were permitted.

Some studies had multiple treatment groups. In this case, the relevant data were used separately in each comparison (sweet-tasting solution versus no treatment or placebo; sweet-tasting solution versus another sweet-tasting solution; sweet-tasting solution versus pharmacological pain-relieving method; sweet-tasting solution versus non-pharmacological pain-relieving method). Where more than one active treatment group was eligible for inclusion in a comparison, the groups were collapsed into a single arm for comparison against the control group. We intended that data would be combined for analysis where there were at least two studies.

If possible, we planned to calculate the RR of benefit or harm with 95% CIs using a fixed-effect model (Morris 1995). We also planned to calculate the number needed to treat (NNT): number needed to treat to prevent (NNTp) and the number needed to treat to harm (NNTh) with 95% CIs using the pooled number of events following the method of Cook and Sackett (Cook 1995). A statistically significant difference from control would have been assumed when the 95% CI of the RR of benefit or harm did not include the number one. Significant differences between the number needed to treat to benefit (NNTB) or number needed to harm (NNTh) for different doses of active treatment, or between groups in the sensitivity analysis, was to be determined using the z test (Tramer 1997).

Subgroup analysis and investigation of heterogeneity

Issues for subgroup analysis were as follows.

1. Method of administration (oral syringe, dropper, pacifier).
2. Type of sweet-tasting solution (e.g. glucose, fructose, sucrose, glycerine, aspartame).
3. Concentration of sweet-tasting solution (percentage).
4. Number of dosages per painful procedure (frequency).
5. Number of painful procedures for each intervention.

6. Characteristics of participants: age (months); weight of infant (Kg).
7. Type of painful procedure.

We could only perform subgroup analysis for 'Concentration of sweet-tasting solution (percentage)'.

Sensitivity analysis

If possible, we intended to perform sensitivity analysis for aspects of the review that might affect the results, for example, where there was a risk of bias associated with the quality of some of the included trials. Studies assessed at low risk of bias were those with: adequate sequence generation, allocation concealment, less than 10% losses, and ITT analysis. Sensitivity analysis was used to explore the effects of fixed-effect or random-effects model analyses for outcomes with statistical heterogeneity and the effects of any assumptions made.

Sensitivity analysis was also undertaken for instance when the intervention may have served as a possible confounder. For example, the use of a pacifier may prevent an infant from crying not because it reduces the infant's pain but because it may not be possible for the infant to cry with a pacifier in the mouth. A minimum of two studies had to be available for any sensitivity analysis.

RESULTS

Description of studies

See: 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

Results of the search

The electronic and non-electronic searches identified 695 citations, of which 86 papers were reviewed for possible inclusion. These papers were read by two review authors (MK & JF) to determine whether they met criteria for inclusion in this review. For most of these papers, it was clear from the title or abstract, that they failed to meet the inclusion criteria, and therefore should be excluded. For example, the term 'newborn' indicated the study included infants less than one month of age. Further examination confirmed whether they did or did not meet all of the inclusion criteria. Our search retrieved six studies published in another language other than English: (Ahn 2006 (South Korean); Montoya 2009 (Spanish); Poulsen 2009 (Danish); Soriano 2003 (Spanish); Idam-Syuryun 2008 (Greek).

Included studies

Fourteen (14) published RCTs with a total of 1551 participants (experimental and control) were included: (Allen 1996 (n = 168); Barr 1995 (n = 65); Dilli 2009 (n = 29); Hatfield 2008a (n = 40); Hatfield 2008b (n = 100); Kassab 2012 (n = 120); Lewindon 1998 (n = 110); Morelius 2009 (n = 100); Mowery 2007 (n = 49); Poulsen 2009 (n = 67); Priambodo 2008 (n = 86); Ramenghi 2002 (n = 184); Soriano 2003 (n = 323) Thyr 2007 (n = 110). See Appendix 2 for more details about overall numbers and numbers used in analysis.

Treatment settings

The following treatment settings were used for the the immunisation procedures.

- Hospital ambulatory clinic (Allen 1996; Dilli 2009; Hatfield 2008a; Hatfield 2008b; Lewindon 1998; Mowery 2007; Priambodo 2008).
- Community health centre/clinic (Barr 1995; Kassab 2012; Priambodo 2008; Ramenghi 2002; Soriano 2003).
- Health department/immunisation clinic (Morelius 2009; Poulsen 2009; Thyr 2007).

Type of sweet solutions

Eleven of the studies compared sucrose and water (Allen 1996; Barr 1995; Dilli 2009; Hatfield 2008a; Hatfield 2008b; Lewindon 1998; Morelius 2009; Mowery 2007; Priambodo 2008; Ramenghi 2002; Soriano 2003); one compared sucrose and normal saline (Poulsen 2009), Two studies compared glucose and water (Kassab 2012; Thyr 2007). Ramenghi 2002 also compared lypasin (glucose) and water.

Strength of sweet solutions

Overall, the strength of sucrose used varied markedly between the studies ranging from 12% to 75%. Three studies used 12% sucrose (Allen 1996; Dilli 2009; Poulsen 2009). The strength of glucose used was 25% in one study (Kassab 2012) and 30% glucose in two studies (Morelius 2009; Thyr 2007). Three studies used 24% or 25% sucrose (Hatfield 2008a; Hatfield 2008b; Ramenghi 2002), three studies used 50% sucrose (Barr 1995; Mowery 2007; Ramenghi 2002) and a further three studies used 75% sucrose (Lewindon 1998; Priambodo 2008; Soriano 2003). Ramenghi 2002 used 40% lypasin. See Appendix 3.

Volume of sweet solutions

The majority of the studies used a total volume of two mLs of sweet solution (Allen 1996; Dilli 2009; Hatfield 2008a; Hatfield 2008b; Kassab 2012; Lewindon 1998; Mowery 2007; Poulsen 2009; Priambodo 2008; Ramenghi 2002; Soriano 2003; Thyr 2007). One study used a total volume of 1 mL (Morelius 2009) (glucose) and 0.75 mLs was used in Barr 1995 (sucrose). One study used a total volume of two mLs (lypasin) (Ramenghi 2002). See Appendix 3.

Method and timing of administration of sweet-tasting solution

The method of administering the sweet-tasting solutions varied between the studies. The solution was administered in six studies via a syringe or similar (e.g. pipette) onto the surface (anterior) of the infant's tongue with no non-nutritive sucking or comfort (Barr 1995; Dilli 2009; Mowery 2007; Poulsen 2009; Ramenghi 2002; Thyr 2007). Hatfield 2008b and Hatfield 2008a administered the solution onto the anterior tongue with non-nutritive sucking but no comfort. The solutions were administered into the infant's mouth (not targeting the tongue) in three studies (Lewindon 1998; Morelius 2009; Priambodo 2008). Morelius 2009 compared glucose alone versus water alone and glucose with non-nutritive sucking versus water with non-nutritive sucking. All of the infants in the Lewindon 1998 study received "soothing and distraction" during the interventions, and some (not all) of the infants received pre-treatment panadol and non-nutritive sucking. In the Priambodo 2008 study, no non-nutritive sucking or comforting was given. Kassab 2012 applied the solution to the 'lateral' side of the tongue using a syringe with no non-nutritive sucking or comfort. Allen 1996 and Soriano 2003 described the administration of the solution as 'oral' with no non-nutritive sucking or comforting.

The majority of the studies administered the sweet-tasting solutions two minutes before immunisation (Allen 1996; Barr 1995;

Dilli 2009; Hatfield 2008a; Hatfield 2008b; Mowery 2007; Poulsen 2009; Priambodo 2008; Ramenghi 2002; Soriano 2003). Kassab 2012 and Lewindon 1998 administered it immediately before immunisation while Thyr 2007 administered it 30 seconds prior to immunisation. Morelius 2009 did not clearly report time of administration. See Appendix 3.

Excluded studies

Fifty-three studies were excluded for a number of reasons (more details are provided in the 'Characteristics of excluded studies' table).

Risk of bias in included studies

Incomplete outcome data were inadequately addressed in only one longitudinal RCT in which data were missing for five infants at the second data collection point (Hatfield 2008b). Six studies were considered to have other problems increasing the risk of bias: four had small sample sizes of subgroups of infants included in this review (Allen 1996; Dilli 2009; Ramenghi 2002; Thyr 2007); pacifier use differed between the groups in another study (Lewindon 1998); and in a third study, insufficient information was given concerning collection of data about infants' like or dislike of the solution, but the outcome suggests a possible lack of blinding (Soriano 2003). Overall results of the 'Risk of bias' assessment are presented in Figure 1 and Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Sample size
Allen 1996	?	+	+	+	?	?
Barr 1995	?	?	?	+	?	?
Dilli 2009	?	+	+	+	?	?
Hatfield 2008a	+	+	+	+	?	+
Hatfield 2008b	+	+	+	-	?	+
Kassab 2012	+	+	+	+	+	+
Lewindon 1998	+	+	+	+	?	?
Morelius 2009	-	+	?	+	?	?
Mowery 2007	+	+	+	+	?	?
Poulsen 2009	+	+	+	+	?	?
Priambodo 2008	?	?	?	+	?	+
Ramenghi 2002	+	+	-	+	?	+
Soriano 2003	?	-	+	+	?	?
Thyr 2007	+	+	-	+	?	?

Allocation

Most of the included studies had adequate concealment of allocation as most trials were deemed to have taken adequate measures to conceal allocation (i.e. central randomisation; numbered or coded syringes or containers; solutions prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other descriptions that contained elements convincing of concealment except for three studies for which the author either did not report an allocation concealment approach or did not clearly describe if they used randomisation to assign participants to groups (Barr 1995; Priambodo 2008; Soriano 2003)).

Blinding

Blinding of interventions was achieved by most studies except in four studies (Barr 1995; Morelius 2009; Priambodo 2008; Ramenghi 2002; Thyr 2007).

Incomplete outcome data

Incomplete outcome data were addressed in all but one study (Hatfield 2008b). Twelve of the 14 studies were rated as having low risk of attrition bias (Barr 1995; Hatfield 2008a; Kassab 2012; Lewindon 1998; Morelius 2009; Mowery 2007; Poulsen 2009; Priambodo 2008; Ramenghi 2002; Soriano 2003) because the total loss to follow-up was less than 15%. However, for the Thyr 2007 study, the authors stated that the total loss for follow-up in the study was eight infants (<10% loss of total data). However, the study publication cites that there were 110 infants at three months, 109 infants at five months and 40 infants at 12 months. We have been unable to clarify this discrepancy. Hatfield 2008b did not include the data from 17 infants in the analysis.

Selective reporting

We were unable to obtain the protocol for most of the studies and, therefore, for most of the included studies the risk for reporting bias is rated 'unclear'. One study seemed to be free of selective reporting (Kassab 2012); and there was risk of 'other' bias in the rest of the studies, due to unclear reporting of sample size (Allen 1996; Barr 1995; Dilli 2009; Lewindon 1998; Morelius 2009; Mowery 2007; Poulsen 2009; Soriano 2003; Thyr 2007) or because of the small sample size in the subgroup of infants included in this review (Allen 1996; Dilli 2009; Ramenghi 2002; Thyr 2007). In addition, we noted that the authors in the Hatfield 2008b study reported data for the outcome 'pain' at two, five, seven and nine minutes post injection. In a subsequent study by Hatfield 2008a, pain was only reported at two and five minutes post injection. In addition, in the Allen 1996 study, infants in the four-month old group were excluded from the analysis. The authors report that the four-month old infants cried significantly more than the infants in the other age groups prior to injection, and thus were omitted from analysis of the outcome measures.

Other potential sources of bias

Several studies had potential for bias due to the small sample size of the subgroups of eligible infants included in this systematic review (Allen 1996; Dilli 2009; Ramenghi 2002; Thyr 2007). For Ramenghi 2002, each baby could only be enrolled once into the study, thus the immunisation groups were totally independent of each other which is in contrast to the Allen 1996 and Thyr 2007 studies in which infants were enrolled in one or more of the immunisation groups.

In Lewindon 1998, the use of pacifier, and paracetamol given to "some of the infants" could affect their "expression of pain and distress". Ten infants used a pacifier (seven in the sterile water group and three in the sucrose group) and eight infants were given paracetamol (three in the sterile water group and five in the sucrose group).

Effects of interventions

All studies included in this review compared sweet-tasting solution versus no treatment or placebo. One study (Dilli 2009) also compared sweet-tasting solution versus a pharmacological pain-relieving method (topical anaesthesia). Crying was the most widely used indicator for pain intensity in infants, followed by physiological and/or behavioural pain indicators and/or composite pain scores. Although there were insufficient data, differences in timing, method of administration, volume and strength of the sweet-tasting solution, we could undertake meta-analysis for crying.

