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Sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years (Review)

Harrison D, Yamada J, Adams-Webber T, Ohlsson A, Beyene J, Stevens B

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[Intervention Review]

Sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years

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ABSTRACT

Background

Extensive evidence exists showing analgesic effects of sweet solutions for newborns and infants. It is less certain if the same analgesic effects exist for children one year to 16 years of age. This is an updated version of the original Cochrane review published in Issue 10, 2011 (Harrison 2011) titled Sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years.

Objectives

To determine the efficacy of sweet tasting solutions or substances for reducing needle-related procedural pain in children beyond one year of age.

Search methods

Searches were run to the end of June 2014. We searched the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Cochrane Methodology Register, Health Technology Assessment, the NHS Economic Evaluation Database, MEDLINE, EMBASE, PsycINFO, and ACP Journal Club (all via OvidSP), and CINAHL (via EBSCOhost). We applied no language restrictions.

Selection criteria

Published or unpublished randomised controlled trials (RCT) in which children aged one year to 16 years, received a sweet tasting solution or substance for needle-related procedural pain. Control conditions included water, non-sweet tasting substances, pacifier, distraction, positioning/containment, breastfeeding, or no treatment.

Data collection and analysis

Outcome measures included crying duration, composite pain scores, physiological or behavioral pain indicators, self-report of pain or parental or healthcare professional-report of the child's pain. We reported mean differences (MD), weighted mean difference (WMD), or standardized mean difference (SMD) with 95% confidence intervals (CI) using fixed-effect or random-effects models as appropriate for continuous outcome measures. We reported risk ratio (RR), risk difference (RD), and the number needed to treat to benefit (NNTB) for dichotomous outcomes. We used the I^2 statistic to assess between-study heterogeneity.

Main results

We included one unpublished and seven published studies (total of 808 participants); four more studies and 478 more participants than the 2011 review. Six trials included young children aged one to four years receiving sucrose or candy lollipops for immunisation pain compared with water or no treatment. Usual care included topical anaesthetics, upright parental holding, and distraction. All studies were well designed blinded RCTs, however, five of the six studies had a high risk of bias based on small sample sizes.

Two studies included school-aged children receiving sweet or unsweetened chewing gum before, or before and during, immunisation and blood collection. Both studies, conducted by the same author, had a high risk of bias based on small sample sizes.

Results for the toddlers/pre-school children were conflicting. Duration of cry, using a random-effects model, was not significantly reduced by sweet taste (six trials, 520 children, WMD -15 seconds, 95% CI -54 to 24, $I^2 = 94\%$).

Composite pain score at time of first needle was reported in four studies ($n = 121$ children). The scores were not significantly different between the sucrose and control group (SMD -0.26, 95% CI -1.27 to 0.75, $I^2 = 86\%$).

A Children's Hospital of Eastern Ontario Pain Scale score > 4 was significantly less common in the sucrose group compared to the control group in one study ($n = 472$, RR 0.55, 95% CI 0.45 to 0.67; RD -0.29, 95% CI -0.37 to -0.20; NNTB 3, 95% CI 3 to 5; tests for heterogeneity not applicable).

For school-aged children, chewing sweet gum before needle-related painful procedures (two studies, $n = 111$ children) or during the procedures (two studies, $n = 103$ children) did not significantly reduce pain scores. A comparison of the Faces Pain Scale scores in children chewing sweet gum before the procedures compared with scores of children chewing unsweetened gum revealed a WMD of -0.15 (95% CI -0.61 to 0.30). Similar results were found when comparing the chewing of sweet gum with unsweetened gum during the procedure (WMD 0.23, 95% CI -0.28 to 0.74). The Colored Analogue Scale for children chewing sweet gum compared to unsweetened gum before the procedure was not significantly different (WMD 0.24 (-0.69 to 1.18)) nor was it different when children chewed the gum during the procedure (WMD 0.86 (95% CI -0.12 to 1.83)). There was no heterogeneity for any of these analyses in school-aged children ($I^2 = 0\%$).

Authors' conclusions

Based on the eight studies included in this systematic review update, two of which were subgroups of small numbers of eligible toddlers from larger studies, and three of which were pilot RCTs with small numbers of participants, there is insufficient evidence of the analgesic effects of sweet tasting solutions or substances during acutely painful procedures in young children between one and four years of age. Further rigorously conducted, adequately powered RCTs are warranted in this population. Based on the two studies by the same author, there was no evidence of analgesic effects of sweet taste in school-aged children. As there are other effective evidence-based strategies available to use in this age group, further trials are not warranted.

Despite the addition of four studies in this review, conclusions have not changed since the last version of the review.

PLAIN LANGUAGE SUMMARY

Sweet taste to ease injection needle pain in children aged one to 16 years

This is an updated version of the original Cochrane review published in Issue 10, 2011: Sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years. We re-ran the search in October 2014.

Review question: Do sweet tasting solutions reduce pain during needles in children aged from one to 16 years, compared to no treatment, water, other non-sweet solutions, or other interventions such as non-nutritive sucking (babies) or sweet foods or chewing gum (children), topical anaesthetics, music, and distraction?

Background: Small amounts of sweet tasting sugar solutions given orally to babies before and during painful needles significantly reduces distress. However it was not known if the same pain-reducing effects of sweet solutions occurred in children older than one year of age. We therefore examined studies looking at pain-reducing effects of sweet solutions such as sucrose or glucose for painful needle procedures in children aged one to 16 years.

Search date: We searched the literature for published and unpublished studies up to October 2014.

Study characteristics: We found six studies focused on young children aged one to four years; two of these studies were included in the original review and four were new studies. The two studies included in the original review used a low concentration of sucrose, just 12%, which is not considered sweet enough for the pain reducing effects. Three of the four new studies were small pilot studies, conducted to inform full trials, and only one study of sweet solutions in young children included large numbers of children. When we compared results of all six studies, only two showed that sugar water (sucrose) reduced pain during injections. However, the four studies that showed no effect all included small numbers of children, therefore they were not considered large enough to detect significant differences in pain. Further well conducted trials with large enough numbers of young children are needed to work out if sweet taste effectively reduces their pain and distress during needles.

For older school-aged children, there were two studies published by the same author, both of which were included in the original review. Neither study showed that sweet taste helped to reduce pain. As other studies show that strategies such as distraction and topical anaesthetics can effectively reduce needle pain in school-aged children, further studies of sweet taste for pain management in school-aged children are not warranted.

Study funding sources:

Of the six studies including young children, two did not acknowledge receipt of research funding. For the remaining four: a state-wide nursing fund supported two of the pilot studies, an internal research institute provided support for the remaining pilot study and another study was supported in part by a Maternal and Child Health grant.

The two studies including school-aged children, conducted by the same author, were supported by a grant from the Canadian Institutes of Health Research.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Sweet tasting solutions or substances compared with no treatment, placebo, milk, or non-sweet solutions for pain during needle-related procedures

Patient or population: Children 1-16 years undergoing needle-related procedures

Summary of sub-analysis findings: Children 1-4 years: Cry time

Settings: Ambulatory or hospital

Intervention: Any sweet taste

Comparison: No treatment, water, non-sweet tasting solutions/substances

Out-comes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Cry duration	-14.99 (-53.89, 23.90), P = 0.61, I ² = 86%	520 participants in six studies.	Low quality: We are uncertain about the estimate. However further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	Only one full-scale study exists including > 50 infants (Yilmaz 2014). This single large RCT has a large mean difference and narrow 95% CI (-57.80 [-64, -51]) demonstrating a large effect size favouring sucrose compared to water in young children during immunisation. However, the remaining five trials had small sample sizes (< 50 participants); there was unexplained heterogeneity and inconsistent results leading to imprecision of meta-analysis result with a wide confidence interval.

CI: Confidence interval, **RCT:** randomised controlled trial

Based on the GRADE Working Group grades of evidence (below), the evidence to support analgesic effects of sweet taste in children aged one to 16 years is: **Low quality**.

- High quality: We are very confident that the true effect lies close to that of the estimate of the effect
- Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
- Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

BACKGROUND

This is an updated version of the original Cochrane review published in Issue 10, 2011 titled Sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years ([Harrison 2011](#)).

Children of all ages are exposed to painful needle-related procedures during intramuscular injections for scheduled childhood immunisations and medical procedures performed during the course of childhood illnesses. These procedures, although vital for public health (early childhood immunisation) ([Andre 2008](#)) and for medical monitoring and diagnosis (such as blood collection), are known to be painful, resulting in anxiety, distress, and fear in children as well as their parents, and the risk of development of longer term fears of needle pain, parental non-adherence with vaccination administration, and avoidance of medical care ([Diekema 2012](#); [Schechter 2007](#); [Taddio 2012](#); [Wright 2009](#)). Needle-related procedures are reported by hospitalised children to be the most frightening and painful procedures ([Cummings 1996](#); [Ellis 2004](#)), especially for young children ([Humphrey 1992](#)). Rennick and co-authors reported that the number of painful procedures was the strongest predictor of poor psychological outcomes in hospitalised children ([Rennick 2004](#)) and that all hospitalised children in their paediatric intensive care outcomes study were scared of needles ([Rennick 2008](#)). It is therefore important that effective pain-management strategies are consistently used in all settings where immunisations and other needle-related procedures take place. The reduction of pain and distress during medical procedures has the potential to minimise subsequent fears of needles, needle phobia, non-compliance with scheduled immunisation and later avoidance of medical care ([Harrison 2014](#); [Taddio 2012](#); [Shah 2009](#)).

Description of the condition

Children undergo painful needle-related procedures such as blood collection and immunisation. Provision of appropriate and effective analgesia for these procedures is important. Untreated pain as a result of medical procedures not only results in immediate pain, distress, and anxiety at the time of the procedure, but has the potential to lead to longer term sequelae, including increased pain at subsequent procedures and fears of needle pain ([Taddio 2012](#); [Taddio 2014](#)).

Description of the intervention

Oral sucrose and other sweet tasting solutions have been used to promote calm and to reduce pain in infants over the past century, and even before. Prophet Mohammed, circa 632 AD, recommended giving infants a well chewed date ([Islamic Voice 2001](#)) and sugar solutions combined with alcohol, cocaine, or opium, were given to infants from the 1840s to early 1900s ([Holbrook 1959](#)). An over-the-counter medication, Perry Davis pain killer, which contained sugar, alcohol, and opium, was widely promoted as an effective intervention to calm infants, cure colic, and reduce pain in young children ([Holbrook 1959](#)). Infant boys undergoing circumcision were often given sugar mixed with wine or whisky ([Blanton 1917](#)) and a report in 1938 recommended that anaesthesia for infants during surgery was often not required, and that “a sucker consisting of a sponge dipped in some sugar water will often suffice to calm a baby” ([Thorek 1938](#), p. 2021). In 1991, the first randomised trial of sucrose for pain reduction during painful procedures in human

infants was published ([Blass 1991](#)). The authors reported that two mL 12% sucrose compared with two mL water significantly reduced crying time in newborn infants during heel lance and circumcision.