Types of outcome measures

Primary outcomes

Sweet-tasting solutions versus placebo or no treatment

Pain assessed by validated pain scale

Because of the different study designs and outcome measures that were used and reported, the results for each of the studies are presented separately.

Seven studies assessed pain using a validated pain scale (Dilli 2009; Hatfield 2008b; Hatfield 2008a; Kassab 2012; Lewindon 1998; Mowery 2007; Poulsen 2009). All of the studies except one (Poulsen 2009), that used sucrose 12%, reported lower pain scores in infants who were given a sweet-tasting solution.

Two studies (Hatfield 2008a; Hatfield 2008b) used the zero to five-point University of Wisconsin Children's Hospital Pain Scale (n = 123). Kassab 2012 and Mowery 2007 used the zero to 10-point ordinal Modified Behavioural Pain Scale (n = 169). Dilli 2009 and Poulsen 2009 used the zero to seven-point Neonatal Infant Pain Scale (n = 67).

Hatfield 2008b used the University of Wisconsin Children's Hospital Pain Scale to compare sucrose 24% (n = 38) and sterile water (n = 45) given to infants at either the two- or four-month immunisation. The sucrose group had lower pain scores than the water group two, five, seven and nine minutes post injection. There was a difference between the sucrose and water Mean (95% confidence interval (CI)) from: baseline to two minutes -1.83 (-2.68 to -0.97), $P = < 0.001$; baseline to five minutes -1.34 (-2.20 to -0.48) $P < 0.001$; baseline to seven minutes -1.01 (-1.86 to -0.15), $P < 0.01$; and baseline to nine minutes -2.16 (-3.01 to -1.30), $P < 0.001$ post treatment administration. Hatfield 2008a also used the University of Wisconsin Children's Hospital Pain Scale to compare sucrose 24% (n = 20) and sterile water (n = 20) given to infants at either their two- or four-month immunisation. The sucrose group had lower pain scores than the water group at from baseline to five minutes (-2.74 (-4.10 to -1.92, $P < 0.0001$) following treatment administration.

Kassab 2012 used the Modified Behavioural Pain Scale to compare glucose 25% (n = 60) and water (n = 60) for infants requiring their two-month immunisation. Pain was assessed at baseline, during

immunisation and immediately post injection. No statistically significant difference was found at baseline between the glucose (Median 2.00 interquartile range (IQR) 0) and water (2.00 IQR 1) groups ($P = 0.867$); but a statistically significant difference was reported during immunisation, glucose (Median 8.00 IQR 1) versus water (Median 9.00 IQR 1), $P = 0.005$; and post immunisation, glucose (Median 4.00 IQR 1) versus water (Median 6.00 IQR 1), $P < 0.001$. [Mowery 2007](#) also used the Modified Behavioural Pain Score to compare sucrose 50% ($n = 25$) and water ($n = 24$) for infants requiring three injections at their two-, four- or six-month immunisation. There were no statistical differences for the pain scores between the sucrose and water groups at baseline 3.00 (standard deviation (SD) 2.42) versus 2.75 (SD 2.71), 10 seconds 8.68 (SD 1.11) versus 8.67 (SD 1.49), and 30 seconds 5.72 (SD 2.67) versus 6.00 (SD 2.80). However, a statistically significant difference was found at 120 seconds 2.81 (SD 1.66) versus 4.04 (SD 2.80), $P = 0.04$ post injection.

[Poulsen 2009](#) used the Neonatal Infant Pain Scale to measure pain in infants given their three- or five-month immunisation. The study compared pain responses for infants given sucrose 12% ($n = 34$) or normal saline ($n = 33$) pre-vaccination, during vaccination, 30 seconds post vaccination, and five and 20 minutes post vaccination. Mean and standard deviations were not calculated and not available (Personal communication ([Poulsen 2009](#))). Rather, the sum of differences was calculated for each infant using the formula: (during - pre-vaccination) + (30 seconds- pre-vaccination) + (five minutes - pre-vaccination) + (20 minutes - pre-vaccination). Using the t-test assuming unequal variances, no statistical difference was found between the sums of differences of the two groups ($P = 0.34$). [Dilli 2009](#) also used the Neonatal Infant Pain Scale during immunisation for infants aged six to 12 months. Infants in the sucrose group ($n = 13$) had lower mean pain scores: 2.84 (SD 1.81) than those in the no intervention ($n = 7$) group: 6.28 (SD 0.75).

Comfort assessed by validated comfort scale

No studies identified.

Sweet-tasting solutions versus a pharmacological pain-relieving method

Pain assessed by validated pain scale

One study ([Dilli 2009](#)) compared the effect of sweet solution (12% sucrose) with a pharmacological intervention (Lidocaine-prilocaine cream). There was no significant difference in pain scores between the two treatments ($P = 0.55$).

Secondary outcomes

Except for 'duration of total crying time upon commencement of the procedure', meta-analysis could not be undertaken because of the different study designs and outcome measures that were used and reported. Therefore, the results for each of the studies are presented separately for all other outcomes.

Sweet-tasting solutions versus placebo or no treatment

Duration of first cry

Three studies reported this outcome of duration of first cry ([Lewindon 1998](#); [Mowery 2007](#); [Priambodo 2008](#)). Two studies favoured sucrose and one found no statistical difference between the intervention and placebo. [Priambodo 2008](#) compared sucrose 75% ($n = 42$) versus sterile water ($n = 44$) in infants following

their third immunisation at four to six months of age. Infants in the sucrose group had a decrease in the duration of first cry of 38 seconds (32%) compared with the water group ($P = 0.03$). The number of infants still crying after three minutes was less in the sucrose group than the water group; 7 (17%) versus 16 (36%). [Lewindon 1998](#) compared sucrose 75% ($n = 54$) and water ($n = 53$) in infants attending their two-, four- or six-month immunisation from the time of injection and within a three-minute period. A statistically significant mean reduction in the duration of first cry (11.4%) was found in the sucrose group compared with the water group: 59 (SD 30) seconds versus 42 (SD 21) seconds (difference in means (standard error (SE)) 13 (3.8) seconds, $P < 0.0003$). However, [Mowery 2007](#) found no statistically significant difference in the mean scores between sucrose 50% ($n = 25$) and water ($n = 24$): 34.36 (SD 24.90) seconds versus 30.54 (SD 30.02) seconds, respectively ($P < 0.05$).

Percentage of time crying during and following procedure

One study ([Barr 1995](#)), reported no statistical significant difference in the mean percentage of time crying during and following injection between the sucrose ($n = 30$) and water groups ($n = 27$): $84.2 \pm 3.8\%$ versus $84.1 \pm 4.0\%$; mean $\pm$ 1 SEM respectively.

Percentage of time spent crying following the procedure

There were disparate findings between the four studies that measured percentage of time spent crying following the procedure ([Allen 1996](#); [Barr 1995](#); [Mowery 2007](#); [Ramenghi 2002](#)). [Allen 1996](#) and [Ramenghi 2002](#) measured the percentage of crying for up to three minutes following injection. [Mowery 2007](#) measured the percentage of crying up to two minutes, and [Barr 1995](#) up to one minute following injection.

[Mowery 2007](#) reported no statistically significant difference between the sucrose 50% ($n = 25$) and water ($n = 24$) groups: 46.64 (SD 24.81) seconds versus 53.13 (SD 29.73) seconds, $P = 0.41$. [Allen 1996](#) also reported no statistically significant difference between the sucrose 12% ($n = 58$) and water ($n = 69$) groups: 68.84 (SD 31.53) seconds versus 59.26 (SD 30.75). However, the sucrose group had less mean crying time versus no treatment: 68.84 (SD 31.53) seconds versus 60.84 (SD 27.49)

[Barr 1995](#) found that infants in the sucrose 50% ($n = 30$) group had significantly less mean crying time in the sucrose group ($69.0 \pm 3.8\%$) versus the water group ($82.8 \pm 4.0\%$; mean $\pm$ SEM respectively), $P < 0.05$.

[Ramenghi 2002](#) reported a difference in the percentage of time crying up to three minutes following injection. The first immunisation was at two months of age ($n = 62$), the second immunisation was at three months of age ($n = 61$) and the third immunisation was at four months of age ($n = 61$) for each of the interventions (50% sucrose, 25% sucrose, lypasin (glucose) and sterile water). The results were presented as medians (% time) and interquartile ranges.

For the first injection, no statistically significant difference was found between the groups at two months ($P = 0.192$) or 3 months ($P = 0.079$) immunisation. However, statistical significant difference was found among the older babies receiving their third (six-month) immunisation ($P = 0.0252$). Percentage of time crying was significantly reduced in the 50% sucrose solution in comparison to the placebo group (adjusted $P = 0.0303$, 95% CI = -50.0 to

-6.7). The difference between the percentage of time crying in the 25% sucrose group and the placebo reached borderline statistical significance ($P = 0.055$).

For the second injection, and across the three age groups, the mean percentage time crying was lowest in the group receiving 50% sucrose solution (19.4, 17.8, 19.4) and highest in the group receiving the placebo (35.6, 38.9, 60.0). Older babies receiving their third immunisation tended to spend longer crying after the second injection than they did after the first injection (median difference between 8 and 14). Overall, the 40% lycasin (glucose) was found to be less effective than 50% sucrose.

Duration of total crying time upon commencement of procedure

We performed a meta-analysis for seven of the nine studies ($n = 790$) that used this outcome ([Analysis 1.1](#)). Duration of cry was significantly reduced in infants who were administered a sweet-tasting solution [mean difference (MD) -13.47 (95% CI -16.80 to -10.15)], $P < 0.00001$ compared with water. However, there was considerable heterogeneity between the studies ($I^2 = 94\%$). We hypothesised this was due to the varying concentrations of the sweet-tasting solutions that were used: [Allen 1996](#) used sucrose 12% versus water, [Dilli 2009](#) sucrose 12% versus no treatment, [Soriano 2003](#) sucrose 75% versus water, [Kassab 2012](#) glucose 25% versus water, [Lewindon 1998](#) sucrose 75% versus water, [Morelius 2009](#) sucrose 30% versus water, and [Mowery 2007](#) sucrose 50% versus water. We carried out subgroup analysis on the effect of concentration of sweet-tasting solution (percentage). Meta-analysis of four studies (30% to 75% sweet-tasting solution) found a significant reduction in crying time [MD -7.66 (95% CI -11.41 to -3.91)], $P < 0.0001$ and meta-analysis of three studies for 12% to 25% sweet-tasting solutions [MD -34.71 (95% CI -41.89 to -27.54)]. However, there remained substantial (73%) to considerable (95%) heterogeneity, respectively, and statistically significant subgroup differences ($P < 0.00001$).

Two studies that also found sucrose to be effective in reducing crying time in the meta-analysis were not included. [Thyr 2007](#) compared mean duration of total crying time for infants given glucose 30% or sterile water at three months ($n = 110$), five months ($n = 109$) and 12 months ($n = 40$). Standard deviations could not be obtained. The study reported a statistically significant reduction in mean crying time in the sucrose group (six seconds) versus the water (16 seconds) group at five months, (-62% difference, $P = 0.017$) and 12 months (sucrose 14 seconds versus water 29 seconds, -52% difference, $P = 0.031$). However, no statistical difference was found between the glucose (18 seconds) and water (23 seconds) groups at three months (-22% difference, $P = 0.664$). [Priambodo 2008](#) found that infants who received sucrose 75% ($n = 42$) compared with sterile water ($n = 44$) had a statistically significant shorter median total duration of cry (108 seconds versus 143 seconds, $P = 0.02$). [Dilli 2009](#) also compared sucrose 12% with topical anaesthetic and found no statistical difference between the two groups.

Maximum Heart rate elevation

[Mowery 2007](#) measured the maximum heart rate elevation and found it to be similar between the sucrose and placebo groups: 39.84 (SD 19.28) beats per minute versus 39.92 (SD 21.45) beats per minute, $t(41) = 0.012$, $P = 0.99$.

Adverse events

[Hatfield 2008a](#) reported that 13% of infants (5/40) experienced an adverse event. In the two-month group, two infants randomised to the sucrose group coughed, and one infant randomised to the sterile-water group gagged. Within the four-month group, two infants randomised to the sucrose group coughed. All infants recovered spontaneously within 10 seconds. None of the events was considered clinically significant by the attending paediatrician or the study's data safety monitoring board.

Other outcome measures

No studies were found for the following outcomes: desaturation, parental stress or satisfaction using a validated scale, pain or crying at subsequent procedure, failure to complete subsequent procedures, measurement of infant development using a validated scale, developmental follow-up (by targeting infants when undergoing painful minor procedures and having sweet solutions as pain relief up to 24 months).

Sweet-tasting solutions versus a pharmacological pain-relieving method

Duration of total crying time upon commencement of procedure

One study ([Dilli 2009](#)) compared the effect of sweet solution (12% sucrose) with a pharmacological intervention (Lidocaine-prilocaine cream). There was no significant difference in duration of total crying time between the two treatments ($P = 0.36$).

DISCUSSION

The Cochrane review by [Stevens 2004](#) examined the effects of sucrose in newborn infants and found sucrose to be effective for reducing pain from heel lancing and venepuncture. Another Cochrane review by [Harrison 2011](#) sought to determine the effects of sweet-tasting solutions on needle-related pain in children aged one to 16 years. However, it was not possible due to insufficient evidence. A non-Cochrane systematic review ([Harrison 2010](#)) that explored the analgesic effect of sweet-tasting solutions in infants beyond the newborn period up to 12 months of age concluded from meta-analysis and from the results of individual studies that sucrose and glucose of various doses and concentrations moderately reduce crying incidence, crying duration and pain scores during or following immunisation. The studies included in the Harrison review are not identical to those included in the current review, primarily due to differing inclusion criteria.

Because of the differences between the included studies in study design and outcome measures, we only conducted meta-analyses on the outcome duration of total crying time upon commencement of procedure. For the other outcome measures, data for each of the included studies were reported separately.

Of the seven studies that reported the primary outcome of pain ([Dilli 2009](#); [Hatfield 2008a](#); [Hatfield 2008b](#); [Kassab 2012](#); [Lewindon 1998](#); [Mowery 2007](#); [Poulsen 2009](#)), all reported lower pain scores in infants in the sweet-tasting solution group as compared to the control group except for the study by [Poulsen 2009](#) that used the lower concentration of 12% sucrose.

Of the three studies that reported the outcome 'duration of first cry', two favoured sucrose ([Lewindon 1998](#); [Priambodo 2008](#)), and one found no statistical difference between the intervention and

placebo (Mowery 2007). Only one study (Barr 1995) reported the outcome 'percentage of time crying during, and following injection' and found no statistical significant difference between the two groups.

Four studies also reported disparate findings for the outcome 'percentage of time spent crying following the procedure'. One study reported a reduction in crying time for the sucrose group (Barr 1995). Two studies (Allen 1996; Mowery 2007) found no statistical difference between the two groups. Ramenghi 2002 only found a statistical reduction in crying time in older infants at six months but not for two- and three-month old infants. In addition, the higher concentration sucrose 50% was more effective than sucrose 25%. Meta-analysis of seven studies (Allen 1996; Dilli 2009; Kassab 2012; Lewindon 1998; Morelius 2009; Mowery 2007; Soriano 2003) for the outcome duration of cry found a statistically significant reduction in crying time in the sweet-tasting solution group. However, there was considerable heterogeneity. Two studies that could not be included in the meta-analysis also reported a reduction in crying in the sweet-tasting solution group (Priambodo 2008; Thyr 2007). Only one study (Mowery 2007) measured maximum heart rate elevation, which was found to be similar for the sucrose and control groups.

Stevens 2004 found 24% sucrose to be the most effective for reducing pain, with no added benefit of administering concentrations greater than 50% in the neonatal population. While we were unable to identify definitively an optimal concentration, all the individual studies in this review found a reduction in pain scores except for the study that used 12% sucrose (Poulsen 2009). Ramenghi 2002 found a greater pain-reducing effect with 50% sucrose than the lower concentration of 25% sucrose indicating that there may be a concentration-related effect in older infants. However, for the outcome 'duration of crying time', one study (Dilli 2009) that used 12% sucrose found a statistical reduction in crying time. Allen 1996 also used 12% sucrose but did not report a reduction. We were not able to determine the reason for this as both studies were conducted almost identically.

Three studies sought to determine if sucrose was effective when multiple injections were given (Hatfield 2008a; Hatfield 2008b; Ramenghi 2002). Hatfield 2008b and Hatfield 2008a found sucrose 24% to be more effective than the control up to nine minutes (two minutes following last injection) when three injections were given. Ramenghi 2002 similarly reported that the pain-reducing effects of sucrose lasted long enough to influence the second injection performed three minutes after the first injection. However, infants given 50% sucrose had the greatest reduction in the percentage of crying time following the second injection when compared with 25% sucrose and 40% lypasin (glucose), and concluded that older infants receiving multiple injections may require a higher concentration of sweet-tasting solution.

It has been found that a sweet solution given two minutes before painful stimulus was not effective during the procedure, but only during the recovery phase in neonates (Bilgen 2001; Bucher 2000; Harrison 2003). None of the included studies in this review separated the period of during and following immunisation time.

The majority (12) of the 14 studies administered the intervention two minutes prior to immunisation. Thyr 2007 administered the solution 30 seconds before immunisation, during and 10 to 30 seconds after immunisation, and Kassab 2012 administered

the solution immediately before injection. We were unable to determine any effect related to the timing of the immunisation. However, Stevens 2004 found the two-minute interval provided the greatest analgesic effect possibly because it coincides with endogenous opioid release in newborn infants. In addition, Stevens 2004 reported a significant reduction in pain scores when the sucrose was given at 30 and 60 seconds following heel lance.

It has been previously reported that administering sweet-tasting solutions in combination with non-nutritive sucking provides an additional calming effect that reduces pain-elicited distress (Blass 1991; Greenburg 2002; Stevens 1999). All three studies that used a combination of sweet-tasting solution and non-nutritive sucking reported a statistically significant reduction in pain compared to the control group (Hatfield 2008a; Hatfield 2008b; Morelius 2009). Morelius 2009 compared sucrose versus water, and sucrose and non-nutritive sucking versus water and non-nutritive sucking. The study found the sucrose and non-nutritive sucking group to be most effective in reducing crying time, followed by sucrose alone and water alone. Water and non-nutritive sucking was the least effective. Stevens 1999 found a pain-relieving effect of water and non-nutritive sucking to be effective in newborn infants. Morelius 2009 reports that older infants may need a sweet-tasting solution to encourage sucking, because the number of sucks is an important factor for the calming effect of non-nutritive sucking to occur (Blass 1999). None of the studies reported adverse effects that were regarded as clinically significant; however, they did not examine the long-term outcomes of using sweet-tasting solutions.

Summary of main results

The results demonstrate a reduction in duration of crying time in infants administered a sweet-tasting solution. However, there was considerable heterogeneity and the results have to be interpreted with caution. No significant difference was found between sucrose and Lidocaine-prilocaine cream in pain and cry duration. We were unable to identify the optimal concentration, volume or method of administration of sweet-tasting solutions or possible long-term effects in infants one to 12 months. Further large RCTs are needed. Also, a further study is needed to explore any possible long-term adverse effects of using sweet solutions.

Overall completeness and applicability of evidence

The available evidence is applicable but only 14 small trials using different study designs and outcome measures could be included in this review.

Quality of the evidence

The quality of the evidence of included studies in this review was reasonable. Of the 14 studies only eight studies adequately reported sequence generation (Hatfield 2008a; Hatfield 2008b; Kassab 2012; Lewindon 1998; Mowery 2007; Poulsen 2009; Ramenghi 2002; Thyr 2007), however, concealment of allocation was insufficiently reported in three studies (Barr 1995; Priambodo 2008; Soriano 2003). Blinding of interventions was achieved by most studies except in five studies (Barr 1995; Morelius 2009; Priambodo 2008; Ramenghi 2002; Thyr 2007). Incomplete outcome data were addressed in all but one study (Hatfield 2008b). One study was free of selective reporting (Kassab 2012); and there was risk of 'other' bias in the rest of the studies, due to unclear reporting of whether a sample size calculation was undertaken (Allen 1996; Barr 1995; Dilli 2009; Lewindon 1998; Morelius 2009; Mowery 2007;

Poulsen 2009; Soriano 2003; Thyr 2007) or because of the small sample size in the subgroup of infants included in this review (Allen 1996; Ramenghi 2002; Thyr 2007; Dilli 2009).

Potential biases in the review process

None known. The methods of the review were designed to minimise the introduction of additional bias. Two people independently completed data screening, data extraction and 'risk of bias' rating (MK and JF). We were able to reach consensus on all of the studies following consultation with the other authors. It is acknowledged that MK is the primary author of one of the included studies in this review.

Agreements and disagreements with other studies or reviews

The conclusions from this review are similar to the systematic review conducted by Harrison 2010.

AUTHORS' CONCLUSIONS

Implications for practice

Parents have a strong desire to comfort their infants during painful procedures. This review found that sucrose could possibly reduce the duration of crying time and pain (scores) from procedural pain following immunisation in infants aged one to 12 months without significant side effects. There is a need for practical interventions for pain management and clinicians should consider using sweet-tasting solutions for this population. However, because meta-analyses were unable to be undertaken for the majority of the outcomes, this precludes us from being able to make firm conclusions about the effectiveness of sweet-tasting solutions for needle-related pain.

Implications for research

This review illustrates the paucity of large randomised controlled trials (RCTs) examining the analgesic effects of sweet-tasting solutions for procedural pain in infants one month to one year of age. Further well-conducted RCTs are warranted in this population especially in relation to the optimal concentration, volume and method of administration of sweet-tasting solutions in infants aged one to 12 months.

Recommendations for further studies include:

- a priori power calculations are performed to ensure RCTs are adequately powered,
- concealment of allocation and blinding of interventions to outcome assessors,
- compare different concentrations of sweet-tasting solution,
- compare the effect of sweet-tasting solution during and following pain procedure,
- compare the use of sweet-tasting solutions with and without non-nutritive sucking or any other similar interventions,
- determine the efficacy and safety of sucrose for repeated administration,
- examine long-term outcomes such as tooth decay and obesity,
- use of a validated pain outcome measure.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Allen 1996

Methods	Parallel randomised controlled trial.
Participants	<p><u>Participants</u>: Infants requiring a needle procedure: Routine immunisation (2 weeks-18 months) subcutaneously.</p> <p><u>Sex</u>: Male and female infants.</p> <p><u>Age of infants</u>: 2 weeks -18 months.</p> <p><u>Number randomised</u>: Overall 285 infants: two weeks old (n = 50); two months old (n = 44); four months old (n = 50); six months old (n = 46); nine months old (n = 28); 15 months old (n = 30); 18 months old (n = 37).</p> <p>Number used in analysis: 168 infants included and randomised in this review (2 - 9 months).</p> <p><u>Setting</u>: A university hospital ambulatory paediatric clinic.</p> <p><u>Inclusion criteria</u>: The clinical sample was drawn from a continuous sample of those infants who presented for regular immunisations. To be included in the study, infants were required to be 37 weeks and above gestation. Healthy infants attending paediatric clinics for their regular immunisation; Infants were required to receive the immunisation within one month of the recommended age criteria.</p>

Allen 1996 (Continued)

Exclusion criteria: Infants with acute or chronic disease.

Interventions

1. Sucrose (n = 58)
2. Sterile water (n = 69)
3. Nil treatment (n = 38)

Strength of Sucrose: 12%.

Method of administration of sucrose and sterile water: orally (not using non-nutritive sucking).

Timing of administration: Two minutes prior to the injection.

Volume of sucrose and sterile water: Two mLs.

Method of administration of injection: subcutaneous.

Number of injections: one, two or three injections.

The number of given immunisation injections differed between the age groups (one, two or three injections of any of these vaccinations: Diphtheria, Tetanus, Pertussis (DPT), Haemophilus influenzae conjugate type b (HIB) & Hepatitis B):

- a. Infants in the two weeks (Hepatitis B), nine months (Hepatitis B) and 18 months (Diphtheria and Tetanus Toxoids and Pertussis vaccine) age group received a single injection for immunisation.
- b. Infants in the two-month (DTP plus HIB), six-month (DTP plus HIB) and 15-month age (Measles-Mumps-Rubella plus HIB) group received two immunisation injections.
- c. Infants in the four-month (DTP plus HIB plus Hepatitis B) group received three immunisation injections.

Videotaping (using a hand-held camera that was located in one corner of the examining room) of crying began 30 seconds prior to the injection, continued throughout the injection/s, and for three minutes after the injection/s. Audiotape recordings of each infant's vocalisations during the immunisations were taken simultaneously.

After the infants were placed on the examining table, a clinical nurse first swabbed the upper part of the thigh with alcohol and injected the appropriate immunisations.

The proportion of crying per 15-second intervals was then recorded by a trained primary observer. A second observer recorded the amount of time that was required for the nurse to administer the injections.

Reliability observations were performed by a second trained observer on approximately 20% of the data. The percentage agreement was calculated by taking the ratio of the smaller value to the larger value that was obtained by the two observers, and this was multiplied by 100.

Outcomes

Cry duration (seconds).

Percentage of crying time: during and three minutes after subcutaneous injection for immunisation.

Notes

Risk of bias

Bias

Authors' judgement

Support for judgement

Random sequence generation (selection bias)

Unclear risk

Randomised control study design. Information reported insufficient for a judgement to be made.