The underlying mechanism of the analgesic effects of sweet tasting solutions is considered to be an orally mediated release of endogenous opioids. Evidence to support a relationship between sweet taste and opioid release primarily emerged from animal studies showing links between sweet taste and opioid release, and the stress-reducing effects of sweet tasting foods or fluids ([Bertiére 1984](#); [Blass 1987](#); [Blass 1989a](#); [Czirr 1986](#); [Dum 1983](#); [Harrison 2012](#); [Lowy 1980](#); [Ren 1997](#); [Rowland 1976](#)). The earliest of these studies ([Rowland 1976](#)) clearly demonstrated that rats that had received mild noxious stimuli (frequent tail pinches) preferentially increased their sweet food intake compared with control rats. [Dum 1983](#) demonstrated an association between sweet food ingestion and the endogenous opiate system, showing that rats consuming chocolate or chocolate milk had an increased occupation of opioid receptors in their hypothalami compared with control animals that were fed water or non-sweet food. The increased opioid receptor occupation was thought to be the result of increased levels of beta-endorphin, resulting from intake of the sweet food. A series of studies confirmed that the sweet tasting solution of sucrose, when given prior to, or during, painful and stressful situations, resulted in a reduction of pain and distress in newborn rat pups ([Blass 1987](#)). These authors established that the analgesic effect was dependent on the sweet taste, with the most concentrated and therefore sweetest taste being more effective than less sweet tasting solutions. Blass and colleagues demonstrated that analgesic effects of sweet taste were blocked by the administration of an opioid antagonist, thereby further confirming an opioid-sweet-taste relationship ([Blass 1987](#)).

In 1989, Blass and colleagues first published a study that evaluated the calming effects of sweet tasting solutions in human infants ([Blass 1989b](#)). Crying, healthy newborn infants given two 0.2 mL doses of 12% sucrose rapidly became calm, with the calming effects persisting up to five minutes following completion of the sucrose doses. Following on from this pioneering study, numerous subsequent studies demonstrated that small volumes of oral sucrose calmed crying infants ([Barr 1994](#); [Barr 1999a](#); [Barr 1999b](#); [Blass 1992](#); [Blass 1995](#); [Graillon 1997](#); [Smith 1992](#); [Smith 1996](#)). Blass and Smith ascertained that the calming effects were sweet-taste mediated, by demonstrating that the sweeter sugars, sucrose and fructose, were more effective than the less sweet tasting sugars, glucose and lactose ([Blass 1992](#)). Lactose was in fact reported to be no more effective than water in reducing crying. Calming effects were shown to be sweet taste- and not volume-dependent, as small volumes of 0.2 mL sucrose were equally as effective as larger volumes of 0.6 mL and 1.0 mL ([Blass 1994](#)). The effects of sweet taste in newborn infants were demonstrated to peak at two minutes following administration and persist up to five to eight minutes ([Blass 1995](#)). However the peak and sustained effects in infants beyond the first month of life were reported to be much shorter, with a peak effect time of less than one minute ([Barr 1994](#)). This shorter effect time needs to be considered for clinical care and further research when including infants beyond the neonatal period, as well as during prolonged painful procedures. For example, Rogers and co-authors ([Rogers 2006](#)) studied infants up to three months of age undergoing urethral catheterisation and [Curtis 2007](#) included infants up to six months of age presenting to the emergency department requiring

venipuncture. In both studies, a single dose of sucrose was given two minutes prior to the procedures. However, venipuncture, especially in sick infants, and urethral catheterisation are more prolonged procedures than immunisation. Both studies showed a lack of analgesic effects of sucrose, however it was argued that the analgesic effects of the single dose of sucrose may not have been sustained in these studies (Harrison 2010a). Repeated doses of sucrose throughout the duration of painful procedures has subsequently been recommended to ensure a sustained analgesic effect (Harrison 2010a).

Sweet taste analgesia is dependent on contact with the tongue, and not ingestion directly via a nasogastric tube (Ramenghi 1999). The authors of both animal and human infant studies report that the sweet-taste induced analgesic effect does not seem to be present within the first day or two of life (Anseloni 2002; Taddio 2009). This could be due to high circulating serum beta endorphins at birth (Facchinetti 1982) negating further increase in response to sweet taste.

Animal and human studies show that sucrose may have analgesic effects extending well beyond the initial dose (Anseloni 2002; Taddio 2009b). In fact, in newborn rat pups, sucrose administration at the time of initial painful procedures and injuries decreased development of subsequent allodynia (pain produced from a stimulus that would not normally produce pain) following cutaneous inflammation (Anseloni 2002). It is unclear whether sucrose has this same protective effect in human infants exposed to multiple procedures. Taddio 2002 reported that despite the use of sucrose during early pain exposure, infants' subsequent pain scores were higher than those of infants who had not been exposed to repeated painful events. However, three studies of prolonged use of sucrose during repeated painful events performed over one to five months showed a lack of increase of pain scores over time (Harrison 2009; Mucignat 2004; Stevens 2005), indicating prolonged ongoing analgesic effects of oral sucrose, with no observable development of sensitisation.

Despite the extensive body of knowledge from the large numbers of published studies conducted in animals and humans, the exact mechanism of analgesic effects of sweet taste in human infants has not been ascertained. Serum beta-endorphin levels in pre-term infants, obtained immediately before administration of a single dose of 30% oral sucrose did not differ compared to levels found two to five minutes following the sucrose administration (Taddio 2003). It was acknowledged, however, that the methods used may not have been appropriate to detect a change in beta-endorphin levels. Future research is warranted to understand the orally mediated mechanism of sucrose as an analgesic in human infants.

Abundant evidence from single RCTs, reviews, and systematic reviews demonstrate that sweet tasting solutions result in profound calming and reduction in behavioral pain responses and pain scores during painful procedures in newborn infants (Bueno 2013; Stevens 2013; Harrison 2010c; Harrison 2012). In addition, there is growing evidence of analgesic effects of sweet tasting solutions in infants beyond the newborn period up to 12 months of age (Harrison 2010a; Kassab 2012). Although sucrose has been the most frequently studied sweet solution (Stevens 2013), various alternative sweet solutions have been studied, including glucose, fructose, glycerine, honey, and non-sucrose artificial sweeteners (Bueno 2013). The administration of sweet solutions is

widely recommended for routine use during painful procedures in neonates (AAP 2006; Anand 2001, Harrison 2006; Harrison 2010c; Henderson-Smart 2007; Lee 2014; RACP 2005; RNAO 2013; Spence 2010).

How the intervention might work

The mechanisms of sweet-taste induced analgesia, thought to be mediated by endogenous opioid systems (Blass 1994; Harrison 2012), may work the same way in children as it does in infants younger than one year of age. Although in animal studies the effects are more pronounced in the newborn period (Anseloni 2002), there is insufficient evidence in humans to inform whether the analgesic effects of sucrose persist into childhood.

Why it is important to do this review

This systematic review is an update of the original Cochrane review (Harrison 2011). Since the publication of a narrative literature review (Harrison 2008), there has been much debate about the effectiveness of sweet tasting solutions in young children. The high prevalence of pain and distress in young children during scheduled childhood immunisations and other needle-related procedures warrants investigation of effective, safe, and feasible pain-management strategies.

The original review included four studies: two focusing on infants and young children (Allen 1996; Dilli 2009) and two on school-aged children (Lewkowski 2003a; Lewkowski 2003b). In the young children, conflicting findings of analgesic effects of 12% sucrose were demonstrated, therefore no conclusions about efficacy or effectiveness could be drawn. For school-aged children, neither sweet tasting chewing gum prior to, nor during immunisations or blood work reduced pain scores, based on the children's self-report.

An ongoing formal systematic review of all relevant studies is warranted to ascertain the efficacy of sweet solutions during needle-related procedures in young children and school-aged children.

OBJECTIVES

To determine the efficacy of sweet tasting solutions or substances for reducing needle-related procedural pain in children beyond one year of age.

To update the original Cochrane systematic review of sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years (Harrison 2011) to determine if studies published since 2011 change the conclusions of the original review. Therefore, to ascertain if sweet tasting solutions, or substances including sucrose, fructose, glucose, or artificial sweeteners, or sweet foods, are analgesic during needle-related procedures in children aged one to 16 years.

Secondly, to determine if the type of painful procedure, the control intervention, the type of sweet tasting solution, the amount and concentration of sweet tasting solution, and incidence of adverse events influence analgesic effects (if numbers warrant subgroup analyses).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs. No language restrictions were imposed.

Types of participants

Participants included children aged one to 16 years undergoing needle-related procedures. These procedures included, but were not limited to: venipuncture, heel lance, finger lance, subcutaneous (SC) or intramuscular injection (IM), lumbar puncture, and suprapubic bladder aspiration.

Types of interventions

Orally administered sweet tasting substances of any concentration and any volume, including sucrose, glucose, fructose, and non-sucrose sweeteners. Breastfeeding, breast milk, or formula were not considered as sweet solutions but were included as comparators.

Solutions could be self-administered or delivered orally by any means (such as syringe, dropper, gauze-soaked pacifier, bottle) with or without a pacifier (non-nutritive sucking on a soother), and with or without additional physical and/or comfort measures (such as cuddling, holding, being spoken to), distraction methods (such as use of toys, visual or verbal distraction; [Uman 2006](#)), psychological interventions ([Chambers 2009](#)), or pharmacological strategies (such as topical anaesthetic agents; [Taddio 2010](#)).

Acceptable interventions in the control group included oral administration of water, formula, breast milk, or other non-sweet substances. In addition, use of pacifiers, positioning, cuddling, distraction, and topical anaesthetic agents could be used.

All settings where sweet solutions were administered and evaluated for pain reduction during needle-related procedures were included. These included hospital, outpatient, community, or school settings.

Types of outcome measures

Types of outcome measures included observational behavioral measures of pain, self-report or parent-report of pain intensity measures, physiological outcomes, or a combination of several measures.

Primary outcomes

Pain intensity assessed by uni-dimensional, multidimensional, or composite pain scores (including a combination of behavioral, physiological, and contextual indicators), or a combination, or self-report of pain.

Secondary outcomes

- Behavioral indicators including crying duration, facial expressions, and body movements.
- Observational pain scores such as those scored by parents, clinicians, and research staff.
- Physiological responses such as heart rate, heart rate variability, respiratory rate, TcpO₂, TcpCO₂, SpO₂, skin conductance.

- Other clinically important outcomes identified in individual studies (not prespecified).
- Adverse events (such as desaturation, bradycardia).
- Choking, spitting up, and vomiting.

As we could not predict all possible adverse effects of sweet tasting substances, we reported on any adverse effects/events described by the authors.

Time(s) of measurement:

Timing of measurements and aggregation of data varied from study to study. Common times of measurement included:

- baseline prior to delivery of intervention/control;
- upon commencement of procedure;
- 30 and 60 seconds following commencement of procedure;
- throughout entire duration of procedure;
- up to 10 minutes following completion of procedure.

Search methods for identification of studies

The systematic review followed the standard search strategy methods outlined by The Cochrane Collaboration ([RevMan 2014](#)).

If publications were in abstract form only, we did not include them in the review, as discrepancies in numbers of participants enrolled between abstracts and final publication of results may exist ([Walia 1999](#)). If identified, we would have contacted authors of abstracts which had not been reported as full text articles to provide unpublished data to assess appropriateness for inclusion.

Electronic searches

We conducted searches in the following databases using the OvidSP interface except where otherwise stated, for the dates specified:

- Cochrane Central Register of Controlled Trials (CENTRAL), June 2014.
- MEDLINE, 1946 to Daily update (July 15, 2014).
- EMBASE, 1947 to week 28 2014.
- PsycINFO, 1806 to July week 2 2014.
- ACP Journal Club, June 2014.
- Cochrane Database of Systematic Reviews (CDSR), 2005 to June 2014.
- Database of Abstracts of Reviews of Effects (DARE), 2nd quarter 2014.
- Cochrane Methodology Register, 2nd quarter 2014.
- Health Technology Assessment, 2nd quarter 2014.
- The NHS Economic Evaluation Database, 2nd quarter 2014.
- CINAHL (EBSCOhost interface), 1982 to July 15 2014.

No language restrictions were applied.

The search terms and strategies for each database are listed in the appendices ([Appendix 1](#); [Appendix 2](#); [Appendix 3](#); and [Appendix 4](#)).

Searching other resources

In addition, we searched relevant bibliographies, relevant recent neonatal, paediatric and pain journals, and paediatric and paediatric pain conference proceedings.

Data collection and analysis

Selection of studies

Two reviewers (JR and CL) independently screened abstracts to identify eligible studies. We considered studies including children aged one to 16 years undergoing a needle-related painful procedure after receiving a sweet tasting solution, substance, or food versus control for inclusion. We retrieved full text articles of all potentially relevant abstracts and the review authors independently assessed them for inclusion. We planned to resolve discrepancies through a consensus process but this was not necessary.

Data extraction and management

Data extracted from each study included: study design, age of the children, overall sample size, sample size per group, number of groups, type of painful procedure, number of interventions, type of sweet solution(s), concentration of solution(s), volume of solution(s), type of sweet substance or food, outcomes, and adverse events. Two reviewers (JR and CL, or AO and CL for Harrison pilot studies) independently extracted data from the studies using a standardized data extraction form. We resolved differences through a consensus process or by consulting a third review author when necessary.

Assessment of risk of bias in included studies

Standard methods of the Cochrane Collaboration were used to assess the potential risk of bias using the Cochrane 'Risk of bias' classification ([Higgins 2011](#)), Chapter 8, section 8.5.

Review authors JY and AO evaluated the following headings and associated questions (based on the questions in the 'Risk of bias' tables) and first author DH entered the details into the [Characteristics of included studies](#) 'Risk of bias' tables. We attempted to obtain the study protocol for each included study to ascertain if there were any deviations between the protocol and the full publication of the study. No review authors were blinded to authors or institutions.

1. Random sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants and personnel (performance bias).
4. Blinding of outcome assessment (detection bias).
5. Incomplete outcome data (attrition bias).
6. Selective outcome reporting (reporting bias).
7. Other potential sources of bias.
8. Size, based on number of participants in each study arm.

Selection bias (random sequence generation and allocation concealment)

1. Random Sequence generation

For each included study, we categorised the risk of selection bias as:

- low risk - adequate (any truly random process, e.g. random number table; computer random number generator);
- high risk - inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk - no or unclear information provided.

2. Allocation concealment

For each included study, we categorised the risk of bias regarding allocation concealment as:

- low risk - adequate (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk - inadequate (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth); or
- unclear risk - no or unclear information provided.

Blinding of participants, personnel, and outcome assessors (performance and detection bias)

3. Blinding of participants and personnel (performance bias)

For each included study, we categorised the methods used to blind study participants and personnel to knowledge of which intervention a participant received (if the study population consisted of young children unable to verbalise, they were considered to be blinded to the study intervention) as:

- low risk - adequate for personnel (a placebo that could not be distinguished from the active solution was used in the control group);
- high risk - inadequate (participants or personnel were aware of group assignment); or
- unclear risk - no or unclear information provided.

4. Blinding of outcome assessment (detection bias)

For each included study, we categorised the methods used to blind outcome assessors to knowledge of which intervention a participant received (if the study population consisted of young children unable to verbalise, they were considered to pose no risk of revealing group assignment). We assessed blinding separately for different outcomes or classes of outcomes. We categorised the methods used with regards to detection bias as:

- low risk - adequate (follow-up was performed with assessors blinded to group);
- high risk - inadequate (assessors at follow-up were aware of group assignment); or
- unclear risk - no or unclear information provided.

Incomplete outcome data

5. Incomplete outcome data (attrition bias)

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), whether reasons for attrition or exclusion were reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we planned to re-include missing data in the analyses. We categorised the methods with respect to attrition bias as:

- low risk - adequate (less than 10% missing data);
- high risk - inadequate (more than 10% missing data); or
- unclear risk - no or unclear information provided.

Selective outcome reporting

6. Selective outcome reporting (reporting bias)

For each included study, we described how we investigated the risk of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk - adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk - inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study failed to include results of a key outcome that would have been expected to have been reported); or
- unclear risk - no or unclear information provided (the study protocol was not available).

Other bias

7. Other potential sources of bias

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk (no concerns of other bias raised);
- high risk (concerns raised about multiple examinations of the data before completion of data collection, differences in the number of patients enrolled in the abstract and final publications of the paper); or
- unclear (concerns raised about potential sources of bias that could not be verified by contacting the authors).

Size

8. Size - based on number of participants in each study arm

According to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS) guidance on sample size, for each included study we evaluated risk of bias based on number of participants included in the studies as:

- low risk (200 participants per arm);
- high risk (<50 participants per arm); or
- unclear risk (50-199 per arm).

Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. If required and if possible, we planned to explore the impact of the level of bias through undertaking sensitivity analyses.

Measures of treatment effect

We used RevMan 5.3 (RevMan 2014) provided by The Cochrane Collaboration. We extracted the mean scores and their standard deviations in the treatment and control groups if data were available.

Unit of analysis issues

If the data were not presented in a format that allowed for their use in the statistical package of RevMan 5.3 (provided in graphic form only), then we reported the data in narrative form. Raw data were requested from authors if required for calculation of means and their standard deviations.

Dealing with missing data

We contacted study authors of Allen 1996; Dilli 2009; Harrison 2014a; Harrison 2014b; Harrison 2014c; and Yilmaz 2014 to request missing information/data and data clarification for the purposes of assessment of risk of bias and data extraction. We did obtain unpublished data from Allen 1996; Dilli 2009; Harrison 2014a; Harrison 2014b, and Harrison 2014c.

Assessment of heterogeneity

We reported in-between-study heterogeneity including the I^2 statistic (Higgins 2002). We attempted to explain the sources of in-between-study heterogeneity.

Assessment of reporting biases

We did not assess reporting biases such as publication bias in this review as there were less than 10 studies included in any meta-analysis.

Data synthesis

We performed meta-analyses where data were presented with sufficient information. We used weighted mean difference (MD) for continuous outcomes when interventions and outcomes of sufficient homogeneity were being analysed. For continuous outcomes, if the assessment instruments differed, we used the standardized mean difference (SMD). For dichotomous outcomes, we used risk ratio (RR) and risk difference (RD). If a statistically significant RD was identified, we calculated the number needed to treat to benefit (NNTB) or the number needed to treat to harm (NNTH). We used the random-effects model for analysis if at least two studies were included in an analysis.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses according to the age of participants: young children (one to four years) and school-aged children.

Sensitivity analysis

There were insufficient studies to perform sensitivity analyses based on methodological quality.

RESULTS

Description of studies

For full details see the 'Characteristics of included studies' table, 'Characteristics of excluded studies' table, and 'Additional

table - Summary of included studies' ([Table 1](#)). No studies awaiting classification were identified.

Results of the search

The original search conducted in 2011 yielded 1212 citations identified for screening, of which we excluded 1202 following screening of abstracts for the following reasons: duplicate ($n = 337$); all participants were younger than inclusion criterion ($n = 262$); not related to paediatric pain management ($n = 315$); not RCTs or quasi RCTs ($n = 162$); did not use sweet solutions/sweet taste ($n = 68$); commentary or editorial ($n = 22$); all participants were older than inclusion criterion ($n = 9$); did not involve painful procedures ($n = 12$); other ($n = 10$); animal studies ($n = 4$); or did not involve needle-related painful procedure ($n = 1$). Upon retrieval of full

papers, we excluded seven further studies: children were younger than the inclusion criterion in five studies, and the procedure was not needle-related in two studies. There were no studies excluded based on being published in abstract form only.

Author TW conducted the updated search, which yielded 601 citations, and three records were identified through other sources. Two duplicates were removed. Research personnel JR and CL screened 599 citations and excluded 596 studies ([Figure 1](#)). We accessed the full text of two publications with three studies (one article reported two studies) and all data for one unpublished pilot study. These four studies were included in our update. Upon retrieval of the full papers, there were no further studies excluded from the updated search.

Figure 1. PRISMA flow diagram of updated search

Figure 1. (Continued)

Figure 1. (Continued)

(one article reported on 2 studies)

Included studies

We included seven published studies and one unpublished study in this review. The two trials included in the original review which focused on infants and young children included a subgroup of eligible participants over 12 months of age (Allen 1996; Dilli 2009). Allen 1996 included a total of 285 participants and we extracted data for 59 children who met the eligibility criterion for this review based on age. The children were aged 15 months and 18 months, undergoing one or two SC injection(s) for scheduled childhood immunisation. The intervention was two mL 12% sucrose given two minutes prior to commencement of scheduled childhood immunisation compared to two mL water or control (no intervention). The outcome used was crying time from the first injection, and for the three minutes following completion of injections. Dilli 2009 included 243 participants in total and we extracted data for 57 children aged 13 to 48 months, undergoing one or more intramuscular (IM) or SC injections for scheduled childhood immunisation. The intervention was the same as Allen 1996; two mL 12% sucrose given two minutes prior to commencement of scheduled childhood immunisation. Comparators were control (no intervention) and topical anaesthetic (lidocaine-prilocaine cream). Outcomes were crying time from the first injection until cessation of crying, and the composite behavioral pain scale Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (McGrath 1985).

Four new studies focusing on young children were added to this review update. The largest study focused on immunisation in children aged 16-19 months (Yilmaz 2014). A total of 537 healthy children were included and randomised to one of three groups: control (water), 25% sucrose, or 75% sucrose. All children were held front-to-front over the parents' shoulder. Outcomes were crying time and the composite pain scale CHEOPS. The remaining three studies focusing on young children were pilot RCTs with small numbers of participants. One publication included two separate pilot RCTs during scheduled childhood immunisation; one was a blinded pilot RCT of 33% sucrose compared to water, and included 29 young children aged 12 and 18 months (Harrison 2014a), and one was a non-blinded pilot RCT, including 30 four-year-old children randomised to receive lollipops prior to and during immunisations or following completion of the procedure (Harrison 2014b). Primary outcomes for the younger children were cry duration and the composite pain score Face, Legs, Activity, Cry, Consolability (FLACC) (Merkel 1997). Secondary outcomes were parental visual analogue scale (VAS) scores on a 10 cm

scale; nurses' score of compliance with study solutions; parents' perception of effectiveness of treatment; and parents' preference of treatment for future immunisations. For the pre-school children in the lollipop study, self report of pain using the Wong Baker Faces Scale® was obtained. The third study by Harrison 2014c was an unpublished, blinded pilot RCT of 25% sucrose compared to water in 21 hospitalised children aged 12-36 months undergoing venipuncture. Primary outcomes were cry duration (seconds) and FLACC scores.