Allen 1996 (Continued)

Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	The 'sterile water' and 'sucrose' solutions were placed in coded oral syringes by the pharmacist to ensure that parents, nurses and investigators were blind to group assignment. There was no blinding of the 'nil treatment' group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for three infants missing. Publication stated 168 infants two to nine months of age. Data provided by authors: 165 infants aged two to nine months.
Selective reporting (reporting bias)	Unclear risk	There is no protocol to access so we do not know the original planned outcomes.
Sample size	Unclear risk	No sample size calculation reported by the authors.

Barr 1995

Methods	Parallel randomised controlled trial.
Participants	<p><u>Participants</u>: Infants attending for their 2nd or 4th diphtheria-tetanus-pertussis immunisation.</p> <p><u>Sex</u>: Male (31 + five dropouts) and female infants (26 + three dropouts).</p> <p><u>Age of infants</u>: Two - four months.</p> <p><u>Number randomised</u>: 65.</p> <p><u>Number used in analysis</u>: 65 infants at two months of age, 57 infants at four months of age.</p> <p><u>Setting</u>: Montreal Children's Hospital.</p> <p><u>Inclusion criteria</u>: Healthy infants with normal postnatal health histories; no present illness or fever; normal physical examination; parents signed informed consent form; acetaminophen not given as prophylaxis against adverse reactions until after the immunisation.</p> <p><u>Exclusion criteria</u>: Nil stated.</p>
Interventions	<p>1. Sucrose</p> <p>2. Water</p> <p><u>Strength of sucrose</u>: 50%</p> <p><u>Method of administration</u>: Solution was applied to the anterior tongue by pipette (no non-nutritive sucking).</p> <p><u>Timing of administration</u>: Two minutes prior to the DTP injection.</p> <p><u>Volume of sucrose or sterile water</u>: 0.75 mLs; the control and experimental groups received three doses of 250 µls (0.25 mL) at 30-second intervals.</p> <p>The infants received the same intervention (sucrose or sterile water) at four months that they received at two months of age.</p> <p>After a physical examination parents and infants were led to an examination room and asked to sit on the examining table comfortably holding their infants on their laps and facing the nurse. They were requested to refrain from comforting their infants other than continuing to hold them in the same position and talking to them until one minute post immunisation.</p>

Barr 1995 (Continued)

After a 20-second baseline, infants received the 3 doses at 30-second intervals of the 250 µls of liquid by a research assistant. After the third dose of sucrose or sterile water, the nurse swabbed the injection site with alcohol and administered the diphtheria-tetanus-pertussis injection intramuscularly into the left thigh.

Number of injections: One

Outcomes

Mean percentage of time crying.

The procedure videotaped starting at 20-second baseline and up to the end of the observation by observer blind to the experimental condition of the participants.

Crying was defined as percentage of time crying during the following periods:

- a. baseline (20 sec);
- b. during injection (10 sec),
- c. post injection (up to 60 sec).

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised control study design. Information reported insufficient for a judgment to be made.
Allocation concealment (selection bias)	Unclear risk	Not stated. Information reported insufficient for a judgment to be made.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated. Information reported insufficient for a judgment to be made.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Nine infants did not participate at four months of age; five missed their appointment; three were missed because of technical recording; one withdrawn because of illness (failure to thrive). Of the eight dropouts, five had received water and three had received sucrose.
Selective reporting (reporting bias)	Unclear risk	There is no protocol to access so the original planned outcomes are not known.
Sample size	Unclear risk	No sample size calculation reported by authors.

Dilli 2009

Methods

Parallel randomised control study design.

Participants

Infants who required immunisations. Single injection at one month, six months (Hepatitis B) and 12 months (Measles-Mumps-Rubella). Multiple injections at two (bacillus Calmette-Guerin, and Hemophilus influenzae b), four, and six months (diphtheria-tetanus-pertussis, inactivated polio virus vaccine, and H influenzae b).

Sex: Not known in the six- to two-month age group.

Age of infants: 6-12 months.

Dilli 2009 (Continued)

Number randomised: 118 infants aged 6 to 48 months.

29 infants 6 to 12 months: sucrose 12% (n = 15), no intervention (n = 7), lidocaine-prilocaine (n = 7).

Number used in analysis: 27 included in this review (6 to 12 months).

Sucrose 12% (n = 13), no intervention (n = 7), lidocaine-prilocaine (topical anaesthetic (n = 7).

Setting: Well-child unit of the Department of Paediatrics.

Inclusion criteria: Healthy infants requiring their regular vaccinations.

Exclusion criteria: Infants with intercurrent illness born at less than 37 weeks completed gestation who were unable to tolerate fluids by mouth, had an allergy to any component of the anaesthetic used in the study, or had a diagnosis of cerebral palsy (in whom the response to painful stimuli may be difficult to interpret).

Interventions

1. Sucrose.

2. Lidocaine-prilocaine (topical).

3. Nil treatment.

Strength of Sucrose: 12%.

Method of administration of sucrose and sterile water: orally (not using non-nutritive sucking).

Timing of administration: Two minutes prior to the injection.

Volume of sucrose and sterile water: Two mLs.

Method of administration of injection: subcutaneous.

Infants randomised to receive sucrose, lidocaine-prilocaine or no intervention.

The mother was seated with the infant or child in her arms. All infants were awake during the procedure. Any verbal distractions by the mother during vaccination were recorded.

Sucrose group: The mother was instructed to hold the infant across her lap in a cross-cradle position while ensuring that the infant's arms or thighs were accessible throughout the procedure. Two minutes before the injection, the sucrose-allocated group received two mLs of 12% sucrose solution orally, as described by Allen 1996 above.

Lidocaine-prilocaine group: One gram of lidocaine-prilocaine was applied to the vaccination area (lateral region of the right thigh or deltoid) one hour before vaccination. The cream was covered with an occlusive dressing (Tegaderm) for one hour. Vaccinations and related interventions were performed in a separate warm and quiet room. All vaccinations were performed by the same experienced nurse.

Number of injections: Single or multiple injections.

Outcomes

Cry duration (seconds), recorded from insertion of needle until all crying activity ceased.

Pain score: Neonatal Infant Pain Scale (NIPS).

Notes

Additional data was obtained.

Risk of bias

Bias

Authors' judgement

Support for judgement

Random sequence generation (selection bias)

Unclear risk

Sequence generation not described.

Dilli 2009 (Continued)

Allocation concealment (selection bias)	Low risk	Sealed envelopes stratified by age.
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessor blinded to interventions in the sub-group included in this review.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two of the 15 infants in the sucrose group discontinued the procedure (post randomisation) because of inadequate co-operation with the children.
Selective reporting (reporting bias)	Unclear risk	There is no protocol to access so we do not know the original planned outcomes.
Sample size	Unclear risk	No sample size calculation reported by the authors. Small sample size in subgroup of infants included in this review.

Hatfield 2008a

Methods	Parallel randomised controlled trial.
Participants	<p>Infants requiring a combined diphtheria, tetanus, acellular pertussis, hepatitis B, and polio vaccine from GlaxoSmithKline, a Haemophilus influenzae type B vaccine from Aventis Pasteur, and a heptavalent pneumococcal conjugate vaccine at two months and four months.</p> <p><u>Sex</u>: Not reported.</p> <p><u>Age of infants</u>: Two - four months.</p> <p><u>Number randomised</u>: 40</p> <p><u>Number used in analysis</u>: 40</p> <p><u>Setting</u>: University affiliated ambulatory paediatric clinic.</p> <p><u>Inclusion criteria</u>: Healthy, full-term infants; born at 37 to 42 weeks gestation; birth weight greater than 2.5 kg; without acute illness.</p> <p><u>Exclusion criteria</u>: Infants fed 30 minutes before immunisations; given acetaminophen the day of the immunisations; introduced to solid food; does not regularly use a pacifier.</p>
Interventions	<p><u>Interventions</u>:</p> <ol style="list-style-type: none"> 1. Sucrose 2. Sterile Water <p>Both solutions were clear, non odours, similar in physical characteristics (texture), and indistinguishable.</p> <p><u>Strength of sucrose</u>: 24%.</p> <p><u>Method of administration</u>: Study solutions were placed onto the surface of their tongues immediately followed by insertion of the pacifier into their mouth. The pacifier was held in the infant's mouth by the parent or clinic nurse two minutes before and during, and three minutes following the immunisations. NNS was encouraged by gentle rhythmic stimulation of a pacifier introduced into the infant's mouth by the parent or nurse without breast milk or formula.</p> <p><u>Timing of administration</u>: Two minutes prior to the injection.</p>

Hatfield 2008a (Continued)

Volume of sucrose or sterile water: Two mLs bolus.

Children's Medical Ventures Inc. (Norwell, MA), manufactured the 24% oral sucrose solution. A weight-based dose of sucrose (0.6 mL/kg) was calculated using the average birth weight of a term infant (3.4 kg). The study dose is consistent with the two mLs dose of oral sucrose for term infants recommended by the Cochrane Database for Systematic Reviews. The control solution was the same weight-based volume of sterile water.

Method of administration of injection: one inch, 25-gauge (intramuscular) disposable needle.

Number of injections: Three injections: a combined diphtheria, tetanus, acellular pertussis (DTP, Hepatitis B, and polio vaccine) haemophilus influenzae type B vaccine a heptavalent pneumococcal conjugate vaccine.

Infants sat supported in their parents' laps facing the clinic nurse. Parents were asked to hold their infants' hands midline to their body to prevent injury to the child. During administration of the oral sucrose or placebo or during data collection, infants participating in the study were not swaddled, cuddled, restrained, or constrained. Following the administration of the three serial immunisations and documentation of pain assessments, participation was completed and no additional study care or monitoring was given. Parents or primary caregivers were offered a follow-up telephone interview within 24 hours of the office visit to answer any subsequent questions or concerns regarding the study.

Outcomes

Acute behavioural pain response:

The University of Wisconsin Children's Hospital (UWCH) pain scale was used to quantify the primary outcome acute behavioural pain response. The instrument consisted of five measurement domains: crying, facial expression, behavioural response, body movement, and sleep, which are documented as valid and reliable indicators of observed infant behavioural response to noxious stimuli. Each category is scored numerically along a six-point ordinal scale from zero denoting the absence of any response to five denoting the highest degree of response.

The score were taken at:

- Baseline pain levels were assessed within five minutes before administration of the oral sucrose or placebo solutions.
- Two minutes after administering the study solutions, the combined diphtheria-tetanus-acellular pertussis, inactivated polio vaccine, and hepatitis B vaccines were administered, and a second pain assessment was performed.
- Exactly three minutes after the combined injection, the H influenzae type b vaccine was administered, and the third pain assessment was obtained.
- Two minutes after this injection, the final injection, pneumococcal conjugate vaccine, was administered and a fourth pain assessment recorded.
- The fifth and final pain observation occurred two minutes after the last pneumococcal conjugate vaccine injection.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment to the placebo control (sterile water) or oral sucrose group was determined using a computer-generated random numbers table in permuted blocks of four.
Allocation concealment (selection bias)	Low risk	Throughout the duration of the study, all study personnel except for the research assistant who prepared the study preparations, were blinded to the assignment of infants.
Blinding (performance bias and detection bias)	Low risk	Throughout the duration of the study, all study personnel except for the research assistant who prepared the study preparations, were blinded to the

Sweet-tasting solutions for needle-related procedural pain in infants one month to one year of age (Review)

Hatfield 2008a (Continued)

All outcomes		treatment conditions. The primary investigator did not have access to randomisation charts or treatment solutions and was not present during randomisation assignment or study preparation. Access to the unblinded data was limited to statisticians and data-monitoring committee members who had no contact with study participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data missing for five infants (two in the control and three in the intervention group).
Selective reporting (reporting bias)	Unclear risk	There is no protocol to access so we do not know the original planned outcomes.
Sample size	Low risk	To achieve 0.80 power to detect a significant difference of 20% reduction in the primary outcome.