Two studies focused on school-aged children during blood sampling by either venipuncture or finger lance (99 children; Lewkowski 2003a) or scheduled childhood immunisation (115 children; Lewkowski 2003b). Outcomes were the children's self-report using the Faces Pain Scale (FPS; Bieri 1990) and the Colored Analogue Scale (CAS; Price 1992).

Details of each study are outlined in the 'Characteristics of included studies' table and 'Additional table - Summary of included studies' (Table 1).

Excluded studies

In the original review, we excluded seven studies following retrieval of the full papers. In five studies (Bovedani 2007; Mowery 2007; Poulsen 2009; Ramenghi 2001; Ramenghi 2002), all were infants younger than 12 months of age at the time of inclusion in the study. Two further studies were excluded as the painful procedure was cold pressor testing (CPT; Miller 1994; Pepino 2005), and therefore not needle-related.

Author TW conducted the updated search, which yielded 601 citations (Figure 1). Three records were identified through other sources. Two duplicates were removed. Research personnel JR and CL screened 599 citations and excluded 596 studies (Figure 1). We accessed the full text of two publications with three studies (one article reported two studies) and all data for one unpublished pilot study. These four studies were included in our update. Upon retrieval of the full papers, there were no further studies excluded from the updated search.

Risk of bias in included studies

Risks of bias in the eight included studies were reported under Characteristics of included studies, as percentages across all included studies in Figure 2, and as 'Risk of bias' summaries in Figure 3.

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

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Size
Allen 1996	?	+	+	+	?	?	+	-
Dilli 2009	?	+	-	+	+	?	+	-
Harrison 2014a	+	+	+	+	+	+	+	-
Harrison 2014b	+	+	-	-	+	+	+	-
Harrison 2014c	?	?	+	?	?	?	+	-
Lewkowski 2003a	?	?	-	-	+	?	+	-
Lewkowski 2003b	?	?	-	-	+	?	+	-
Yilmaz 2014	?	?	+	?	?	?	+	?

Random sequence generation (selection bias)

Random sequence generation was deemed to be at low risk in the two published pilot studies by Harrison et al, and at unclear risk in the remaining six studies as it was not sufficiently described.

Allocation concealment (selection bias)

Four of the eight studies were deemed to be at low risk, while for the remaining four studies ([Harrison 2014c](#); [Lewkowski 2003a](#); [Lewkowski 2003b](#); [Yilmaz 2014](#)) the risk of selection bias due to

insufficient allocation concealment was unclear. [Yilmaz 2014](#) and [Harrison 2014c](#) described concealment as "closed envelopes" but did not state opaque, sealed, and sequentially numbered. There was no description of allocation concealment in the two studies by [Lewkowski 2003a](#); [Lewkowski 2003b](#).

Blinding of participants and personnel (performance bias)

Three of the eight studies were scored as having low risk of performance bias for adequate blinding of sucrose and water interventions to participants and personnel ([Allen 1996](#); [Harrison 2014a](#); [Yilmaz 2014](#)) while the remaining five studies were at high risk of bias. Participants and personnel could not be blinded to the use of lollipops in [Harrison 2014b](#), and for [Harrison 2014c](#), the young children able to verbalise may have made it evident to personnel that they had been given water or a sweet solution. However for the younger non-verbal children, the risk of bias was low. Masking of the interventions (sucrose, topical anaesthetic cream, or no treatment) were not possible in the [Dilli 2009](#) study. For the two studies involving school-aged children ([Lewkowski 2003a](#); [Lewkowski 2003b](#)), the experimenter and the technician were both blinded to the sweetness condition of the chewing gum, but not to whether or not the children continued to chew during the procedure.

Blinding of outcome assessment (detection bias)

Four studies scored low risk of bias for blinding of outcome assessment ([Allen 1996](#); [Dilli 2009](#); [Harrison 2014a](#); [Harrison 2014c](#)), unclear risk of bias was scored for [Yilmaz 2014](#) and outcome assessments were not able to be blinded for the studies by [Harrison 2014b](#); [Lewkowski 2003a](#); and [Lewkowski 2003b](#).

Incomplete outcome data (attrition bias)

Five of the eight studies were deemed to be at low risk of bias and three at unclear risk of bias due to incomplete outcome data. In the study by [Allen 1996](#), it was unclear whether there were incomplete outcome data reported. Data were provided by the study authors, which included data for 59 infants aged 15 and 18 months, although the published report included 67 infants at 15 and 18 months. The unpublished study by [Harrison 2014c](#) did not include a proposed

sample size in the trial registration, and for [Yilmaz 2014](#), numbers of participants were not included in the results tables.

Selective outcome reporting (reporting bias)

Protocols of five studies ([Allen 1996](#); [Dilli 2009](#); [Lewkowski 2003a](#); [Lewkowski 2003b](#); [Yilmaz 2014](#)) could not be found on registers of RCTs, and although the trial protocol for the pilot RCT by [Harrison 2014c](#) was registered, the proposed sample size was not stated. Therefore, the risk of bias for these six studies was unclear. The pilot RCTs by [Harrison 2014a](#) and [Harrison 2014b](#) scored low for risk of attrition bias, as the registered trial protocol's specified proposed sample size matched the number of randomised and studied children.

Other potential sources of bias

All eight studies scored a low risk of bias in this category due to there being no other unaccounted sources of bias identified.

Size

Seven of the eight included studies scored a high risk of bias in this category, according to the PaPaS guidance on sample size based on number of participants included in each study arm.

With the exception of [Yilmaz 2014](#), all studies were limited by small sample sizes. The studies by [Allen 1996](#) and [Dilli 2009](#) comprised subgroups of eligible children included in this systematic review; Harrison's three pilot RCTs ([Harrison 2014a](#); [Harrison 2014b](#); [Harrison 2014c](#)) included 30 participants or less in total and the two studies by [Lewkowski 2003a](#); [Lewkowski 2003b](#)) included <50 children in each study group.

Effects of interventions

See: [Summary of findings for the main comparison](#)

Effectiveness of sucrose for toddlers/young children

SUCROSE VERSUS CONTROL IN YOUNG CHILDREN AGED ONE TO FOUR YEARS (Comparison 1)

Cry duration (seconds) (Outcome 1.1) Analysis 1.1 Figure 4

Figure 4. Sucrose or sweet taste (lollipop) compared to control in pre-school children (cry duration - seconds).

Six studies enrolling 520 children reported on cry duration (seconds). To ensure the interventions were as similar as possible across the studies, data used from [Yilmaz 2014](#) included only the 25% sucrose group compared to water, and for [Dilli 2009](#), 12% sucrose compared to no treatment. Using a random-effects model, there was no significant difference between the sucrose

and the control groups in cry duration (WMD -15 seconds, 95% CI -54 to 24 seconds, $P = 0.45$); there was very high between-study heterogeneity ($I^2 = 94\%$).

Composite pain scores (Outcome 1.2). Analysis 1.2 Figure 5

Figure 5. Sucrose compared to control in pre-school children (composite pain score at time of first needle).

FLACC data were pooled from three pilot RCTs enrolling 80 children (Harrison 2014a; Harrison 2014b; Harrison 2014c) with CHEOPS data (Dilli 2009) (using data provided by the authors for 41 enrolled children). These data were included in a meta-analysis using standardized mean differences (SMD) and a random-effects model. There was no significant difference between the sucrose and the

control groups in composite pain score at time of first needle (SMD -0.26, 95% CI -1.27 to 0.75, $P = 0.61$). There was very high between-study heterogeneity ($I^2 = 86\%$).

Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) > 4 (Outcome 1.3) Analysis 1.3 Figure 6

Figure 6. Sucrose compared to control in pre-school children (CHEOPS scores > 4).

One study enrolling 472 children (Yilmaz 2014) reported CHEOPS data during immunisation for the three randomised groups (water, 25% sucrose, and 75% sucrose) as dichotomous aggregated data, thus precluding their use in this meta-analysis. Data for the control (water) and 25% sucrose groups were therefore included in an individual meta-analysis, using the CHEOPS cut-off score of > 4 (indicating high pain level). As seen in Analysis 1.3, Figure 6, the relative risk (RR) for having high pain scores was 0.55 (95% CI 0.45 to 0.67, $P < 0.00$; RD -0.29, 95% CI -0.37 to -0.20; NNTB 3, 95% CI 3 to 5) favouring the 25% sucrose group. Tests for heterogeneity were not applicable.

Effectiveness of sucrose for school-aged children

SWEET GUM VERSUS UNSWEETENED GUM BEFORE PROCEDURE IN SCHOOL-AGED CHILDREN (Comparison 2)

Faces Pain Scale (Outcome 2.1) Analysis 2.1.

Two studies enrolling 111 school-aged children (Lewkowski 2003a; Lewkowski 2003b) reported on the FPS. These data were pooled for inclusion in meta-analysis. There was no significant difference in children's self report of pain using the FPS between those who chewed sweet gum versus unsweetened gum before the procedure (WMD -0.15, 95% CI -0.61 to 0.30, $P = 0.51$). There was no heterogeneity between the two studies ($I^2 = 0\%$).

Colored Analogue Scale (Outcome 2.2) Analysis 2.2.

The same two studies enrolling 111 children (Lewkowski 2003a; Lewkowski 2003b) reported on the CAS. There was no significant difference in the children's self report of pain between those who

chewed sweet gum compared to unsweetened gum before the needle procedures (WMD 0.24, 95% CI -0.69 to 1.18, $P = 0.83$). There was no heterogeneity between the two studies ($I^2 = 0\%$).

SWEET GUM VERSUS UNSWEETENED GUM DURING PROCEDURE IN SCHOOL-AGED CHILDREN (Comparison 3)

Faces Pain Scale (Outcome 3.2) Analysis 3.1.

Two studies enrolling 103 participants reported on the FPS during the procedure. Pooled data revealed no significant difference between those who chewed sweet gum compared to unsweetened gum (WMD 0.23, 95% CI -0.28 to 0.74, $P = 0.38$). There was no heterogeneity between the two studies ($I^2 = 0\%$).

Colored Analogue Scale (Outcome 3.1) Analysis 3.2.

The same two studies enrolling 103 participants reported on the CAS during the procedure. Pooled data revealed no significant difference between those who chewed sweet gum compared to unsweetened gum (WMD 0.86, 95% CI -0.12 to 1.83, $P = 0.09$). There was no heterogeneity between the two studies ($I^2 = 0\%$).

DISCUSSION

Eight studies were eligible to be included in this systematic review of sweet tasting solutions for needle-related pain in children. Two studies included sub-groups of children and three were pilot RCTs with small numbers of participants. The efficacy of sweet taste was assessed in children from 12 months to 16 years of age during IM or SC injection, venipuncture, or finger lance. All studies were

prospective blinded RCTs with a control group and one or more treatment intervention(s).

Summary of main results

This updated review continues to illustrate the paucity of studies examining analgesic effects of sweet solutions or foods for procedural pain in children beyond one year of age.

For young children aged one to four years, results were conflicting. Sucrose significantly reduced crying time and/or pain scores compared with placebo or no treatment in two studies (Dilli 2009; Yilmaz 2014). Dilli 2009 reported that children randomised to the 12% sucrose and topical anaesthetic groups had significantly shorter cry durations and lower pain scores compared to no treatment, but no differences were found between the two intervention groups. Yilmaz 2014 - the only full-scale RCT with > 50 participants in each study group included in this review - reported that 75% sucrose was significantly more effective in reducing crying duration and CHEOPS scores compared to 25% sucrose, however 25% sucrose was significantly more effective compared to water. Data for crying duration in seconds was pooled from the six studies for meta-analysis (Figure 4). To ensure the interventions were as similar as possible across the studies, data used from Yilmaz 2014 included only the 25% sucrose group compared to water; from Dilli 2009, only data comparing 12% sucrose to no treatment were used. Despite these attempts, heterogeneity between the studies was very high, with no significant effect of sweet tasting solutions for reducing crying time. In our original review, in an attempt to reduce heterogeneity, and as Dilli 2009 included children up to 48 months of age, compared with an upper age limit of 18 months by Allen 1996, we repeated the meta-analysis after removing data for seven children aged 19 months of age and older from Dilli 2009. Results at that time, however, remained similar, with no significant differences in crying time for children who received sucrose compared with control; there remained significant heterogeneity between the studies ($I^2 = 90\%$) (Harrison 2011). We did not, therefore, repeat this sensitivity analysis in this updated review.

Only two studies examining analgesic effects of sweet taste for needle-related procedural pain in older children were identified (Lewkowski 2003a; Lewkowski 2003b). Sweet taste delivered in the form of sweetened chewing gum, compared to the control condition, delivered in the form of unsweetened gum, had no effect on self-report ratings of pain, as per the FPS, or unpleasantness, as per the CAS, during IM injections and blood collection (venipuncture or finger lance) in school-aged children. This lack of effect was evident when sweet gum chewing ceased prior to commencement of the procedures, as well as when chewing was continued throughout the procedure.

Overall completeness and applicability of evidence

Available evidence is generally applicable, but limited in numbers. It should be noted that the solution used in the two published studies included in our original review (Allen 1996; Dilli 2009) was a weak 12% sucrose solution, which is less concentrated, and therefore less sweet, than the solutions used in the majority of studies of analgesic effects of sucrose in newborn and young infants (Harrison 2010a; Harrison 2010c; Stevens 2013). Only one study (Yilmaz 2014) was a sufficiently powered full-scale RCT, therefore results must be treated with caution.

Quality of the evidence

Based on the published findings, no study in this review was rated as having a low risk of bias for all seven categories. All studies with the exception of Yilmaz 2014, were assessed as high risk in the added category of 'size' (number of participants).

Potential biases in the review process

The first author (DH) is an author of three studies included in this systematic review. All data extraction and 'Risk of bias' ratings were completed by co-authors (JY, AO) or research personnel (JR, CL) not affiliated with the studies by Harrison, or any other studies included in this review.

Agreements and disagreements with other studies or reviews

The conflicting findings of analgesic effects of sucrose in young children, and the evidence of no effect of sweet taste in school-aged children, are inconsistent with the results of other published systematic reviews of sucrose and glucose for procedural pain reduction in newborn infants and infants beyond the newborn period, up to 12 months of age (Bueno 2013; Harrison 2010a; Harrison 2010c; Kassab 2012; Stevens 2013). However, the small number of eligible studies included in this systematic review and the small numbers of participants in all except one study (Yilmaz 2014) preclude firm conclusions. In contrast, large numbers of RCTs were included in a Cochrane systematic review of oral sucrose in newborn infants (Stevens 2013) and a systematic review of non-sucrose sweet solutions for procedural pain reduction in newborn infants (Bueno 2013). Stevens 2013 most recent Cochrane systematic review update of sucrose for pain management included 57 studies and 4730 infants, and Bueno 2013 included 38 studies and 3785 infants. Both of these large systematic reviews showed that sweet solutions compared with placebo, non-nutritive sucking, no intervention, wrapping (swaddling), positioning, or breast milk or formula, reduced behavioral pain responses (facial expressions, crying time, pain scores) during heel lance, venipuncture, and injections. In addition, the systematic review of 14 RCTs (1674 injections for 1618 infants) of sucrose or glucose during immunisation in infants between one and 12 months (Harrison 2010a) and the Cochrane systematic review of 14 RCTs (1551 infants) of sweet solutions for needle-related procedural pain in infants between one and 12 months (Kassab 2012), both showed that sweet solutions reduced crying and other behavioral responses of pain in most of the studies.

The 3-armed RCT by Yilmaz et al (Yilmaz 2014) was by far the largest study included in this review (537 participants) and the only full-scale RCT including only young children beyond 12 months of age. Results clearly showed analgesic effects of both 25% and 75% sucrose concentrations, with 75% sucrose demonstrated to be more effective in reducing pain than 25% sucrose. This result agrees with results of studies including neonates and young infants, comparing different concentrations of sweet solutions (Harrison 2010c). Of the remaining five studies in this review which included young children, all three studies by Harrison and co-authors were pilot RCTs with less than 30 participants each, and only small numbers of sub-groups of children from Allen 1996 and Dilli 2009 were included. These five studies are therefore most likely underpowered to detect any differences. Yet, despite the small numbers of participants, the large treatment effect of

two mL 12% sucrose reported by [Dilli 2009](#), and the opposing results reported by [Allen 1996](#), using the same sucrose delivery technique and timing, precludes explanation. [Allen 1996](#) concluded that a low concentration 12% sucrose solutions was insufficiently sweet to exert demonstrable analgesic effects even in newborn infants. Differences in results may be attributed to the different techniques used to hold the children. Standard of care for the control group and the sucrose group in the [Dilli 2009](#) study was to be securely held in the mother's arms, whilst in the [Allen 1996](#) study, infants were placed on an examination table for the injections. The role of parents during the painful procedure, holding the infants securely, may therefore have resulted in a synergistic effect of sucrose in [Dilli 2009](#), contributing to the significant reduction in crying and pain scores compared with those infants in the control group. Alternatively, as these two studies were conducted 15 years apart, and in different countries (USA and Turkey), there may be unexplained cultural differences in the children's response to sweet taste. However another study of pain responses during immunisation in infants aged three to nine months of age used 12% sucrose as the study solution ([Poulsen 2009](#)) and reported no differences in pain responses between infants receiving 12% sucrose compared with water. Based on the large majority of studies including newborn infants and infants up to 12 months of age ([Bueno 2013](#); [Harrison 2010a](#); [Harrison 2010c](#); [Stevens 2013](#)), sufficiently sweet sucrose concentrations of at least 20% and glucose concentrations of at least 24% are required for analgesic effects. The same recommendations need to apply to further research in young children.

The use of sweet taste for analgesia in school-aged children was not shown to be effective during the needle-related procedures of IM injection or blood collection by venipuncture or finger lance. Three other studies examining analgesic effects of sweet taste in school-aged children have used cold pressor testing (CPT) as the model of pain ([Mennella 2010](#); [Miller 1994](#); [Pepino 2005](#)). [Miller 1994](#) studied 42 healthy children, aged eight to 12 years of age, over two successive days, who held either 20 mL of a 24% sucrose solution or water in their mouths for 30 seconds prior to cold water immersion, and for the duration of the CPT. Sucrose significantly increased the length of time that children were able to hold their arms in the cold water before they felt pain (threshold) by 35%, but sucrose had no effect on tolerance (removal of arm from the water), or self-report of pain. However, tolerance data were not available for over half the children, and self-reports of pain intensity using a VAS were not available for 10 of the 42 children enrolled. [Pepino 2005](#) and [Mennella 2010](#) not only examined analgesic effects of sucrose during CPT, but also whether children's preference for sweet taste was a factor in whether sucrose exerted analgesic effects. Both studies included children aged five to ten years of age; [Pepino](#) included 242 children and [Mennella](#) included 250 children. Both studies used pain tolerance and pain threshold as outcomes, and both used 15 mL to 20 mL of 24% sucrose or water as the study solutions, which were held in the mouth for the duration of the CPT. Analgesic effects of sucrose, based on cold tolerance and cold threshold were demonstrated, but only in those children with a preference for sweet taste. Furthermore, [Mennella 2010](#) reported that sucrose exerted no analgesic effects in children who were depressed, based on self-report using the Pictorial Depression Scale ([O'Connor 2006](#)). All three studies of sucrose analgesia during CPT were limited by incomplete data, as significant numbers of children failed to report cold threshold, or kept their arms in the water for the entire four-minute observation

period, therefore precluding the use of cold tolerance data. In summary, oral sucrose had some analgesic effects during CPT, but the effects were moderate, dependent upon preference for sweet taste, and - based on one study - influenced by self-report of depression ([Mennella 2010](#)).

AUTHORS' CONCLUSIONS

Implications for practice

For toddlers and pre-school children: The conflicting evidence from only six studies which included young children, two of which were small sub-groups of children, and three of which were small pilot RCTs, is currently insufficient to recommend sucrose as a pain-management strategy in young children beyond 12 months of age. Further evidence, including effectiveness of dosing in aliquots prior to and during the procedure and comparisons of different concentrations of sweet solutions is required before evidence-based recommendations for practice can be made.

For school-aged children: Based on a lack of difference in self-reported pain scores between children randomised to sweet taste condition and unsweetened taste condition during needle-related procedures, there is no evidence to support analgesic efficacy of sweet taste during needle-related procedures. This strategy should not, therefore, be considered in this population.

Implications for research

General: There is sufficient evidence from large numbers of RCTs of the analgesic effects of sucrose or glucose for newborn infants, and infants up to one year of age. However, there remains a state of equipoise relating to analgesic effects of sweet taste during needle-related and other procedures in young children.

For young children: Further RCTs in this population are warranted. When planning further studies, particular attention should be paid relating to the following points:

Design:

- Conduct *a priori* power calculations to ensure RCTs are adequately powered.
- Ensure concealment of allocation and blinding of outcome assessors to interventions.
- Implement current evidence-based distraction techniques ([Chambers 2009](#)) as well as parental upright holding if possible, and comforting, as standard of care.
- Particularly for venipuncture studies, topical anaesthetics should be considered as standard of care.
- Standardize control interventions; e.g. upright parental holding, distraction techniques used.
- Use sufficient concentration and dose of sweet solution; i.e. $\geq 20\%$ glucose or sucrose, administered one minute before procedures in this age group, and repeated throughout the duration of procedures.

Measurement:

- Use recommended, comparable, reliable, and valid pain outcome measures.