Hatfield 2008b

Methods	Parallel randomised controlled trial.
Participants	<p>Infants requiring a combined diphtheria, tetanus, acellular pertussis, hepatitis B, and polio vaccine from GlaxoSmithKline, a Haemophilus influenzae type B vaccine from Aventis Pasteur, and a heptavalent pneumococcal conjugate vaccine at 2 months and 4 months.</p> <p><u>Sex</u>: Male (44) and female infants (39).</p> <p><u>Age of infants</u>: Two to four months.</p> <p><u>Number randomised</u>: 100 (equally divided among the two treatment and age groups).</p> <p><u>Number used in analysis</u>: 83 (17 excluded post-randomisation).</p> <p><u>Setting</u>: University-affiliated ambulatory paediatric clinic.</p> <p><u>Inclusion criteria</u>: Healthy, developmentally appropriate infants born at 37 to 42 weeks' gestation With birth weight 2.5 kg without evidence of recent illness.</p> <p><u>Exclusion criteria</u>: If infants had been: fed 30 minutes before immunisation; given acetaminophen the day of the immunisations; introduced to solid food; or were not regularly using a pacifier.</p>
Interventions	<p>1. Sucrose.</p> <p>2. Sterile water.</p> <p><u>Strength of sucrose</u>: 24% (A weight-based doses of sucrose (0.6mL/kg) was calculated on the average birth weight of a term infant (3.4 kg). Authors state: this dose is consistent with the 2 mL dose of oral sucrose for term infants recommended by the Cochrane Database of Systematic reviews.</p> <p><u>Method of administration</u>: Via a syringe onto the surface of the tongue followed immediately by the insertion of a pacifier into the mouth. Non-nutritive sucking was provided without breast milk or formula. Non-nutritive sucking was encouraged by gentle rhythmic stimulation of the pacifier by the parent or clinic nurse.</p> <p><u>Timing of administration</u>: Intervention given two minutes before immunisation. The pacifier was held in place by the parent or the clinic nurse two minutes before, during, and seven minutes after the initial immunisation.</p> <p><u>Volume of sucrose or sterile water</u>: Two mLs bolus.</p> <p><u>Method of administration of injection</u>: one inch, 25-gauge (intramuscular) disposable needle.</p>

Hatfield 2008b (Continued)

Number of injections: Three injections.

1. Combined DTP, IPV (inactivated polio vaccine) & Hepatitis B injection.
2. H influenzae b.
3. Pneumococcal conjugate vaccine.

Infants participating in the study were not swaddled, cuddled, restrained, or constrained during the administration of the oral sucrose or placebo or during the data collection period.

Infants sat supported in their parent's lap facing the clinic nurse. Parents were asked to hold the infants' hands midline to their body to prevent injury to the child. A very small percentage of parents did not wish to support their infants during the immunisations and placed their infants in a supine position on the examining table. Once all of the immunisations were administered and pain assessments recorded, the study was completed, and no additional study care or monitoring was required. A follow-up telephone interview with the parent or primary caregiver was offered to all of the participants within 24 hours of the office visit to address any subsequent questions or concerns regarding the study.

Outcomes

Acute behavioural pain response using the University of Wisconsin Children's Hospital (UWCH) Pain Scale. This instrument consists of five behavioural pain response scores (crying, facial expression, behavioural response, body movement, and sleep) for each study participant.

Baseline pain levels were assessed:

Within five minutes before administration of the oral sucrose or placebo solutions.

Two minutes after administering the study solutions, the combined diphtheria-tetanus-acellular pertussis, inactivated polio vaccine, and hepatitis B vaccines were administered, and a second pain assessment was performed.

Exactly three minutes after the combined injection, the H influenzae type b vaccine was administered, and the third pain assessment was obtained.

Two minutes after this injection, the final injection, pneumococcal conjugate vaccine, was administered and a fourth pain assessment recorded.

Two minutes after the last pneumococcal conjugate vaccine injection.

Notes

Non-nutritive sucking was provided without breast or formula milk. Non-nutritive sucking was encouraged by gentle rhythmic stimulation of the pacifier by the parent or clinic nurse.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment was determined using a computer-generated random-numbers table. Infants were assigned by progressive random assignment to the stratified two- or four-month group and then further randomly assigned into the placebo control (sterile water) or oral sucrose group. Infants participated in the study at one point, at either their two- or four-month scheduled appointment.
Allocation concealment (selection bias)	Low risk	All study personnel except for the research assistant who prepared the study preparations, were blinded to the treatment assignment.
Blinding (performance bias and detection bias) All outcomes	Low risk	All of the study personnel, except for the research assistant who prepared the study solutions, were blinded to the treatment conditions throughout the duration of the study. Only the statisticians and data monitoring committee had access to the unblinded data, but none had any contact with study participants.

Hatfield 2008b (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	During the study period (March 2004 to April 2005) 100 eligible infants were consented and enrolled in the study. Data from 17 infants were not included in the analysis for the following reasons: infant moved before appointment (1), infant was inconsolable after physical examination (7), parent fed infant before study solution administration (1), mother was on maintenance methadone (1), infant exhibited sympathy crying when sibling received immunisation (n = 1), infant refused solution (3), infant choked and refused the solution (n = 1, self-resolved within ten seconds), mother did not want to wake child to receive solution (1), and infant received immunisations before study solution was administered (1). Intention-to-treat analysis not used.
Selective reporting (reporting bias)	Unclear risk	There is no protocol to access so the original planned outcomes are not known.
Sample size	Low risk	Sample size was calculated on the basis of the numbers of subjects exposed to each treatment condition to yield sufficient statistical power capable of detecting a 20% reduction in the primary outcome.

Kassab 2012

Methods	Parallel randomised controlled trial.
Participants	<p>Participants: Infants who required a routine two-month Immunisation. The number of given immunisation injections were two (the first injection consists of the diphtheria, tetanus toxoid and pertussis (DTP) vaccine, Hepatitis B (HepB) vaccine and inactivated polio vaccine (IPV) vaccines, while the second injection consists of Haemophilus influenzae type B (HiB) vaccine.</p> <p><u>Sex</u>: Male (52) and female (68) infants.</p> <p><u>Age of infants</u>: Two months.</p> <p><u>Number randomised</u>: 120 infants.</p> <p><u>Number used in analysis</u>: 120 infants.</p> <p><u>Setting</u>: Mother and child healthcare setting.</p> <p><u>Inclusion criteria</u>:</p> <p>Healthy full-term infants who were attending the immunisation clinic to undergo routine two-month immunisation for DTP/hepatitis B vaccine (Comvax), Polio (IPV), and Haemophilus influenzae type B intramuscular immunisations, as part of a routine vaccination programme according to the Jordanian Ministry of Health recommendations.</p> <p>3. Exclusion criteria:</p> <p>Complaining of moderate or severe acute illness with or without fever (equal or over 40.5 C). Infant weighing less than 2000 g.</p> <ul style="list-style-type: none"> History of hypersensitivity reaction following a previous dose of tetanus and/or diphtheria toxoid-containing vaccine. Have had a family history of severe reaction after eating eggs. Have had convulsions (fits) in the past, or any other progressive or unstable neurological disorders. Have had, or are having, treatment for cancer. Have any illness which affects the immune system, for example, HIV/AIDS, or if the infant is within close contact with an immunosuppressed person.

Kassab 2012 (Continued)

- Taking any medicine, which affects the immune system, for example; immunosuppressants (given after organ transplant or for malignant disease) or high-dose steroids.
- Recent receipt of antibody-containing blood product.
- Receipt of specific antiviral (i.e., acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination.
- History of thrombocytopenia or thrombocytopenic purpura.

Interventions
Intervention:

Immediately prior to the first injection, the control and experimental groups received orally two mLs of either:

1. Glucose solution
2. Sterile water

Strength of glucose: 25%.

Method of administration: using syringe to the lateral side of tongue. Non-nutritive sucking not used.

Timing of administration: Two minutes prior to the injection.

Volume of glucose or sterile water: Two mLs given slowly via syringe.

Method of injection: Intramuscular.

Number of injections: Two injections.

The first injection consists of the Diphtheria, Tetanus toxoid and Pertussis (DTP) vaccine, Hepatitis B (Hep B) vaccine and Polio (IPV) vaccines, while the second injection consists of Haemophilus influenzae type B (HiB) vaccine.

For the purpose of the study, each infant was videotaped for about fifteen seconds for baseline data immediately before being given the solution and videotaping continued during the immunisation, while the infant was laying down on the examination table and up to two minutes after last injection.

Outcomes
Behavioural pain response.

The Modified Behavioral Pain Scale (MBPS) was used to assess three behavioural dimensions coded from the videotape.

The code of MBPS was divided into three phases:

1. Baseline (15-seconds prior to injection).
2. During immunisation.
3. Post-immunisation (0-10 seconds immediately after giving the last injection (see Appendix six).

The duration of full-lung cry after the last injection was measured to assess pain severity.

Total Crying Time

- a) during immunisation, and
- b) up to two minutes following immunisation.

Notes
Risk of bias
Bias
Authors' judgement
Support for judgement

Random sequence generation (selection bias)

Low risk

A computer-based randomisation procedure was used to produce a randomisation sequence prior to the study by the collaborating statistician. The

Kassab 2012 (Continued)

		process produced a random sequence of intervention allocations linked with study identification numbers, running from one to 120.
Allocation concealment (selection bias)	Low risk	A pharmacist prepared the study solutions A and B and put inactivated polio vaccine into them using sequentially numbered envelopes according to the randomisation sequence prepared in discussion between the pharmacist and study statistician. The pharmacist ensured that all syringes were numbered and each number had to correspond to the same numbered envelope.
Blinding (performance bias and detection bias) All outcomes	Low risk	All nursing staff, patients, researchers were blinded to the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All incomplete outcomes were addressed.
Selective reporting (reporting bias)	Low risk	Outcome measures reported as stated in study protocol.
Sample size	Low risk	For a two-sided hypothesis test with a type 1 error rate of 5% (95% CI) and a type two error rate of 10% (90% power), and a standard deviation of 1.7 (from the Lindh study), the sample size required to detect a meaningful reduction of one point in MBPS between the intervention and control group is 90 (45 infants in each group).

Lewindon 1998

Methods	Parallel randomised controlled trial.
Participants	<p><u>Participants</u>: Infants 34 weeks and above gestation who required routine immunisation at two, four and six months of age.</p> <p><u>Sex</u>: Male (56) and female (51) infants.</p> <p><u>Age of infants</u>: two, four and six months.</p> <p><u>Number randomised</u>: 110</p> <p><u>Number used in analysis</u>: 107</p> <p><u>Setting</u>: Women's and children's hospital immunisation clinics.</p> <p><u>Inclusion criteria</u>: Healthy infants attending immunisation clinic for the routine two, four and six months immunisation.</p> <p><u>Exclusion criteria</u>:</p> <ul style="list-style-type: none"> • Have intercurrent illness. • Infants born at less than 34 weeks completed gestation. • Infants receiving tier immunisation at their arm. • Infants unable to tolerate fluids by mouth. • Infants with cerebral palsy. • Infants with a modification of standard protocol (e.g. combined injection).
Interventions	<p><u>Interventions</u>:</p> <p>1. Sucrose.</p>

Lewindon 1998 (Continued)

2. Sterile water.

Strength of sucrose: 75%.

Method of administration: via syringe given into infant's mouth.

Timing of administration: Immediately before administration of injection.

Volume of sucrose or sterile water: Two mLs given over a period of up to 15 seconds.

Method of injections: Intramuscular.

Number of injections: two injections.

The nurse who gave the immunisation also administered the study solutions. Polio vaccine was given by mouth first, followed by the test solution. H influenzae type b was then administered in the left leg and immediately (within five seconds) DTP was administered in the right leg.

In addition, the same nurse who gave immunisation to infants in the thigh administered all the test solutions given by mouth. Polio was given by mouth first, followed by the test solution that was given over a period of up to 15 seconds. H influenzae type b immunisation was then administered in the left leg and immediately after (within five sec) DTP was administered in the right leg. The nurse used her usual soothing techniques (encouraging parents to cuddle the infant over one shoulder while she employed a distracting, low pitched rattling noise). The use of an infant pacifier or pre-treatment with paracetamol was specifically noted. All infants were in the awake state at the time of procedure.

Outcomes	<p><u>Crying time</u>:</p> <p>Crying time was taken from onset after the first injection until all crying activity had ceased up to a maximum of three minutes was recorded on audio tape and analysed blindly for the duration of crying.</p> <p>Crying time was analysed in three ways:</p> <ol style="list-style-type: none"> 1. First cry (seconds): taken from onset until a crying free interval of more than five sec. 2. Total sum (seconds): taken within the first three minutes from onset. <p>Total duration (seconds) from start of crying until the finish of the last cry (maximum three minutes).</p> <p><u>Distress</u>:</p> <p>Visual Analogue Scale (VAS): at the end of the consultation the nurse and caregiver recorded their subjective assessment of distress suffered by the infant on an Oucher chart, a Visual analogue score from 0 to 100. A score of 0 indicated no distress, whereas a score of 100 was the worst distress possible for infant.</p>
Notes	<p>The use of an infant pacifier or pretreatment with paracetamol was specifically noted. Ten infants used pacifier (seven in the sterile water group and three in the sucrose group).</p> <p>Eight infants received paracetamol (three in the sterile water group and five in the sucrose group) at home pre-immunisation.</p> <p>One child had haemophilia and another was in a hip spica for congenital hip dislocation.</p> <p>3 children were withdrawn after randomisation: Technical difficulties with cry recording for 2 infants and, in the third, the parent did not complete an Oucher chart.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Infants were randomised consecutively to receive solutions of two mLs 75% sucrose solution or sterile water according to the closed envelope technique. Solutions were drawn from coded bottles and administered by syringe. The

Lewindon 1998 (Continued)

		nurse and parents were blinded to the nature of the solutions through the study.
Allocation concealment (selection bias)	Low risk	Solutions were drawn from coded bottles.
Blinding (performance bias and detection bias) All outcomes	Low risk	The nurse and parents were blinded to the nature of the solutions throughout the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three infants withdrew after randomisation (two for technical failure and one parent did not complete the VAS).
Selective reporting (reporting bias)	Unclear risk	There is no protocol to access so the original planned outcomes were unknown.
Sample size	Unclear risk	Not reported by authors.

Morelius 2009

Methods	Parallel randomised controlled trial.
Participants	<p><u>Participants</u>: Infants eligible for the three-month routine Immunisation: Diphtheria, tetanus, pertussis), Hemophilus influenzae type B and polio.</p> <p><u>Sex</u>: Male (46) and female (52) infants.</p> <p><u>Age of infants</u>: Infants categorised into three groups depending on the age of immunisation: less than three months minus one week; three months plus or minus one week; and more than three months + one week. No other information provided.</p> <p><u>Number randomised</u>: 100.</p> <p><u>Number used in analysis</u>: 98 (two parents did not complete the whole sequence).</p> <p><u>Setting</u>: Well-baby Clinic.</p> <p><u>Inclusion criteria</u>: Healthy infants who had stopped feeding one hour prior to the procedure to minimise the risk for contamination of the saliva sample.</p> <p><u>Exclusion criteria</u>: Nil stated.</p>
Interventions	<p><u>Interventions</u>:</p> <ol style="list-style-type: none"> 1. Glucose via syringe (n = 20). 2. Sterile water via syringe (n = 24). 3. Glucose followed by pacifier (n = 29). 4. Sterile water followed by pacifier (n = 25). <p><u>Strength of sucrose</u>: 30%.</p> <p><u>Method of administration</u>: Non-nutritive sucking and/or syringe.</p> <p><u>Timing of administration</u>: Not reported.</p> <p><u>Volume of sucrose or sterile water</u>: one mL bolus.</p>

Morelius 2009 (Continued)

Method of injections: Intramuscular.

Number of injections: one injection.

Nurse one gave the immunisation into the right thigh, while nurse two clocked the crying-time. The parent graded his/her own stress on a VAS a second time just after the immunisation. The parent was instructed to sit down in the waiting room until the next saliva collection; they were not allowed to feed, change diaper, or weigh the infant. Saliva was collected using cotton buds. A radioimmunoassay for cortisol was used to analyse the cortisol concentrations.

Outcomes

Crying time taken from onset until three minutes following immunisation.

Crying was defined as the presence of audible negative vocalisations in combination with facial grimacing. Crying time was calculated as percentage of time the infant was vocalising during a period of three minutes during and after immunisation.

Crying incidence. Percentage of infants crying before and during immunisation.

Parental stress. Parents' own emotional stress was measured before and after immunisation by measuring level of cortisol in their saliva.

Salivary Cortisol levels:

Saliva was collected before (baseline) and 30 minutes after (response) the immunisation from both the infants and parents.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Due to ethical considerations randomisation of the infant to pacifier or not was not done. Instead, infants who ordinarily used a pacifier were randomised to either glucose or water depending on pacifier use. The study sequence was always the same starting with the parent selecting a random envelope for glucose or water depending on pacifier use. No information on how, or who randomised the envelopes is provided.
Allocation concealment (selection bias)	Low risk	Once an infant was randomised, nurse one, then left the room to prepare the vaccine and the glucose/water solution. In the meantime, the parent was grading stress on the VAS and nurse two collected saliva from infant and parent. Nurse two also clocked the crying.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Nurse two and parents were unaware of which solution the infant was given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Authors state: In nine infants, it was impossible to calculate the difference between baseline (before immunisation) and response (after immunisation) cortisol because of insufficient amounts of saliva in either the baseline or the response sample ($n = 8$) or because the fact that the response sample was never taken because the infant was accidentally fed ($n = 1$). In these cases the infants but not their parents were excluded from paired analyses.
Selective reporting (reporting bias)	Unclear risk	There is no protocol to access so we do not know the original planned outcomes.
Sample size	Unclear risk	Not reported by authors.

Mowery 2007

Methods	Parallel randomised controlled trial (pilot).
Participants	<p>Participants: Infants requiring their two-, four- and six-monthly routine immunisations: 1) Pediatix: diphtheria and tetanus toxoids and acellular pertussis absorbed, hepatitis B (recombinant) and inactivated poliovirus vaccine combined 2) Haemophilus influenzae b conjugate vaccine 3) Prenar (pneumococcal 7-valent conjugate vaccine).</p> <p>Sex: Male (24) and female (25) infants.</p> <p>Age of infants: Two to six months.</p> <p>Number randomised: 49 infants.</p> <p>Number used in analysis: 49 infants.</p> <p>Setting: Paediatric clinic in a children's hospital.</p> <p>Inclusion criteria: Hispanic parent, healthy infant with no acute or chronic illness, who underwent routine two-, four-, six-month immunisation consisting of Diphtheria, Tetanus toxoid and Pertussis (DTP) vaccine, Hepatitis B (Hep B) vaccine and Polio (IPV) vaccines, Haemophilus influenzae type B (HiB) vaccine and Pneumococcal.</p> <p>Exclusion criteria: Born at less than 37 weeks gestation; hospitalised since birth, and unable to tolerate intraoral fluid.</p>
Interventions	<p>Interventions:</p> <ol style="list-style-type: none"> 1. Sucrose (n = 25) 2. Sterile water (n = 24) <p>Strength of sucrose: 50%.</p> <p>Method of administration: squirting it via syringe over the anterior one-third of the infant's tongue for one minute.</p> <p>Timing of administration: Two minutes prior to the injections.</p> <p>Volume of sucrose or sterile water: Two mLs bolus.</p> <p>Method of injections: Intramuscular (into both thighs).</p> <p>Number of injections: Three injections with the most painful given last.</p> <p>All infants were placed on an examination table for the injections as per clinic protocol. Baseline state was evaluated immediately before the injections were given and categorised as sleeping/quiet, alert or crying. The clinic nurses gave the injections using a standard recommended technique. The investigator moved the video camera, which was mounted on a tripod, to track the baby's face and body during injections and for two minutes after the last injection. The name of the nurse and the length of time required for the injections were recorded. Evaluations of the pain scores and crying dimensions were conducted from the videotapes. The clinic staff provided instructions for post-immunisation care per setting protocol.</p>
Outcomes	<p>Pain scores: Obtained from the MBPS. Assessed at baseline, ten seconds post last injection, 30 seconds post last injection, and 120 seconds after last injection.</p> <p>Crying was defined as the presence of audible negative vocalisations accompanied by facial grimace. Crying was measured as:</p> <p>First cry duration: Defined as the length of time in seconds that the baby cries after the first injection until the first pause in crying of greater than three seconds.</p>

Mowery 2007 (Continued)

Total cry duration: Defined as the length of time in seconds that the baby cries after the first injection until the end of the observation period of two minutes.

Percentage of time spent crying: Defined as the number of seconds in the infant was crying after the first immunisation until the end of the two minutes observation period divided by 120 seconds.

Maximum heart rate elevation: Defined as the maximum heart rate elevation, and was calculated as the difference between baseline and maximum heart rate.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to their treatment group using a computer-generated randomisation table.
Allocation concealment (selection bias)	Low risk	A scientist (not the investigator) labelled study solutions and maintained the associated list of random numbers, which was not disclosed until the analyses were complete.
Blinding (performance bias and detection bias) All outcomes	Low risk	To ensure blinding, both solutions were commercially prepared by Children's Medical Ventures Respironics, Inc. and packaged in identical containers labelled as <i>Sweet-ease</i> . Parents, staff and the investigator were blind to the treatment group assignment. The investigator and a nurse, trained to perform Brazelton Neonatal Assessments, blindly evaluated MBPS scores. The investigator blindly evaluated the following dimensions of crying from the videotapes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All incomplete outcome data were addressed.
Selective reporting (reporting bias)	Unclear risk	There was no protocol available so the original planned outcomes are unknown.
Sample size	Unclear risk	A sample of 21 in each group will have 80% power to detect a difference in means of -1.70 [pain scale] assuming that the Group one standard deviation is 2.10 and the Group two standard deviation is 1.70, with a 005 two-sided significance level. To accommodate missing data, total sample size was increased by 10% to 46 participants.

Poulsen 2009

Methods	Parallel randomised controlled trial.
Participants	<p><u>Participants</u>: Infants attending their three- or five-monthly routine immunisation (Diphtheria, Tetanus toxoid and Pertussis (DTP), Polio (IPV) and Haemophilus influenzae type B (HiB) vaccines).</p> <p><u>Sex</u>: Male (38) and female (29) infants.</p> <p><u>Age of infants</u>: Three- five months.</p> <p><u>Number randomised</u>: 67.</p> <p><u>Number used in analysis</u>: 67.</p>

Poulsen 2009 (Continued)

Setting: General practices.

Inclusion criteria: Infants age three and five months who were vaccinated in consensus with the Danish National Health Board recommendations.

Exclusion criteria: If parental consent could not be obtained.

Interventions	<p><u>Interventions</u>:</p> <ol style="list-style-type: none"> 1. Sucrose (34) 2. Normal Saline (33) <p><u>Strength of sucrose</u>: 12%.</p> <p><u>Method of administration</u>: Solutions placed on the tongue.</p> <p><u>Timing of administration</u>: Two minutes prior to the injection.</p> <p><u>Volume of sucrose or normal saline</u>: Two mLs bolus.</p> <p><u>Method of injection</u>: Intramuscular.</p> <p><u>Number of injections</u>: One injection.</p>
Outcomes	<p><u>Pain</u></p> <p>Measured using the Neonatal Infant Pain Scale (NIPS).</p>
Notes	Additional data sought and provided by authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to their treatment group using a computer-generated randomisation program.
Allocation concealment (selection bias)	Low risk	Randomisation and packing of the solutions was conducted by a pharmacist separate to the study.
Blinding (performance bias and detection bias) All outcomes	Low risk	The codes were received by the researcher after completion of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All incomplete outcome were addressed.
Selective reporting (reporting bias)	Unclear risk	There was no protocol to access so the original planned outcomes are unknown.
Sample size	Unclear risk	Not reported

Priambodo 2008

Methods	Parallel randomised controlled trial.
Participants	<u>Participants</u> : Infants attending their 3rd DTP immunisation (Diphtheria, Tetanus, Pertussis).

Sweet-tasting solutions for needle-related procedural pain in infants one month to one year of age (Review)

Priambodo 2008 (Continued)

Sex: Male (52) and female (36) infants.

Age of infants: Four to six months.

Number randomised: 86.

Number used in analysis: 86 (two dropped out).

Setting: Growth & development clinic and public health centres.

Inclusion criteria: Infants requiring their 3rd Diphtheria, Tetanus toxoid and Pertussis (DPT) vaccine and four to six months old.

Exclusion criteria:

- Born prematurely.
- Born with low birth weight (< 2500 g).
- Previous history of hospitalisation.
- Where given other intramuscular immunisation e.g. HiB.
- Given paracetamol.
- Suspected to suffer from Down Syndrome, other congenital defects.
- Presence of stomatitis.
- Using pacifier or breast fed during immunisation.

Interventions	<p><u>Interventions</u>:</p> <ol style="list-style-type: none"> 1. Sucrose (42) 2. Plain water (44) <p><u>Strength of sucrose</u>: 75%.</p> <p><u>Volume of sucrose or plain water</u>: Two mLs bolus.</p> <p><u>Timing of administration</u>: About Two minutes before immunisation.</p> <p><u>Method of administration</u>: Using a syringe, solution dropped into the infant's mouth.</p> <p><u>Method of injection</u>: Intramuscular (anterolateral thigh).</p> <p><u>Number of injections</u>: one injection.</p> <p>Sound recording via a tape recorder began from a few seconds before injection until three minutes after injection.</p>
Outcomes	<p>Duration of crying was divided into two parameters:</p> <p><u>Duration of first cry</u> (in seconds), which was the duration of crying from the start of the procedure until the first - lasted more than five seconds.</p> <p><u>Total duration of crying</u> (in seconds), which was the total crying heard within three minutes from the start of the procedure.</p>
Notes	Additional outcome data were requested from the authors and were reported to be lost.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Eligible infants were randomised using a random table in block of six. Every location of the study had its own random lists. Information reported insufficient for a judgment to be made.

Priambodo 2008 (Continued)

Allocation concealment (selection bias)	Unclear risk	Information reported insufficient for a judgment to be made.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information reported insufficient for a judgment to be made.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All incomplete outcome data were addressed.
Selective reporting (reporting bias)	Unclear risk	There is no protocol to access so the original planned outcomes are unknown.
Sample size	Low risk	Calculation of sample size was performed using estimation of clinically significant difference of 13 seconds and a standard deviation of 21 seconds. With significance level of 95% and power of 80%, a minimum of 41 subjects were needed for each group (n = 82).

Ramenghi 2002

Methods	Parallel randomised controlled trial.
Participants	<p><u>Participants</u>: Infants undergoing routine immunisation (diphtheria, tetanus, pertussis (DTP) and haemophilus influenzae, type B (HiB) at two, three or four months after birth.</p> <p><u>Sex</u>: Male (92) and female (92) infants.</p> <p><u>Age of infants</u>: Two, three or four months.</p> <p><u>Number randomised</u>: 184.</p> <p><u>Number used in analysis</u>: 184.</p> <p><u>Setting</u>: Immunisation clinic.</p> <p><u>Inclusion criteria</u>: Healthy infants, Infants born between 37 to 42 weeks gestation Birth weight > 2,500 g No hospital admission since discharge from the postnatal ward.</p> <p><u>Exclusion criteria</u>: (N/A)Each infant could only be enrolled once into the study (i.e., only at either 1st, 2nd or 3rd immunisation). Thus, immunisation groups were independent of each other.</p>
Interventions	<p><u>Interventions</u>:</p> <ol style="list-style-type: none"> 1. Sucrose 50% (45) 2. Sucrose 25% (46) 3. Lycasin (glucose) 40% w/v hydrogenated glucose (46) 4. Sterile water (47) <p><u>Method of administration</u>: Solutions syringed for 1 minute onto the anterior part of the baby's tongue to best stimulate taste perception and sucking. Non-nutritive sucking used by some infants.</p> <p><u>Timing of administration</u>: Two minutes prior to injection.</p> <p><u>Volume of sucrose, lycasin (glucose) or water</u>: Two mL bolus.</p> <p><u>Method of injection</u>: Intramuscular (both thighs used).</p>

Ramenghi 2002 (Continued)

Number of injections: Two injections.

The study injections were given by the same operator, using the same kind of disposable needles. The same commercial vaccines were used in all cases.

During the procedure, the parents were allowed to interact with their child by cuddling and speaking to them. The baby was allowed to receive a pacifier after the injection, if the parents wished.

A tape recording was made for three minutes following both the injections.

Outcomes Percentage of total time spent crying: Crying time which was taken as the percentage of time spent crying during the period following the DTP injections.

Difference in the percentage of time spent crying following the HiB and DTP injections (crying HiB - DYTP).

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list was generated (see below).
Allocation concealment (selection bias)	Low risk	Each eligible infant was enrolled following progressive numeration from randomised lists stratified for the three immunisation groups (1st, 2nd, 3rd immunisation). Each number in the list corresponded to different letter. Each letter corresponded to an individual sterile plastic bottle with five mLs of the test solution. The "randomisation list" was generated by a person who was not involved in entering patients into the trial.
Blinding (performance bias and detection bias) All outcomes	High risk	The sterile water and the two sucrose solutions were indistinguishable and was blinded to the investigator. However, lycasin (glucose) could not be blinded because it was pink in colour. The tape recording was analysed by a single investigator unaware of the solution the baby received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All incomplete outcomes were addressed.
Selective reporting (reporting bias)	Unclear risk	There is no protocol to access so the original planned outcomes were unknown.
Sample size	Low risk	The sample size was based on a similar previous study in newborn babies where it was shown that 15 babies were required in each treatment group to achieve 80% power to show a 50% reduction in crying time. Hence, for this study, 180 babies were required to enter the study, 60 in each of the immunisation groups.

Soriano 2003

Methods	Parallel randomised control trial.
Participants	Infants requiring immunisation against hepatitis B virus or against Diphtheria, Tetanus toxoid and Pertussis (DTP) and Haemophilus influenzae type B (HiB) vaccine. Sex: Male (169) and female (154) infants.

Soriano 2003 (Continued)

Age of infants: One to six months (Median 3.2 months).

Number randomised: 323.

Number used in analysis: 323.

Setting: Unknown.

Inclusion criteria: Unknown.

Exclusion criteria: Crying before administration of vaccine; chronic sickness or recurrent sickness; infants receiving medications except vitamins; babies born < 34 weeks with apgars < seven at one minute or < eight at five minutes; infants unable to tolerate oral fluids because of sickness or neurological problems.

Interventions	1. Sucrose 2. Drinking water <u>Strength of sucrose:</u> 75%. <u>Method of administration of sucrose and sterile water:</u> Unknown. <u>Timing of intervention:</u> Two minutes prior to procedure. <u>Volume of sucrose and sterile water:</u> Two mLs bolus. <u>Method of administration of injection:</u> intramuscular. <u>Number of injections:</u> One injection.	
Outcomes	Duration of crying time.	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised control study design. Information reported insufficient for a judgement to be made.
Allocation concealment (selection bias)	High risk	Not stated. Information reported insufficient for a judgement to be made.
Blinding (performance bias and detection bias) All outcomes	Low risk	Randomised, Double blind, placebo-controlled trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcomes were addressed.
Selective reporting (reporting bias)	Unclear risk	There was no protocol to access so the original planned outcomes were unknown.
Sample size	Unclear risk	No sample size calculation reported by authors.

Thyr 2007

Methods	Parallel randomised controlled trial.
Participants	<p><u>Participants</u>: Infants who attended routine immunisation at three, five and 12 months of age (vaccination Infanrix Polio Hib).</p> <p><u>Sex</u>: Male (59) and female (51) infants at three-month immunisation.</p> <p><u>Age of infants</u>: (three to 12 months)</p> <p><u>Number randomised</u>: 110</p> <p><u>Number used in analysis</u>: 110 (three months); 109 (five months); 40 (12 months).</p> <p><u>Setting</u>: Immunisation clinic.</p> <p><u>Inclusion criteria</u>: Healthy infant</p> <p><u>Exclusion criteria</u>:</p> <ul style="list-style-type: none"> • Infants born < 34 complete weeks of gestation • Infants who had a modification of their standard protocol
Interventions	<p><u>Interventions</u>:</p> <ol style="list-style-type: none"> 1. Glucose (n = 55) 2. Sterile water (n = 55) <p><u>Strength of glucose</u>: 30% (0.5 g).</p> <p><u>Method of administration</u>: Syringed onto the infant's tongue (no nutritive sucking).</p> <p><u>Timing of administration</u>: 30 seconds before, during and 10 to 30 seconds after immunisation.</p> <p><u>Volume of glucose or sterile water</u>: Two mLs bolus.</p> <p><u>Method of injection</u>: Intramuscular (left thigh three and 12-month vaccination; right thigh at five-month vaccination).</p> <p><u>Number of injections</u>: one injection.</p> <p>For the three- and five-month vaccination, the infants were lying down on a table, and for the 12-month vaccination they were sitting on the knee of a parent. None of the infants used a pacifier or any kind of pain relief. The parents were allowed to cuddle the infant during the procedure.</p>
Outcomes	<p><u>Crying time</u>: Taken from onset of the injection until all crying activity had ceased and up to maximum of 120 seconds.</p> <p><u>Crying intensity</u>:</p> <p>Defined as moaning (1-point) and out right crying (2-points).</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Consecutive randomisation according to the "closed envelope" technique. Infants who were randomised to receive glucose or water at three months received the same solution at five and 12 months respectively.

Thyr 2007 (Continued)

Allocation concealment (selection bias)	Low risk	Two nurses took part in the study and the same nurses were present on all occasions. The nurse whose turn it was to give the immunisation opened the envelope. One nurse opened the coded envelope while the other nurse prepared to conduct the observations.
Blinding (performance bias and detection bias) All outcomes	High risk	The sterile water and the glucose solutions were indistinguishable and blinded to the investigator. Throughout the study, the observation nurse and parents were blind to the nature of the solution. The nurse who performed the immunisation was aware of the intervention and a possible source of bias. The authors acknowledge this possible source of bias if this awareness affected the technique used by the nurse when performing the injection. However, the nurses in question had many years of experience and a stable technique for immunisation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The total loss for follow-up in the study was eight infants. At the five-month immunisation, one girl in the control group was lost because the parents did not want her to complete the immunisation program. At the 12-month immunisation, three girls and one boy from glucose group, and three girls from control group were lost for follow-up due to moving from the district.
Selective reporting (reporting bias)	Unclear risk	There was no protocol to access so the original planned outcomes were unknown.
Sample size	Unclear risk	Not reported by the authors.

DPT: Diphtheria, Tetanus, Pertussis

HIB: Haemophilis influenzae conjugate type b

IPV: (inactivated polio vaccine

MBPS: Modified Behavioral Pain Scale

NIPS: Neonatal Infant Pain Scale

WCH: University of Wisconsin Children's Hospital

VAS: Visual analogue scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abad 2001	Not in the age range (less than one month old newborn)
Ackam 2004a	Not in the age range (less than one month old newborn)
Ackam 2004b	Not in the age range (less than one month old newborn)
Ahn 2006	Not in the age range (less than one month old newborn)
Barr 1993	Not in the age range (less than one month old newborn)
Barr 1994	No needle procedure applied
Bauer 2004	Not in the age range (less than one month old newborn)
Blass 1995	Not in the age range (less than one month old newborn)

Study	Reason for exclusion
Blass 1999	Not in the age range (less than one month old newborn)
Bucher 2000	Not in the age range (less than one month old newborn)
Carbajal 1999	Not in the age range (less than one month old newborn)
Carbajal 2002	Not in the age range (less than one month old newborn)
Carbajal 2003	Not in the age range (less than one month old newborn)
Chermont 2010	Not in the age range (less than one month old newborn)
Codipietro 2008	Not in the age range (less than one month old newborn)
Cohen 2002	Inappropriate intervention (distraction versus typical care)
Curtis 2007	Data include infants less than one month old
Dilen 2010	Not in the age range (less than one month old newborn)
Eriksson 1999	Not in the age range (less than one month old newborn)
Eriksson 2004	Not in the age range (less than one month old newborn)
Gal 2005	Not in the age range (preterm)
Gharehbaghi 2007	Not in the age range (less than one month old newborn)
Gibbins 2002	Not in the age range (less than one month old newborn)
Gibbins 2003	Not in the age range (less than one month old newborn)
Gradin 2002	Not in the age range (less than one month old newborn)
Gradin 2004	Not in the age range (less than one month old newborn)
Gradin 2005	Not in the age range (less than one month old newborn)
Graillon 1997	Not in the age range (less than one month old newborn)
Greenberg 2002	Not in the age range (less than one month old newborn)
Guala 2001	Not in the age range (less than one month old newborn)
Haouari 1995	Not in the age range (less than one month old newborn)
Harrison 2003	Not in the age range (less than one month old newborn)
Idam-Syuryun 2008	Could not translate data (In Russian)
Isik 2000	Not in the age range (less than one month old newborn)
Jatana 2003	Not in the age range (less than one month old newborn)
Johnston 2002	Not in the age range (less than one month old newborn)

Study	Reason for exclusion
Lindh 2003	Inappropriate intervention (multiple intervention-glucose and topical analgesia)
Ling 2005	Not in the age range (less than one month old newborn)
Liu 2010	Not in the age range (less than one month old newborn)
Montoya 2009	Not in the age range (less than one month old newborn)
Ogawa 2005	Not in the age range (less than one month old newborn)
Overgaard 1999	Not in the age range (less than one month old newborn)
Ramenghi 1996	Not in the age range (less than one month old newborn)
Ramenghi 1999	Not in the age range (unhealthy preterm)
Ramenghi 2002b	Not in the age range (less than one month old newborn)
Reis 2003	Sweet-tasting solution given by bottle with other interventions such as parental holding versus no intervention. This make it hard to separate effect of used sweet solution from other interventions.
Rogers 2006	No needle procedure (Bladder catheterisation)
Sajedi 2006	Not in the age range (less than one month old newborn)
Shadkam 2008	Not in the age range (less than one month old newborn)
Skogsdal 1997	Not in the age range (less than one month old newborn)
Taddio 2008	Not in the age range (less than one month old newborn)
Taddio 2009	Not in the age range (less than one month old newborn)
Taskande 2005	Not in the age range (less than one month old newborn)

DATA AND ANALYSES

Comparison 1. Sweet-tasting solution versus Control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cry Duration (seconds)	7	790	Mean Difference (IV, Fixed, 95% CI)	-13.47 [-16.80, -10.15]
1.1 30% to 75% sweet-tasting solutions	4	523	Mean Difference (IV, Fixed, 95% CI)	-7.66 [-11.41, -3.91]
1.2 12% to 25% sweet-tasting solutions	3	267	Mean Difference (IV, Fixed, 95% CI)	-34.71 [-41.89, -27.54]

Analysis 1.1. Comparison 1 Sweet-tasting solution versus Control, Outcome 1 Cry Duration (seconds).

Comparison 2. Sweet-tasting solution versus pharmacological intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	1	20	Mean Difference (IV, Fixed, 95% CI)	0.42 [-0.95, 1.78]
2 Cry Duration (sec)	1	20	Mean Difference (IV, Fixed, 95% CI)	9.78 [-9.00, 30.56]

Analysis 2.1. Comparison 2 Sweet-tasting solution versus pharmacological intervention, Outcome 1 Pain.

Analysis 2.2. Comparison 2 Sweet-tasting solution versus pharmacological intervention, Outcome 2 Cry Duration (sec).

APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

1. Needles/
2. needle*.mp.
3. (blood sampl* or immuni* or inoculat* or vaccin* or inject* or "finger prick*" or finger-prick or "heel prick*" or heel-prick* or "heel lance*" or heel-lance* or "heel puncture*" or heel-puncture* or "heel stick" or suture* or (laceration* adj3 repair*)).mp.
4. ("lumbar puncture*" or lumbar-puncture* or "spinal tap*" or spinal-tap*).mp.
5. (("bone marrow" adj4 aspiration) or ("bone marrow" adj4 biops*)).mp.
6. (intravenous or intra-venous or venepuncture* or venipuncture* or "venous cannulation*" or ("arterial blood gas*" adj6 cannul*)).mp.
7. (catheter* or port-a-cath* or portacath*).mp.
8. ("central line" adj6 (insert* or remov*)).mp.
9. (central venous catheter* adj6 insert*).mp.
10. (local analges* or local anaesthe* or local anesthe*).mp.
11. ((arterial puncture or artery) adj6 punctur*).mp.
12. "arterial line*".mp.
13. (thoracocentesis or paracentesis).mp.
14. or/1-13
15. exp Pain/
16. Pain Measurement/
17. PAIN THRESHOLD/
18. pain*.mp.
19. or/15-18
20. 14 and 19
21. ((vaccin* adj6 pain*) or (cannul* adj6 pain*) or (needle* adj6 pain*) or (needle* adj6 distress*) or (needle* adj6 discomfort) or (needle* adj6 fear*) or (needle* adj6 fright*) or (needle* adj6 anxious) or (needle* adj6 anxiet*) or (procedure* adj6 pain*) or (intervention* adj6 pain*) or (intervention* adj6 distress*) or (procedure adj6 distress*) or (procedure* adj6 discomfort*) or (procedure-related adj6 pain)).mp.
22. or/20-21
23. exp sucrose/
24. (sucrose* or lactose* or glucose* or fructose* or glycerine* or lycerine* or dextrose* or aspartame* or polycose* or sacchar* or sugar* or ((sweet* or pleasant* or nice*) adj6 (solution* or taste or tasting))).mp.
25. 23 or 24
26. exp adolescent/ or exp child/ or exp infant/
27. (paediat* or pediat* or baby or babies or neonate* or newborn or infant* or child* or toddler or adolesc* or teen*).mp.
28. 26 or 27
29. 25 and 22
30. 28 and 29

CENTRAL

1. MeSH descriptor Needles explode all trees
2. needle*

3. blood sampl* or immuni* or inoculat* or vaccin* or inject* or "finger prick*" or finger-prick* or "heel prick*" or heel-prick* or "heel lance*" or heel-lance* or "heel puncture*" or heel-puncture* or "heel stick*" or heel-stick* or suture* or (laceration* near/3 repair*)
4. "lumbar puncture*" or lumbar-puncture* or "spinal tap*" or spinal-tap*
5. ("bone marrow" near/4 aspiration) or ("bone marrow" near/4 biops*)
6. intravenous or intra-venous or venepuncture* or venipuncture* or "venous cannulation*" or ("arterial blood gas*" near/6 cannul*)
7. catheter* or port-a-cath* or portacath*
8. "central line" near/6 (insert* or remov*)
9. "central venous catheter*" near/6 insert*
10. "local analges*" or "local anaesthe*" or "local anesthe*"
11. (arterial or artery) near/6 punctur*
12. "arterial line*"
13. thoracocentesis or paracentesis
14. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
15. MeSH descriptor Pain explode all trees
16. MeSH descriptor Pain Measurement explode all trees
17. MeSH descriptor Pain Threshold explode all trees
18. pain*
19. (#15 OR #16 OR #17 OR #18)
20. (#14 AND #19)
21. (vaccin* near/6 pain*) or (cannul* near/6 pain*) or (needle* near/6 pain*) or (needle* near/6 distress*) or (needle* near/6 discomfort) or (needle* near/6 fear*) or (needle* near/6 fright*) or (needle* near/6 anxious*) or (needle* near/6 anxiet*) or (procedure* near/6 discomfort*) or (procedure-related near/6 pain)
22. (#20 OR #21)
23. MeSH descriptor Sucrose explode all trees
24. (sucrose* or lactose* or glucose* or fructose* or glycerine* or lycerine* or dextrose* or aspartame* or polycose* or sacchar* or sugar* or ((sweet* or pleasant* or nice*) near/6 (solution* or taste or tasting)))
25. (#23 OR #24)
26. MeSH descriptor Adolescent explode all trees
27. MeSH descriptor Child explode all trees
28. MeSH descriptor Infant explode all trees
29. (paediat* or pediat* or baby or babies or neonate* or newborn or infant* or child* or toddler* or adolesc* or teen*)
30. (#26 OR #27 OR #28 OR #29)
31. (#22 AND #25)
32. (#30 AND #31)

Appendix 2. Participant numbers in included studies

Study	Overall number	Number participated	Number used in analysis
Allen 1996	285	168 (Subgroup of infants aged 2-9 months) 44 (two months); 50 (four months); 46 (six months); 28 (nine months)	168
Barr 1995	65	65 at 2 months 57 at 4 months	65
Dilli 2009	118	29 (Subgroup of infants aged 6–12 months)	27 (2 excluded post randomi- sation)
Hatfield 2008a	40	40	40

(Continued)

Hatfield 2008b	100	100	83 (17 excluded post randomisation)
Kassab 2012	120	120	120
Lewindon 1998	110	110	107 (3 infants excluded post randomisation)
Morelius 2009	100	100	98 (2 infants excluded post randomisation)
Mowery 2007	49	49	49
Priambodo 2008	86	86	86
Poulsen 2009	67	67	67
Ramenghi 2002	184	184	184
Soriano 2003	323	323	323
Thyr 2007	110	110 at 3 months 109 at 5 months (1 dropped out of 110) 40 at 12 months (69 dropped out of 109)	110
TOTAL	1757	1551	1527

Appendix 3. Overview of included randomised controlled trials

Study	Age of infants (months)	Number of injections	Sweet-tasting solution	Concentration of solution (%)	Volume of solution mL	Timing of administration	Method of administration	Non-nutritive sucking (NNS)
Allen 1996	2 to 9	1, 2 or 3	Sucrose	12	2	2 minutes prior to injection	'Oral' using syringe-bolus	No
Barr 1995	2 to 4	1	Sucrose	50	0.75	2 minutes prior to injection	Anterior tongue using pipette-3 doses of 0.25 mls at 30 second intervals	No
Dilli 2009 ;	6 to 12	Single or multiple	Sucrose	12	2	2 minutes prior to injection	Oral using syringe-bolus	No
Hatfield 2008b	2 and 4	3	Sucrose	24	2	2 minutes prior to injection	Surface of tongue using syringe-bolus	Yes
Hatfield 2008a	2, 4 and 6	3	Sucrose	24	2	2 minutes prior to injection	Surface of tongue using syringe	Yes
Kassab 2012	2	2	Glucose	25	2	Immediately prior to injection	Lateral side of tongue using syringe-bolus	No
Lewindon 1998	2, 4 and 6	2	Sucrose	75	2	2 minutes prior to injection	Oral using syringe over 15 seconds.	Yes-some infants
Morelius 2009	3	1	Glucose	30	1	Not mentioned	Oral using syringe-bolus	Yes-Only with sucrose and NNS and water and NNS groups

(Continued)

Mowery 2007	2 to 6	3	Sucrose	50	2	2 minutes prior to injection	Anterior tongue using syringe-bolus	No
Poulsen 2009	3 to 5	1	Sucrose	12	2	2 minutes prior to injection	On the tongue-bolus	No
Priambodo 2008	4 to 6	1	Sucrose	75	2	2 minutes prior to injection	Oral using syringe-bolus	No
Ramenghi 2002	2,3 or 4	2	Sucrose	25	2	2 minutes prior to injection	Anterior tongue using syringe over 1 min.	Yes-Some infants
			Sucrose	50				
			Glucose	40				
Soriano 2003	1,2,4 or 6	1	Sucrose	75	2	2 minutes prior to injection	oral using syringe-bolus	No
Thyr 2007	3, 5 and 12	1	Glucose	30	2	30 seconds before, during and after injection	On the tongue using syringe-dose divided into 3 allocates: 30 seconds before, during and 0-30 seconds after injection	No

Appendix 4. Types of needle-related procedures

Procedure	Definition
Immunisation	Protection against a particular disease or treatment of an organism by protecting against certain pathogen attacks; the introduction of micro-organisms that have previously been treated to make them harmless.
Venepuncture	The surgical puncture of a vein typically for withdrawing blood or administering intravenous medication.
Injection	The act of forcing a liquid into tissue, the vascular tree, or an organ.
Subcutaneous injection	Injection administered under the skin.
Intramuscular injection	Injection administered by entering a muscle.

FEEDBACK

Amended incorrect reference, 19 December 2012

Summary

Name: Gabriel Rada

Comment: Dear authors and editorial group. I wanted to know if the reference to the included study by the review authors (Kassab 2012) is the correct one. The reference correspond to a systematic review by the first author, and as far as I could check, there is no information about such trial in that publication. Considering the academic conflict of interest determined by this issue, I imagine other readers will have the same doubt.

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

From lead author:

Thanks a lot for your provided note. Yes, we did include the wrong reference and the correct one which we were talking about is :

Manal Kassab, Annabel Sheehy, Madeleine King, Cathrine Fowler. A double-blind randomised controlled trial of 25% oral glucose for pain relief in 2-month old infants undergoing immunisation. International Journal of Nursing Studies (2012), Vol. 49, Issue 3, Pages 249-256.

I would also advise you that I have identified myself as an author of included RCT in the Cochrane review under 'Declaration of Interest'. I hope that is answering what you want to identify.

Contributors

Kate Seers, Feedback Editor for PaPaS.

Manal Kassab, lead author of this review.

WHAT'S NEW

Date	Event	Description
7 February 2019	Review declared as stable	See Published notes .

HISTORY

Protocol first published: Issue 3, 2010

Review first published: Issue 12, 2012

Date	Event	Description
17 November 2016	Review declared as stable	See Published notes .
31 January 2013	Feedback has been incorporated	One reference was incorrect and has been amended in response to feedback. See full details here: Feedback .

CONTRIBUTIONS OF AUTHORS

Manal Kassab (MK): undertook the administration of the review, protocol development, study searching, study retrieval, study selection, data extraction, data entry, statistical analyses, and report writing. She worked on drafting of the protocol; and for the review designing a search strategy, screening search results, selection of studies, writing to authors of papers for additional information, quality assessment, data extraction, carrying out the analysis, interpreting the analysis, drafting the final review and taking responsibility for any updates.

Jann Foster (JF): provided expertise in conducting systematic reviews, assisted with protocol development, study searching, study retrieval, study selection, data extraction, data entry, statistical analyses, and report writing, study selection, interpretation of results, report editing, statistical analyses, protocol development, reporting results and drafting of the final review.

Maralyn Fourer (MF): guided the process of drafting of the protocol, review of included studies, and for the review drafting and editing the final review.

Cathrine Fowler (CF): drafting the protocol; and for the review drafting and editing the final review.

DECLARATIONS OF INTEREST

The primary, third and fourth authors of this review are authors of one of the studies ([Kassab 2012](#)) included in this systematic

SOURCES OF SUPPORT

Internal sources

- Jordan University of Science and Technology, Jordan.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

No differences.

NOTES

2015

Updated searches in February and December 2015 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

2019

Updated searches in November 2018 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitates major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Crying; Dietary Sucrose [*administration & dosage]; Glucose [administration & dosage]; Needles [*adverse effects]; Pain [etiology] [*prevention & control]; Randomized Controlled Trials as Topic; Sweetening Agents [*administration & dosage]

MeSH check words

Humans; Infant