For school-aged children: Despite the small number of studies examining analgesic efficacy of sweet taste in school-aged children,

the available evidence from the two studies included in this review, as well as three studies of sweet taste during CPT ([Mennella 2010](#); [Miller 1994](#); [Pepino 2005](#)), suggest that this intervention is not of sufficient benefit to recommend at this time. Further studies of sweet tasting solutions, substances, or foods to reduce procedural pain cannot be recommended as a research priority in this population.

For funders: Further funding for well conducted sufficiently powered trials of sweet solutions for procedural pain management are warranted in young children from one to three years of age. As there is no uncertainty as to the calming effects of sweet solutions compared to placebo or no treatment in infants during single episodes of painful procedures ([Bueno 2013](#); [Stevens 2013](#); [Harrison 2010c](#)), further placebo controlled trials of sweet solutions should not be funded unless they meet existing knowledge gaps. Such existing gaps include minimal effective dose of sweet solutions, effect of repeated doses of solutions over weeks to months in preterm and/or sick hospitalised infants, and effects of concomitant treatments such as opioid analgesics. As there are alternative effective pain management strategies for school-aged children, and sweet solutions seem to have no analgesic effects,

funding for studies of analgesic effects of sweet solutions are not warranted in this population.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Allen 1996

Methods	Blinded randomised controlled trial
Participants	285 infants between 2 weeks and 18 months old; 59 included in this review (children 15 and 18 months of age)
Interventions	2 mL of 12% sucrose (n = 24) 2 mL of sterile water (n = 20) No treatment (n = 15)
Outcomes	Cry duration (seconds) and percentage crying time during and 3 minutes after subcutaneous injection for immunisation.
Notes	Data for percentage crying time were presented in graphical form only. Data were requested and obtained directly from the author for this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Low risk	Water and sucrose-coded oral syringes prepared by the pharmacist to ensure that parents, nurses, and investigators were blind to group assignments. However for the no-intervention group the risk of bias was high.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Parents, nurses, and investigators were blind to group assignments for the water and sucrose groups but not for the no-intervention group.
Blinding of outcome assessment (detection bias)	Low risk	Parents, nurses, and investigators were blind to group assignments for the water and sucrose groups but not for the no-intervention group. Infants were

Sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years (Review)

Allen 1996 (Continued)

All outcomes		videotaped during immunisation for later interval recording of pain induced vocalisations. The proportion of crying per 15 second interval was recorded by a trained primary observer.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data provided from the authors contained data for 59 infants 15 and 18 months only; publication stated 67 infants at 15 and 18 months included.
Selective reporting (reporting bias)	Unclear risk	Protocol not available to us, nor published in trials register, therefore we were unable to judge if there was selective outcome reporting or not.
Other bias	Low risk	No other sources of bias identified.
Size	High risk	Limitation - small sample size in subgroup of infants (< 50 children/group) included in this review.

Dilli 2009

Methods	Blinded randomised controlled trial
Participants	118 infants aged 6 to 48 months. 57 included in this review (children 13 to 48 months of age).
Interventions	2 mL of 12% sucrose (n = 19) Control (n = 23) Topical anaesthetic (n = 16)
Outcomes	Cry duration (seconds), recorded from insertion of needle until all crying activity ceased. CHEOPS (McGrath 1985).
Notes	Data were requested and obtained directly from the author for this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Low risk	Sealed envelopes stratified by age.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Masking of assignment to 12% sucrose solution, lidocaine-prilocaine cream, or no intervention was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The paediatrician responsible for recording crying time and pain score was not present during the interventions and was blinded to each subject's allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	According to publication, there were 58 children aged 13 to 48 months. Provided raw data included 57 children (22 instead of 23 controls).

Dilli 2009 (Continued)

Selective reporting (reporting bias)	Unclear risk	Protocol not available to us, nor published in trials register, therefore we are unable to judge if there was selective outcome reporting or not.
Other bias	Low risk	No other sources of bias identified.
Size	High risk	Limitation - small sample size in subgroup of infants included in this review (< 50 children/group).

Harrison 2014a

Methods	Blinded randomised controlled trial (pilot)
Participants	Children receiving 12 month (n = 14) or 18 month (n = 15) immunisations at drop in immunisation centre
Interventions	2 mL (maximum) 33% sucrose (n = 15) 2 mL (maximum) water (n = 14)
Outcomes	<ul style="list-style-type: none"> - Crying duration (seconds) from two minutes prior to injection to 30 seconds following completion of procedure - FLACC (Merkel 1997) at four time points: <ul style="list-style-type: none"> • Baseline (15 seconds before the 1st injection) • Upon first injection • 15 seconds after final injection • 30 seconds after final injection - Parental VAS score on a 10 cm scale - Nurses' score of compliance with study solutions (3-point scale): <ul style="list-style-type: none"> • Fully compliant • Somewhat compliant • Not compliant - Parental perception of effectiveness of treatment and Parental preference for future pain management: <ul style="list-style-type: none"> • Yes • No • Uncertain
Notes	<p>DECLARATION</p> <p>Study conducted by 1st author (Harrison)</p> <p>Additional data provided. Data extraction completed by author AO and research personnel external to this study.</p> <p>Risk of bias assessment by authors JY and AO.</p> <p>Trial registered: ACTRN12610000355077</p> <p>Funding: Victorian Nurses Board Legacy Limited</p>

Risk of bias

Harrison 2014a (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Concealed, computer generated random-number sequence in blocks of two and four were generated with Stata 11 by the hospital's clinical epidemiology and biostatistics unit and codes were held at the hospital's pharmacy department.
Allocation concealment (selection bias)	Low risk	Study solutions for toddlers were prepared by the hospital's pharmacy department on a monthly basis in identical three mL syringes, as per the randomisation code, and numbered sequentially. A label obscured the syringe contents. Codes were placed in opaque, sealed envelopes and opened sequentially for each participating child. Randomisation codes were not released to the investigators until completion of the trial and completion of summary statistics.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Toddlers were randomised to receive 33% sucrose weight/volume as per the hospital's sucrose guidelines, or water, in addition to standard care (upright parental holding, comforting, and age-appropriate distraction supported by the immunisation nurse). The nurse administered the study solution orally via a syringe onto the toddler's tongue in 0.5 mL aliquots, commencing two minutes prior to the first injection and repeating 0.5 mL aliquots immediately prior to each injection. The nurse and parents were instructed not to comment about the toddler's response to the solution to assist the coders in remaining blinded to the study solution.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See blinding of participants and personnel above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data presented for 29 of 30 randomised infants (one video recording failed).
Selective reporting (reporting bias)	Low risk	The protocol for the study was available - there does not seem to be selective outcome reporting. However, planned sample size was not stated in the protocol.
Other bias	Low risk	No other sources of bias identified.
Size	High risk	Limitation - pilot study, therefore small sample size with < 50 children/group.

Harrison 2014b

Methods	Non-blinded randomised controlled trial (pilot)
Participants	Children aged 4 years undergoing immunisation
Interventions	Glucose lollipop to suck on prior to and during immunisations (n = 14) Usual care (distraction) and lollipop following immunisations (n = 17)
Outcomes	As per Harrison 2014a with addition of children's self report using Wong-Baker Faces Scale®.
Notes	DECLARATION Study conducted by 1st author (Harrison)

Harrison 2014b (Continued)

Additional data provided. Data extraction completed by author AO and research personnel external to this study.

Risk of bias assessment by authors JY and AO.

Trial registered: ACTRN12610000355077

Funding: Victorian Nurses Board Legacy Limited.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Concealed, computer generated random-number sequence.
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes opened sequentially.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind lollypops during immunisation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors scoring off videos - not possible to blind lollypops during immunisation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for 30 of 31 randomised children (one refused to suck lollypop).
Selective reporting (reporting bias)	Low risk	The protocol for the study was available - there does not seem to be selective outcome reporting. However, planned sample size was not stated in the protocol.
Other bias	Low risk	No other sources of bias identified.
Size	High risk	Limitation - pilot study, therefore small sample size with < 50 children/group.

Harrison 2014c

Methods	Blinded randomised controlled trial (pilot)
Participants	Hospitalised children aged 12-36 months undergoing venipuncture
Interventions	2 mL (maximum) of 25% sucrose (n = 11) 2 mL (maximum) sterile water (n = 10) Standard of care - topical anaesthetic (Ametop)
Outcomes	Crying duration (seconds) - From administration of study solution to 30 seconds following completion of procedure FLACC (Merkel 1997) at seven time points: <ul style="list-style-type: none"> Baseline prior to administration of study solution Immediately following first dose of study solution

Sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years (Review)

Harrison 2014c (Continued)

- Upon placement of tourniquet
 - Upon first needle insertion (Used in data extraction for meta-analysis)
 - At time of last needle insertion (if > 1 attempt)
 - At time of last needle removal
 - 60 seconds following completion of procedure
- Parental VAS score on a 10 cm scale
- Nurses' score of compliance with study solutions (3-point scale):
- Fully compliant
 - Somewhat compliant
 - Not compliant
- Parental perception of effectiveness of treatment and parental preference for future pain management:
- Yes
 - No
 - Uncertain

Notes	<p>DECLARATION</p> <p>Unpublished pilot study conducted by 1st author (Harrison)</p> <p>All data provided. Data extraction completed by author AO and research personnel external to this study.</p> <p>Risk of bias assessment by authors JY and AO.</p> <p>Funding: Children's Hospital of Eastern Ontario Research Institute.</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	Closed envelopes (does not say opaque, sealed, and sequentially numbered).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Water and sucrose solutions were prepared in advance by a pharmacist. Solutions were drawn from coded bottles and were administered using a syringe. The nurse and parents were blinded to the nature of the solutions used throughout the study. The solutions were placed in coded oral syringes by the pharmacist to ensure that parents, nurses, and investigators were blind to group assignments. Two minutes prior to the injection, the control and experimental groups received orally 2 mL of either the sterile water or the 25% or 75% sucrose solution.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described on page 1528 - The primary study outcome, crying time, defined as crying from the moment of needle insertion until all crying activity had ceased was recorded by the paediatrician. Pain was assessed by the CHEOPS. The CHEOPS forms were completed by the same paediatrician. But also states "The principal investigator responsible for recording the crying time and pain score was not present during the interventions and was blinded to each subject's treatment." Therefore it is unclear who the rater is.

Harrison 2014c (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The text under results says “one hundred fifty-seven infants were withdrawn after randomisation”. Fig.1. says that 157 infants were excluded before randomisation. 537 infants were randomised and there were 179 infants in each group (3 groups).
Selective reporting (reporting bias)	Unclear risk	Protocol not available to us, nor published in trials register, therefore we were unable to judge if there was selective outcome reporting or not.
Other bias	Low risk	No other sources of bias identified.
Size	High risk	Limitation - pilot study, therefore small sample size with < 50 children/group.

Lewkowski 2003a

Methods	Randomised controlled trial
Participants	99 Children aged 7 to 12 years during blood collection
Interventions	Sweet taste alone (n = 25) Sweet taste and rhythmic oral movements (sweetened chewing gum; n = 23) Control (n = 28) Rhythmic oral movements (unsweetened chewing gum; n=23)
Outcomes	CAS (Price 1992). FPS (Bieri 1990).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Staff blinded to whether the chewing gum was sweet or not sweet but not blinded to chewing or not during the procedure. Children were not blinded to whether the chewing gum was sweet or not.
Blinding of outcome assessment (detection bias) All outcomes	High risk	As above. Children themselves assessed their pain - they were not blinded to sweetness and chewing.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data accounted for and all outcome data included.

Lewkowski 2003a (Continued)

Selective reporting (reporting bias)	Unclear risk	Protocol not available to us, nor published in trials register, therefore we were unable to judge if there was selective outcome reporting or not.
Other bias	Low risk	No other sources of bias identified.
Size	High risk	Limitation - < 50 children in each group.

Lewkowski 2003b

Methods	Randomised controlled trial
Participants	115 Children aged 9 to 11 years during immunisation.
Interventions	Sweet taste alone (n = 28) Sweet taste and rhythmic oral movements (sweetened chewing gum; n = 27) Control (n = 30) Rhythmic oral movements (unsweetened chewing gum; n = 30)
Outcomes	CAS (Price 1992) FPS (Bieri 1990)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Staff blinded to whether the chewing gum was sweet or not sweet but not blinded to chewing or not during the procedure. Children were not blinded to whether the chewing gum was sweet or not.
Blinding of outcome assessment (detection bias) All outcomes	High risk	As above. Children themselves assessed their pain - they were not blinded to sweetness and chewing.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data accounted for and all outcome data included.
Selective reporting (reporting bias)	Unclear risk	Protocol not available to us, nor published in trials register, therefore we were unable to judge if there was selective outcome reporting or not.
Other bias	Low risk	No other sources of bias identified.
Size	High risk	Limitation - < 50 children in each group.

Yilmaz 2014

Methods	Blinded randomised controlled trial
Participants	537 children aged 16-19 months during immunisation
Interventions	2 mL 75% sucrose (n = 179) 2 mL 25% sucrose (n = 179) Control (water) (n = 179)
Outcomes	Cry duration CHEOPS (McGrath 1985)
Notes	CHEOPS data and clarification of methods requested from author. Data and information were not received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Stated that closed envelope technique was used, but does not state opaque, sealed, and sequentially numbered.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Although allocated low risk, it is unclear which method was used to blind personnel. Two descriptions within the same paragraph are given (page 1528). Described that water and sucrose solutions were prepared in advance by a pharmacist and solutions were drawn from coded bottles and were administered using a syringe. Also described that the solutions were placed in coded oral syringes by the pharmacist to ensure that parents, nurses, and investigators were blind to the group assignments. Although the second description is more fail-safe to ensure blinding, the first description is also indicative of low risk.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Description does not allow a judgement to be made. Although the "entire procedure was video-taped", no explanation given as to when the scoring was carried out. Description that the paediatrician completed crying duration and CHEOPS scores, however it is also described that the PI was responsible for recording the crying time and pain score. Unclear if the paediatrician and PI are the same individual.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Table 2 does not state the number of infants therefore it is unclear if there was attrition bias.
Selective reporting (reporting bias)	Unclear risk	No details of publication of original protocol in trials registry.
Other bias	Low risk	No other sources of bias identified.
Size	Unclear risk	179 children in each group.

CHEOPS: Children's Hospital of Eastern Ontario Pain Scale
FLACC: Face, Legs, Activity, Consolability, Crying

VAS: visual analogue scale
CAS: Coloured Analogue Scale
FPS: Faces Pain Scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brovedani 2007	Children younger than inclusion criterion
Miller 1994	Procedure not needle-related
Mowery 2007	Children younger than inclusion criterion
Pepino 2005	Procedure not needle-related
Poulsen 2009	Children younger than inclusion criterion
Ramenghi 2001	Children younger than inclusion criterion
Ramenghi 2002	Children younger than inclusion criterion

DATA AND ANALYSES

Comparison 1. Sucrose versus control in toddlers/pre-school children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cry Duration (seconds)	6	520	Mean Difference (IV, Random, 95% CI)	-14.99 [-53.89, 23.90]
2 Composite Pain Score at time of first needle	4	121	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-1.27, 0.75]
3 CHEOPS Scores > 4	1	472	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.45, 0.67]

Analysis 1.1. Comparison 1 Sucrose versus control in toddlers/pre-school children, Outcome 1 Cry Duration (seconds).

Analysis 1.2. Comparison 1 Sucrose versus control in toddlers/pre-school children, Outcome 2 Composite Pain Score at time of first needle.

Analysis 1.3. Comparison 1 Sucrose versus control in toddlers/pre-school children, Outcome 3 CHEOPS Scores > 4.

Comparison 2. Sweet gum versus unsweetened gum before procedure in school-aged children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Faces Pain Scale	2	111	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.61, 0.30]
2 Colored Analogue Scale	2	111	Mean Difference (IV, Random, 95% CI)	0.24 [-0.69, 1.18]

Analysis 2.1. Comparison 2 Sweet gum versus unsweetened gum before procedure in school-aged children, Outcome 1 Faces Pain Scale. **Analysis 2.2. Comparison 2 Sweet gum versus unsweetened gum before procedure in school-aged children, Outcome 2 Colored Analogue Scale.** **Comparison 3. Sweet gum versus unsweetened gum during procedure in school-aged children**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Faces Pain Scale	2	103	Mean Difference (IV, Random, 95% CI)	0.23 [-0.28, 0.74]
2 Colored Analogue Scale	2	103	Mean Difference (IV, Random, 95% CI)	0.86 [-0.12, 1.83]

Analysis 3.1. Comparison 3 Sweet gum versus unsweetened gum during procedure in school-aged children, Outcome 1 Faces Pain Scale.

Analysis 3.2. Comparison 3 Sweet gum versus unsweetened gum during procedure in school-aged children, Outcome 2 Colored Analogue Scale.

ADDITIONAL TABLES

Table 1. Summary of included studies

Study	Participants	Procedures	Intervention	Outcomes	Metrics	Results
Allen 1996	59 children aged 15 months (n = 24) and 18 months (n = 35)	SC injections: single episodes of SC injection (18 month old children) or two injections (15 month old children)	Sucrose (S) 2 mL 12% via syringe n = 24 Control - Water (W) 2 mL via syringe n = 20 No Intervention (NI) n = 15	Cry duration (%) in 3 minutes after injection	Proportion crying time Raw data obtained from author for calculation of mean and SD crying times	No differences between groups Mean proportion crying time % (SD): S: 50.6 (27) W: 48.7 (30.7) NI: 43.1 (28.4) MD between S & W (95% CI): 1.90 (-15.38 to 19.18) Mean difference between S & NI (95% CI): 14.50 (-3.50 to 32.50)
Dilli 2009	Raw data for 57 children aged 13 to 48 months (publication states 58 children) obtained	IM or SC injections: single or two injections	Sucrose (S) 2 mL 12% via syringe n = 19 No Intervention (NI) n = 23 Topical anaesthetic (T)	CHEOPS and crying time	Mean, SD Raw data obtained from author for calculation of mean and SD crying times	S more effective than NI No differences between S & T Mean cry duration in seconds (SD) S: 31.9 (17.01) NI: 110.8 (67.6)

Table 1. Summary of included studies (Continued)

	from au- thor		n = 16				T: 45.6 (48.8) MD between S & NI (95% CI): -78.90 (-112.89 to -44.91) MD between S & T (95% CI): -13.70 (-38.80 to 11.40) Mean CHEOPS (SD) S: 4.1 (0.9) NI: 8.7 (3.4) T: 5.4 (4.5) MD between S & NI (95% CI): -4.60 (-6.08 to -3.12) MD between S & T (95% CI): -1.30 (-3.23 to 0.63)
Yilmaz 2014	537 chil- dren aged 16 to 19 months	IM injec- tions: two or three given si- multane- ously	Sucrose (S1) 2 mL 25% via syringe n = 179 Sucrose (S2) 2 mL 75% via syringe n = 179 Control - Water (W) 2 mL via syringe n = 179	CHEOPS and crying time	Cry duration re- ported in Mean, SD. CHEOPS report- ed as n > 4 and n > 4. Raw or mean, SD data requested but not obtained from author.	Effectiveness of S2 > S1 > W. Mean cry duration in sec- onds (SD): S2: 43.4 (17.2) S1: 62.2 (26) W: 120 (34.4) Number with CHEOPS >4: S2 = 39 S1 = 84 W = 152	
Harrison 2014a	29 chil- dren aged 12-18 months	IM injec- tions: 2 or 3 given consecu- tively	Sucrose (S) 2 mL 33% via syringe n = 15 Control - Water (W) 2 mL via syringe n = 14	Cry time, FLACC scores, par- ent VAS scores	Cry duration, VAS scores re- ported separate- ly for 12 month & 18 months. Raw data ob- tained from au- thor for calcu- lation of means and SDs.	No differences between groups	
Harrison 2014b	30 chil- dren aged 4 years	IM injec- tions: 1-2 given con- secutively	Lollypop during procedure n = 13 Lollypop following proce- dure n = 17	Cry time, FLACC scores, par- ent VAS scores, Child Wong-	Medians and IQR reported. Raw data ob- tained from au- thor for calcu- lation of means and SDs.	No differences between groups	

Table 1. Summary of included studies (Continued)

				Baker scores		
Harrison 2014c	21 hospitalised children aged 13-33 months	Venipuncture	Sucrose (S) 2 mL 25% via syringe n = 11 Control - Water (W) 2 mL via syringe n = 10	Cry time, FLACC scores, parent VAS scores	Unpublished data. Raw data obtained from author for calculation of means and SDs.	No differences between groups
Lewkows-ki 2003a	99 children, 7 to 12 years	Blood sampling (either venipuncture or finger prick: numbers not specified)	1. Unsweetened gum before procedure n = 28 2. Sweet gum before procedure n = 25 3. Unsweetened gum before and during procedure n = 23 4. Sweet gum before and during procedure n = 23	CAS FPS	Mean, SD	No differences between groups on either outcome: CAS: $F(1, 89) = 0.01$, $P = 0.94$ Mean CAS (SD): Condition 1: 3.6 (2.9) Condition 2: 3.9 (1.2) Condition 3: 3.5 (2.5) Condition 4: 3.9 (2.8) FPS: $F(1, 89) = 1.06$, $P = 0.31$ Mean FPS (SD): Condition 1: 2.2 (1.4) Condition 2: 2.2 (1.0) Condition 3: 2.3 (1.6) Condition 4: 2.9 (1.5)
Lewkows-ki 2003b	115 children, 9 to 11 years	IM injection	1. Unsweetened gum before procedure n = 30 2. Sweet gum before procedure n = 28 3. Unsweetened gum before and during procedure n = 30 4. Sweet gum before and during procedure n = 27	CAS FPS	Mean, SD	No differences between groups Mean CAS (SD): Condition 1: 3.5 (2.3) Condition 2: 3.6 (2.7) Condition 3: 2.7 (2.5) Condition 4: 3.8 (2.4) FPS: $F(1, 89) = 1.06$, $P = 0.31$ Mean FPS (SD): Condition 1: 2.2 (1.1) Condition 2: 2.0 (1.3) Condition 3: 2.2 (1.4)

Table 1. Summary of included studies (Continued)

Condition 4: 2.3 (0.98)

SC: subcutaneous
SD: standard deviation
MD: mean difference
CI: confidence interval
IM: intramuscular
CHEOPS: Children's Hospital of Eastern Ontario Pain Scale
IQR: interquartile range
CAS: Coloured Analogue Scale
FPS: Faces Pain Scale

APPENDICES

Appendix 1. MEDLINE & EMBASE search strategy

MEDLINE, EMBASE search strategy (via OvidSP)

1. needle*.mp.
2. (blood sampl* or immuni* or inoculat* or vaccin* or inject* or finger prick* or heel prick* or heel lanc* or heel punctur* or heel stick* or sutur* or (laceration* adj3 repair*)).mp.
3. (lumbar punctur* or spinal tap*).mp.
4. (bone marrow adj4 (aspiration* or biops*)).mp.
5. (intravenous or intra venous or venepuncture* or venipuncture* or venous cannulation* or (arterial blood gas* adj6 cannul*)).mp.
6. (catheter* or port-a-cath* or portacath*).mp.
7. (central line adj6 (insert* or remov*)).mp.
8. (central venous catheter* adj6 insert*).mp.
9. (local analges* or local anaesthe* or local anesthe*).mp.
10. (arterial punctur* or (artery adj6 punctur*)).mp.
11. arterial line*.mp.
12. (thoracocentesis or paracentesis).mp.
13. or/1-12
14. exp pain/
15. pain*.mp.
16. ((needle* adj6 distress*) or (needle* adj6 discomfort) or (needle* adj6 fear*) or (needle* adj6 fright*) or (needle* adj6 anxious) or (needle* adj6 anxiet*) or (intervention* adj6 distress*) or (procedur* adj6 distress*) or (procedur* adj6 discomfort*)).mp.
17. (cry or crying or cried or cries).mp.
18. 14 or 15 or 16 or 17
19. 13 and 18
20. exp sucrose/
21. (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.
22. 20 or 21
23. 19 and 22
24. (paediat* or pediat* or baby or babies or neonat* or newborn* or infant* or child* or toddler* or adolesc* or teen*).mp.
25. 23 and 24

Appendix 2. All EBM Reviews search strategy

All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED (via OvidSP)

1. needle*.mp.
2. (blood sampl* or immuni* or inoculat* or vaccin* or inject* or finger prick* or heel prick* or heel lanc* or heel punctur* or heel stick* or sutur* or (laceration* adj3 repair*)).mp.
3. (lumbar punctur* or spinal tap*).mp.
4. (bone marrow adj4 (aspiration* or biops*)).mp.
5. (intravenous or intra venous or venepuncture* or venipuncture* or venous cannulation* or (arterial blood gas* adj6 cannul*)).mp.
6. (catheter* or port-a-cath* or portacath*).mp.
7. (central line adj6 (insert* or remov*)).mp.
8. (central venous catheter* adj6 insert*).mp.
9. (local analges* or local anaesthe* or local anesthe*).mp.

10. (arterial punctur* or (artery adj6 punctur*)).mp.
11. arterial line*.mp.
12. (thoracocentesis or paracentesis).mp.
13. or/1-12
14. pain*.mp.
15. ((needle* adj6 distress*) or (needle* adj6 discomfort) or (needle* adj6 fear*) or (needle* adj6 fright*) or (needle* adj6 anxious) or (needle* adj6 anxiet*) or (intervention* adj6 distress*) or (procedur* adj6 distress*) or (procedur* adj6 discomfort*)).mp.
16. (cry or crying or cried or cries).mp.
17. 14 or 15 or 16
18. 13 and 17
19. (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.
20. 18 and 19
21. (paediat* or pediat* or baby or babies or neonate* or newborn or infant* or child* or toddler or adolesc* or teen*).mp.
22. 20 and 21

Appendix 3. PsycINFO search strategy

PsycINFO (via OvidSP)

1. needle*.mp.
2. (blood sampl* or immuni* or inoculat* or vaccin* or inject* or finger prick* or heel prick* or heel lanc* or heel punctur* or heel stick* or suture* or (laceration* adj3 repair*)).mp.
3. (lumbar punctur* or spinal tap*).mp.
4. (bone marrow adj4 (aspiration* or biops*)).mp.
5. (intravenous or intra venous or venepuncture* or venipuncture* or venous cannulation* or (arterial blood gas* adj6 cannul*)).mp.
6. (catheter* or port-a-cath* or portacath*).mp.
7. (central line adj6 (insert* or remov*)).mp.
8. (central venous catheter* adj6 insert*).mp.
9. (local analges* or local anaesthe* or local anesthe*).mp.
10. (arterial punctur* or (artery adj6 punctur*)).mp.
11. arterial line*.mp.
12. (thoracocentesis or paracentesis).mp.
13. or/1-12
14. exp pain/
15. pain*.mp.
16. ((needle* adj6 distress*) or (needle* adj6 discomfort) or (needle* adj6 fear*) or (needle* adj6 fright*) or (needle* adj6 anxious) or (needle* adj6 anxiet*) or (intervention* adj6 distress*) or (procedur* adj6 distress*) or (procedur* adj6 discomfort*)).mp.
17. (cry or crying or cried or cries).mp.
18. 14 or 15 or 16 or 17
19. 13 and 18
20. (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.
21. 19 and 20
22. (paediat* or pediat* or baby or babies or neonate* or newborn or infant* or child* or toddler or adolesc* or teen*).mp.
23. 21 and 22

Appendix 4. CINAHL search strategy

CINAHL (via EBSCOhost)

- S25 S23 and S24
- S24 TX (paediat*) or TX (pediat*) or TX (baby) or TX (babies) or TX (neonat*) or TX (newborn*) or TX (infant*) or TX (child*) or TX (toddler*) or TX (adolesc*) or TX (teen*)
- S23 S19 and S22
- S22 S20 or S21
- S21 TX (sucrose*) or TX (lactose*) or TX (glucose*) or TX (fructose*) or TX (glycerine*) or TX (lycerine*) or TX (dextrose*) or TX (aspartame*) or TX (polycose*) or TX (sacchar*) or TX (sugar*) or TX (sweet* N6 solution*) or TX (sweet* N6 taste) or TX (sweet* N6 tasting) or TX (pleasant* N6 solution*) or TX (pleasant* N6 taste) or TX (pleasant* N6 tasting) or TX (nice* N6 solution*) or TX (nice* N6 taste) or TX (nice* N6 tasting)
- S20 (MH "Sucrose+")
- S19 S13 and S18
- S18 S14 or S15 or S16 or S17
- S17 TX (cry) or TX (crying) or TX (cried) or TX (cries)
- S16 TX (needle* N6 distress*) or TX (needle* N6 discomfort) or TX (needle* N6 fear*) or TX (needle* N6 fright*) or TX (needle* N6 anxious) or TX (needle* N6 anxiet*) or TX (intervention* N6 distress*) or TX (procedur* N6 distress*) or TX (procedur* N6 discomfort*)

S15 TX pain*
S14 (MH "Pain+")
S13 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12
S12 TX (thoracocentesis) or TX (paracentesis)
S11 TX (arterial line*)
S10 TX (arterial punctur*) or TX (artery N6 punctur*)
S9 TX (local analges*) or TX (local anaesthe*) or TX (local anesthe*)
S8 TX (central venous catheter* N6 insert*)
S7 TX (central line N6 insert*) or TX (central line N6 remov*)
S6 TX (catheter*) or TX (port-a-cath*) or TX (portacath*)
S5 TX (intravenous) or TX (intra venous) or TX (venepunctur*) or TX (venipunctur*) or TX (venous cannulation*) or TX (arterial blood gas* N6 cannul*)
S4 TX (bone marrow N4 aspiration*) or TX (bone marrow N4 biops*)
S3 TX (lumbar punctur*) or TX (spinal tap*)
S2 TX (blood sampl*) or TX (immuni*) or TX (inoculat*) or TX (vaccin*) or TX (inject*) or TX (finger prick*) or TX (heel prick*) or TX (heel lanc*) or TX (heel punctur*) or TX (heel stick*) or TX (sutur*) or TX (laceration* N3 repair*)
S1 TX (needle*)

WHAT'S NEW

Date	Event	Description
28 January 2020	Amended	Author deceased (AO).
7 October 2019	Review declared as stable	See Published notes .

HISTORY

Protocol first published: Issue 3, 2010

Review first published: Issue 10, 2011

Date	Event	Description
6 May 2015	Review declared as stable	This review will be assessed for further updating in 2020, or sooner if new evidence becomes available.
10 April 2015	New citation required but conclusions have not changed	This is an updated version of the original Cochrane review published in Issue 10, 2011 (Harrison 2011) on Sweet tasting solutions for reduction of needle-related procedural pain in children aged one to 16 years.
10 April 2015	New search has been performed	This review has been updated to include the results of a new search, which retrieved four new studies: three pilot randomised controlled trials and one large RCT. In addition, risk of bias tables and a summary of findings table have been added.

CONTRIBUTIONS OF AUTHORS

Denise Harrison: conceptualisation of problem and methods; literature search and identification of trials for inclusion; evaluation of methodologic quality of included trials; abstraction and meta-analysis of data; verification and input of data into RevMan; writing of text of review; update of this review.

Bonnie Stevens: conceptualisations of problem and methods; statistical and methodological support; principle investigator of CIHR Synthesis Grant: Knowledge Translation (Systematic Review of Sweet Solutions for Acute Pain Relief in Infants) which supported the original systematic review; writing text of review.

Janet Yamada: literature search and identification of trials for inclusion; evaluation of methodologic quality of included trials; abstraction and meta-analysis of data; verifying and entering data into RevMan; writing text of review.

Arne Ohlsson: statistical and methodological support; evaluation of methodologic quality of included trials; abstraction and meta-analysis of data; verifying and interpreting data in RevMan; substantive writing text of review.

Joseph Beyene: statistical and methodological support; evaluation of methodologic quality of included trials; abstraction and meta-analysis of data; verification and interpretation of data in RevMan.

Thomasin Adams-Webber: literature search and identification of trials for inclusion; writing of text of review.

DECLARATIONS OF INTEREST

Denise Harrison conducted three of the pilot RCTs included in this review, and is currently involved in the planning of full-scale trials which will be included in future updates to this systematic review. No other declarations of interest to declare. Bonnie Stevens has no declarations of interest to declare. Janet Yamada has no declarations of interest to declare. Arne Ohlsson has no declarations of interest to declare. Joseph Beyene has no declarations of interest to declare and Thomasin Adams-Webber has no declarations of interest to declare.

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Internal sources

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- Canadian Institutes of Health Research Team Grant in Children's Pain, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

No differences.

NOTES

At October 2019, this review has been stabilised and will not be updated. It can be viewed for historical interest.

INDEX TERMS

Medical Subject Headings (MeSH)

*Candy; *Needles; Age Factors; Chewing Gum; Pain [physiopathology] [*prevention & control]; Pain Measurement [methods]; Punctures [*adverse effects]; Randomized Controlled Trials as Topic; Sucrose [administration & dosage]; Sweetening Agents [*administration & dosage]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant