PRESS RELEASE

EDITOR'S CHOICE

Efficacy of sweet solutions for analgesia in infants between 1 and 12 months of age: a systematic review

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ABSTRACT

Objective To compare the efficacy of oral sweet solutions to water or no treatment in infants aged 1–12 months during immunisation.

Methods Randomised controlled trials (RCTs) were retrieved through internet searches or manual searches of reference lists. Search terms included newborn, infant, pain, sucrose and alternative names for sweet solutions. Summary estimates with 95% CIs were calculated and included relative risk (RR), risk difference (RD) and number needed to treat to benefit (NNTB) for dichotomous outcomes, and weighted mean differences (WMD) for continuous outcomes. Where pooling of results was not possible, a narrative summary of study results is presented.

Results Of the 695 studies identified, 14 RCTs with 1674 injections met the inclusion criteria. Sucrose or glucose, compared to water or no treatment decreased crying during or following immunisation in 13 of the 14 studies. Infants receiving 30% glucose (three trials, 243 infants) had a decreased RR in crying incidence following immunisation (typical RR 0.80, 95% CI 0.69 to 0.93; RD −0.17, 95% CI −0.29 to −0.05; NNTB 6, 95% CI 3 to 20). With sucrose or glucose, there was a 10% WMD reduction in proportion of crying time (95% CI −18 to −2) and a 12 s reduction in crying duration (95% CI −23 to −0.7 s). An optimal dose of sucrose or glucose could not be ascertained due to the varied volumes and concentrations used.

Conclusion Infants aged 1–12 months administered sucrose or glucose before immunisation had moderately reduced incidence and duration of crying. Healthcare professionals should consider using sucrose or glucose before and during immunisation.

What is already known on this topic

- There is abundant high quality evidence of the analgesic efficacy of sucrose and glucose in newborn infants, especially during heel lance and venepuncture.
- There are a growing number of studies evaluating the analgesic effects of sweet solutions in infants beyond the newborn period.

What this study adds

- Sucrose and glucose also reduce pain during immunisation in infants up to 12 months of age.
- The analgesic effects of sweet solutions in older infants are more moderate than those seen in newborn infants.

BACKGROUND

Extensive research shows that oral sucrose, glucose and other sweet tasting solutions are effective analgesics during minor painful procedures in neonates.[1 2] The administration of sweet solutions (in particular sucrose and glucose) is now widely recommended for routine use prior to painful procedures in newborn infants.[3–7] Although the analgesic effect of sucrose and glucose on newborns is well established, little is known about whether these solutions or other sweet tasting solutions are effective in reducing procedural pain in infants beyond the newborn period. This gap in knowledge was the subject of a recent narrative literature review of 10 published randomised controlled trials (RCTs) in which conflicting results across studies were highlighted.[8] A systematic review and meta-analyses were recommended to ascertain whether current evidence supports the use of sweet solutions for pain management beyond the neonatal period. Therefore, the aim of our study was to conduct a systematic review and meta-analyses on the effectiveness of sweet solutions during painful procedures for infants beyond the neonatal period up to 12 months of age.

METHODS

Ethics approval

As this was a systematic review of RCTs already completed, with no research activities involving humans, there was no requirement for ethics committee approval.

Sources of data

We followed the methods for conduct of systematic reviews as outlined by the Cochrane Collaboration.[9] Electronic databases searched were MEDLINE (1950–March 2009), Embase (1980–March 2009), CINAHL (1982–March 2009), PsycINFO (1967–March 2009) and all

EBM Reviews. Search terms were newborn, infant, neonate, sucrose and pain with appropriate truncation symbols. To expand the search to include sugar solutions in addition to sucrose, we also included the following search terms: lactose, glucose, fructose, glycerine, dextrose, aspartame, polycose, saccharose and saccharide. Language restrictions were not imposed. Reference lists from articles retrieved for the review were searched, as were personal files and recent major paediatric or paediatric pain conference proceedings for further relevant trials. For studies including both neonates and infants beyond the neonatal period, we extracted data for the subgroup of infants of interest if possible or we contacted authors for additional information. When means and SDs were not reported, we attempted to obtain information from the authors.

Study selection

RCTs of sucrose, glucose or other sweet solutions administered orally during immunisations in infants beyond the neonatal period (corrected for post menstrual age at birth) to 12 months of age were included.

Critical appraisal technique

Methodological quality was assessed using the standard methods of the Cochrane Collaboration. With a six-point quality rating scale, we evaluated potential biases according to the following criteria: randomisation generation; concealment of allocation; blinding of intervention; incomplete outcome data reported; selective outcome reporting; other sources of bias.[9] Two raters (DH, MB) independently assessed the methodological quality of each study and any disagreements were resolved through consensus or arbitration by a third rater (JY).

Methods for synthesising findings

Two authors (DH, MB) independently extracted data on study design, sample, intervention and outcomes (cry behaviours, validated pain scales, physiological indicators) including raw data for the meta-analyses. When appropriate comparable data were available (eg, means, SDs, proportions) from at least two trials, we conducted a meta-analysis.

Statistical analysis

Review Manager 5.0 (RevMan) software was used for the meta-analysis of outcome data.[10] When pooling binary outcomes, we used the relative risk ratio (RR) and its 95% CI. If the RR was significant, the risk difference (RD) and number needed to treat to benefit (NNTB) were computed. Weighted mean difference (WMD) and its 95% CI were calculated for continuous outcomes and heterogeneity was measured using the I-squared (I^2) test. All data were combined using the random effects model. For studies where pooling of results was not possible, we present a narrative descriptive summary account of study results.

RESULTS

The search yielded 695 citations, of which 14 RCTs, including a total of 1674 injections, met the inclusion criteria.[11–24] The selection process is summarised in figure 1. Details including the demographic characteristics of the 14 included RCTs are presented in table 1 and a summary of the quality ratings of the studies are presented in table 2. Immunisation and sweet solution details are summarised in online appendix A. Authors of included trials provided additional data for three studies.[11 13 20]

The 14 studies were all RCTs and generally of high quality. Five studies did not describe the generation of allocation sequence,[11–13 18 23] but only two studies failed to report concealment of allocation.[12 23] Knowledge of allocated intervention was adequately prevented in most studies, with the exception of two RCTs, in which outcome assessments were adequately blinded, but parents as well as the nurses administering injections were not blinded.[22 24] The glucose solution could not be concealed in one study that compared two different sucrose concentrations, a 40% glucose solution and water.[21] Incomplete outcome data were inadequately addressed in only one longitudinal RCT in which data were missing for five infants at the second data collection point.[14] Three studies were considered to have other problems increasing the risk of bias: one had small sample sizes of subgroups of infants included in this review,[13] pacifier use differed between the groups in another study,[16] and in a third study, insufficient information was given concerning collection of data about infants' like or dislike of the solution, but the outcome suggests a possible lack of blinding[23] (table 2).

Characteristics and results of included studies

All identified trials used sucrose or glucose of various concentrations; no studies using other sweet tasting solutions were identified. With the exception of one study,[20] sucrose or glucose in different doses and concentrations reduced various behavioural pain indicators, including crying characteristics, and composite pain scores, during or following completion of immunisation compared to either placebo (water) or no treatment. In one of the studies in which a 12% sucrose solution was used, the effects were only evident during a single immunisation, and ineffective for the second and third injections.[11] No studies reported adverse events.

Ten studies used sucrose solutions in concentrations ranging from 12% to 75%.[11–16 19 20 22 23] In three studies, 30% glucose was utilised[17 18 24] and in one study, the analgesic effects of two sucrose concentrations (25% and 50%) and 40% glucose were compared with water.[21] Volumes of solutions given were mainly 2 ml or less, with the exception of

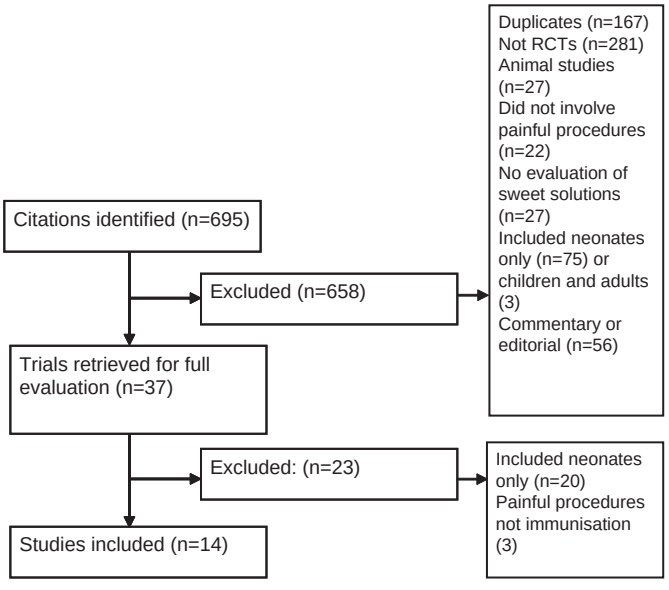

Figure 1 Flow chart for selection of eligible studies.

Table 1 Characteristics of randomised controlled trials meeting inclusion criteria

Study	N and population	Number of injections	Intervention/dose of sucrose/glucose	Outcomes
Allen *et al*[11]	285 healthy term infants Age: 2 weeks to 18 months	1, 2 or 3 injections	3 groups: 2.0 ml of 12% sucrose 2.0 ml water, 2 min prior to immunisation Nil treatment	Cry duration
Barr *et al*[12]	57 healthy term infants Age: 2 and 4 months	1 injection	2 groups: 3 doses at 30 s intervals: 0.25 ml of 50% sucrose 0.25 ml water, 2 min prior to immunisation	Cry duration during and following completion of injections
Dilli *et al*[13]	118 infants Age: 6–48 months Data for subgroup of infants aged 6–12 months supplied (N=29)	Either single or multiple injections	3 groups: 2.0 ml of 12% sucrose, 2 min prior to procedure Topical anaesthetic Control	Cry duration Pain score: NIPS[36]
Hatfield *et al*[15]	83 healthy term infants Age: 2 and 4 months	3 injections	2 groups: 2.0 ml of 24% sucrose 2.0 ml water, 2 min prior to immunisation	Pain score: UWCH[37]
Hatfield[14]	40 healthy term infants Age: 2 and 4 months	3 injections	2 groups: 2.0 ml of 24% sucrose 2.0 ml water, 2 min prior to immunisation	Pain score: UWCH[37]
Lewindon *et al*[16]	107 healthy infants Age: 2, 4 and 6 months	2 injections	2 groups: 2.0 ml of 75% sucrose 2.0 ml water, 2 min prior to immunisation	Cry duration Pain score: Oucher[40] Parent VAS (0–100)
Lindh *et al*[17]	70 healthy term infants Age: 3 months	1 injection	2 groups: 1.0 ml of 30% glucose, 2 min prior to injection and EMLA 1.0 ml water, 2 min prior to injection and topical placebo	Cry duration Cry incidence Pain score: MBPS[39] Parent and staff VAS (0–10) Heart rate and HRV
Mörelius *et al*[18]	98 healthy term infants Age: 3 months	1 injection	4 groups: 2.0 ml of 30% glucose - with NNS - without NNS 2.0 ml water - with NNS - without NNS, 2 min prior to procedure	Cry duration Cry incidence Salivary cortisol
Mowery[19]	49 healthy term infants of Hispanic origin Age: 2–6 months	3 injections	2 groups: 2.0 ml of 50% sucrose 2.0 ml water, 2 min prior to procedure	Cry duration Pain score: MBPS[39] Heart rate elevation
Poulsen[20]	67 healthy term infants Age: 3–9 months	1 injection	2 groups: 2.0 ml of 12% sucrose 2.0 ml water, 2 min prior to procedure	Pain score: NIPS[36]
Reis *et al*[22]	116 healthy term infants Age: 2 months	4 injections	2 groups: Combination of: 10 ml of 25% sucrose, 2 min prior to injections+NNS+parental holding Standard care	Cry duration Heart rate Injection duration VAS (0–100) for parents' preference for future pain management and nurses' score for ease of injection
Ramenghi *et al*[21]	184 healthy term infants Age: 2, 3 or 4 months	2 injections	4 groups: 2.0 ml of 25% sucrose 2.0 ml of 50% sucrose 2.0 ml of 40% glucose 2.0 ml water, 2 min prior to procedure	Cry duration
Soriano and Gomez[23]	323 healthy term infants Age: 1, 2, 4 or 6 months	1 injection	2 groups: 2.0 ml of 75% sucrose 2.0 ml water, 2 min prior to procedure	Cry duration
Thyr *et al*[24]	110 healthy term infants Age: 3, 5 and 12 months	1 injection	2 groups: 2.0 ml of 30% glucose 2.0 ml water, 2 min prior to procedure	Cry duration Cry intensity score Cry incidence

HRV, heart rate variability; MBPS, Modified Behavioural Pain Scale; NIPS, Neonatal Infant Pain Scale; NNS, non-nutritive sucking; UWCH, University of Wisconsin Children's Hospital Pain Scale; VAS, visual analogue scale.

one study where 10 ml of 25% sucrose was administered.[22] In one study, a combination of 30% glucose and EMLA was compared to a placebo oral solution and a topical cream, [17] and another study compared non-nutritive sucking (NNS) with glucose.[18]

A variety of pain outcomes were used as shown in table 1. Various crying characteristics were measured in all but two studies.[18 20] Four composite pain assessment tools were used and three studies included four different visual analogue scales.[16 17 22] Physiological responses were assessed as outcome measures in three studies,[17 19 22] including heart rate, heart rate changes from baseline, or heart rate variability (HRV). Salivary cortisol measurements of both infants and parents were measured in one study.[17]

Table 2 Quality assessment of randomised controlled trials

Study	Adequate generation of allocation sequence	Adequate concealment of allocation	Knowledge of allocated intervention adequately prevented	Incomplete outcome data adequately addressed	Reports free of suggestion of selective outcome reporting	Free of other problems that could put study at a high risk of bias	Comments
Allen *et al*[11]	No	Yes	Yes	Yes	Yes	Yes	
Barr *et al*[12]	No	No	Yes	Yes	Yes	Yes	
Dilli *et al*[13]	No	Yes	Yes	Yes	Yes	No	Small sample size in subgroup of infants included
Hatfield *et al*[15]	Yes	Yes	Yes	Yes	Yes	Yes	Non-nutritive sucking part of control condition
Hatfield[14]	Yes	Yes	Yes	No	Yes	Yes	Data missing for 5 infants at 2nd observation
Lewindon *et al*[16]	Yes	Yes	Yes	Yes	Yes	No	Pacifier use differed
Lindh *et al*[17]	Yes	Yes	Yes	Yes	Yes	Yes	Combination of interventions
Mörelius *et al*[18]	No	Yes	Yes	Yes	Yes	Yes	
Mowery[19]	Yes	Yes	Yes	Yes	Yes	Yes	
Poulsen[20]	Yes	Yes	Yes	Yes	Yes	Yes	
Ramenghi *et al*[21]	Yes	Yes	Yes for control and sucrose. No for glucose	Yes	Yes	Yes	
Reis *et al*[22]	Yes	Yes	Yes for outcome assessors. No for parents and nurses	Yes	Yes	Yes	
Soriano and Gomez[23]	No	No	Yes	Yes	Yes	No	Insufficient details given of assessment of infants' liking of the solution
Thyr *et al*[24]	No	Yes	Yes for outcome assessors. No for nurse giving injections	Yes	Yes	Yes	

Efficacy of sucrose and glucose

Administration of either sucrose or glucose resulted in reduced crying incidence and duration and composite pain scores, compared to either placebo (water) or no treatment in 13 of the 14 studies (table 3). In one study, 2 ml of 12% sucrose had no effect on pain scores,[20] and in another, although sucrose was more effective compared to no treatment during a single injection, no differences in crying time between infants receiving 12% sucrose compared to water were demonstrated.[11] The more concentrated 50% sucrose solution was more effective than 25% sucrose, 40% glucose and water in reducing crying time following immunisation.[21] As these latter results were reported in medians and interquartile ranges (IQRs), we could not combine data from this study using meta-analytic techniques.

Neither sucrose nor glucose, including glucose combined with EMLA, resulted in significant reductions in mean heart rate, mean heart rate change from baseline, or mean HRV.[17 19 22] The study measuring salivary cortisol following immunisation showed that infants who received combined glucose and NNS had a 33% mean reduction in salivary cortisol levels from baseline, while infants receiving water with and without pacifier, or oral glucose alone, had an increase in salivary cortisol levels following immunisation.[18]

Meta-analyses could be performed for three cry outcomes following immunisation: (1) proportion of cry; (2) duration of cry (s) until crying cessation; and (3) incidence of cry. For proportion of crying times following immunisation, data were pooled from three studies and included 150 infants.[12 18 19] Barr *et al*[12] used three doses of 0.25 ml of 50% sucrose, Mowery[19] used 2 ml of 50% sucrose and Morelius *et al*[25] used 2 ml of 30% glucose. Results showed a 10% mean reduction in proportion of crying time following immunisation in the sweet solutions groups compared to placebo (WMD −10, 95% CI −18 to −2%) (figure 2).

Data were pooled for crying duration (s) from six studies (five using sucrose and one using glucose) (N=716 injections).[11 13 16 17 19 20 23] Results showed a non-significant mean reduction in crying duration of 16 s in the sweet solutions group (95% CI −32 to 0.08; p=0.05) (figure 3A). Due to a high degree of heterogeneity (I^2=88%), we repeated the meta-analysis without the two studies which used a 12% sucrose solution,[11 13] as the results of these two studies differed widely. When we removed these two studies from the meta-analysis, the I^2 value was reduced from 88% to 72%. The results then showed a statistically significant, but clinically small WMD of −12 s in crying duration (s), favouring sweet solutions (95% CI −23 to −0.78; p=0.04) (four studies, 568 injections) (figure 3B). We performed a subgroup analysis to further explore conflicting results in the two studies which used 12% sucrose. As Dilli *et al*[13] included infants 6–12 months old, and the control group received standard care only with no oral placebo, we included a subgroup of

Table 3 Results

Study	Results	Metrics used
Allen *et al*[11]*	12% sucrose no more effective than sterile water but more effective than no intervention during a single injection. No differences in groups for multiple injections	Mean crying time data obtained from author. Calculated SD
Barr *et al*[12]	Sucrose group: reduction in crying time post injection at 2 and 4 months. No differences in cry duration during injection	Mean±SEM. SEM converted to SD for meta-analysis
Dilli *et al*[13]*	Sucrose and topical anaesthetic reduced cry duration and pain score compared to control. No differences between sucrose and topical anaesthetic	Median, range. Mean±SD supplied by author for meta-analysis
Hatfield *et al*[15]	Reduced pain score in sucrose group at 5, 7 and 9 min following immunisation	Mean, 95% CI, SMD
Hatfield[14]	Reduced pain score in sucrose group at 5 min following immunisation	Mean, 95% CI, SMD
Lewindon *et al*[16]	Sucrose group: reduction in cry duration and pain score. No reduction in VAS	Mean±SD
Lindh *et al*[17]	Combination of glucose and EMLA resulted in significant reduction in nurse and parent VAS, pain score, presence of cry and latency to cry	Mean±SD
	No difference in total crying time. No difference in heart rate or HRV	
Mörelius *et al*[18]	Reduced salivary cortisol response and crying duration (s) in NNS and glucose, compared to NNS and water. No differences in any groups on parent VAS scores	Median and ORs for salivary cortisol. N and % for crying incidence. Means±SD for crying duration
Mowery[19]	Sucrose group: reduced high pain score. No difference in cry duration and heart rate	Mean±SD
Poulsen[20]*	12% sucrose no more effective than sterile water	Sum of differences and area under the pain/time curve
Reis *et al*[22]	Sucrose group: reduction in cry duration and significantly higher parent preference for pain management No difference in heart rate, vaccination time or ease of administration of vaccination	Cry duration and VAS scores: median and IQR Heart rate: mean±SD, 95% CI
Ramenghi *et al*[21]	Sucrose group (50%): significantly reduced cry duration at 3 and 4 months	Median and IQR
Soriano and Gomez[23]	Sucrose group (75%): clinically modest, statistically significant reduction in crying duration	Mean±SD
Thyr *et al*[24]	Sucrose group: significant reduction in cry duration at 5 and 12 months immunisation, but not at 3 months	Mean and difference between groups for crying time
	No difference in cry intensity at any time point	N and difference between groups for crying incidence

*Additional data supplied by authors
HRV, heart rate variability; IQR, interquartile range; NNS, non-nutritive sucking; SMD, standardised mean difference; VAS, visual analogue scale.

infants in the study by Allen *et al*[11] matched on age and treatment in the meta-analysis. Results showed that 12% sucrose was effective for reducing cry duration (WMD −48, 95% CI −71 to −24; p<0.0001); however, there was significant heterogeneity between these two studies (I^2=93%) and the total sample size was only 62 infants (figure 4).

A meta-analysis was conducted with data pooled from three studies reporting incidence of cry following immunisation[17 18 24] (N=243 infants). Results showed a 20% reduction in RR for crying for infants when administered 1–2 ml of 30% glucose (RR 0.80, 95% CI 0.69 to 0.93) (figure 5). There was no significant heterogeneity (I^2=10%). RD was −0.17 (95% CI −0.29 to −0.05) and NNTB was 6 (95% CI 3 to 20).

Due to inconsistencies in the volumes and concentrations of sucrose and glucose that were reported to be effective, an optimal analgesic dose of either sweet solution to be used in infants beyond the neonatal period during immunisation could not be determined.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analyses conducted to explore the analgesic effects of sweet solutions in infants beyond the newborn period up to 12 months of age. Only studies investigating the effect of sucrose and glucose were identified. In general, the quality of the studies was high. We found that oral administration of either sucrose or glucose was associated with small but statistically significant reductions in crying incidence, crying duration and composite pain scores during and following immunisation. These results extend the findings of the systematic review and meta-analyses of sucrose in newborn infants, which reported that effective doses for neonates ranged between 0.05 ml and 2 ml of 24% sucrose.[1]

For infants beyond the neonatal period up to 12 months, higher concentrations of either sucrose or glucose seemed to be more effective. This was highlighted in the study by Lewindon *et al*,[16] in which a 75% sucrose solution was used following a pilot study where 50% sucrose was considered ineffective. Conversely, in a recently published study, 12% sucrose significantly reduced pain scores and crying time compared to no treatment, in all groups of infants, including the subgroup of 20 infants aged 6–12 months included in this systematic review.[13] Previous to this study, 12% sucrose was considered insufficiently sweet to exert an analgesic effect,[11] and more recently, Poulsen also showed no analgesic effect of 12% sucrose during immunisation.[20] The reasons for the conflicting results of the studies using 12% sucrose during immunisation are inexplicable; however, they may be related to the additional physical interventions used (ie, maternal holding and distraction offered by the majority of mothers in the study by Dilli *et al*[13]) or possibly by unknown cultural or contextual differences. Such differences could potentially be related to different responses to sweet taste. As the procedure of sucrose administration in the Dilli *et al* study[13] was based on that used by Allen *et al*,[11] this cannot explain the different responses.

There are important differences in the efficacy of sweet solutions in older infants compared to newborn infants. In most studies, the analgesic effects were more moderate than previously reported for newborn infants[1] and pain reduction was primarily evident in the period immediately following completion of the procedure, rather than during the procedure.[12] In addition to the included studies of sucrose or glucose during immunisation, two studies including infants beyond the neonatal period up to 12 months of age were conducted in sick infants presenting to emergency departments.[26 27] The analgesic effects of 2 ml of 44% sucrose during venepuncture[26] and 2

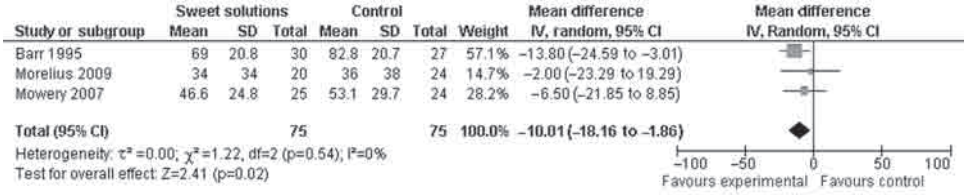

Figure 2 Weighted mean difference for cry proportion following immunisation (%).

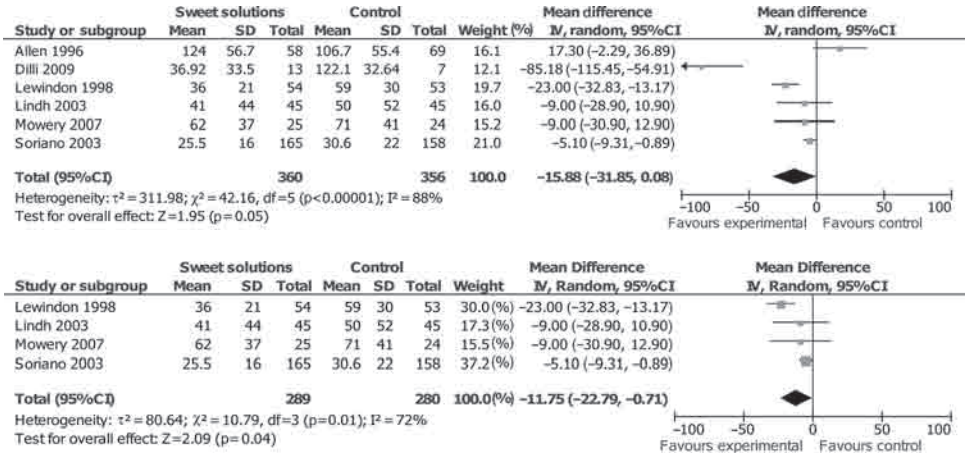

Figure 3 (A) Weighted mean cry duration following immunisation (s). (B) Weighted mean cry duration following immunisation (s) following removal of two randomised controlled trials of 12% sucrose.

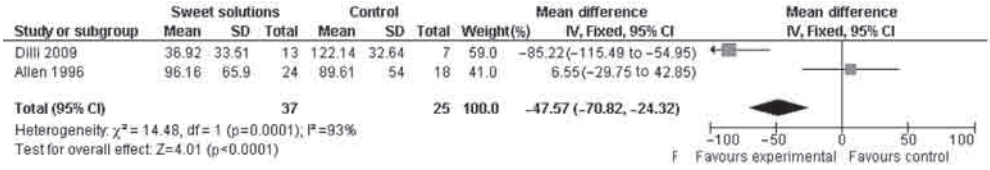

Figure 4 Weighted mean differences for cry duration (s) following immunisation. Only the two studies using 12% sucrose versus control (no placebo) are included. The subgroup of infants only included those aged 6–12 months.

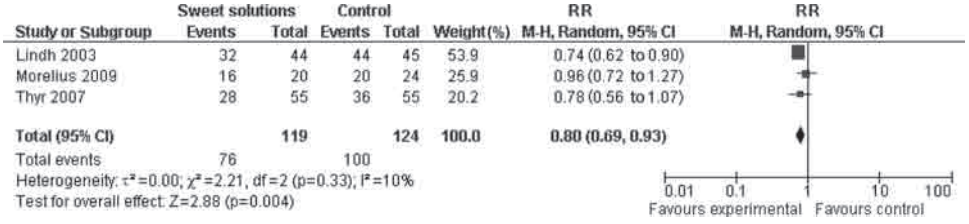

Figure 5 Typical relative risks (or risk ratios) (RRs with 95% CIs) for crying incidence following immunisation. All studies used 30% glucose.

ml of 24% sucrose during urethral catheterisation were studied.[27] In both studies, sucrose was more effective than water in reducing pain scores and crying duration only in the youngest groups of infants. These two studies warrant further discussion. Firstly, these two procedures may be associated with higher pain intensity, cause more stress and require more restraint than intramuscular injections, rendering sucrose, a mild analgesic, insufficient for pain relief. Secondly, in these two RCTs, single doses of 2 ml of 24% sucrose[27] and 2 ml of 44% sucrose,[26] respectively, were administered 2 min prior to commencement of the procedure. This practice is widely accepted, based on studies conducted by Blass *et al*, where sweet taste mediated analgesic effects peaked at 2 min and lasted for between 3 and 5 min, an interval considered to coincide with endogenous opioid release.[28 29] However, as both urethral catheterisation and venepuncture generally take longer to perform than immunisations, the analgesic effects of sweet solutions may not have been sustained in these studies. A shorter effect time of sweet

solutions in older infants was demonstrated in a study where 24% sucrose was effective for 1 min only.[30] In both studies conducted in the emergency department, subgroup analyses showed that sucrose was more effective than placebo in the youngest group of infants only.[26 27] In a longitudinal study of sucrose effectiveness over the course of a prolonged hospitalisation, sucrose given in aliquots prior to, upon commencement of, and during heel lancing continued to provide analgesia in infants aged 1–5 months throughout the period of hospitalisation.[31] Therefore, dividing the dose and administering repeated small volumes throughout the procedure may optimise sustained analgesic effects for those procedures in older infants lasting more than a few minutes.[31–33] Further studies in infants beyond the neonatal period, comparing a single dose of sweet solution to divided doses given over the duration of a prolonged procedure are needed.

As combined strategies were used in two studies,[17 22] the effects of sweet solutions alone could not be isolated. A combination of topical anaesthetic cream and oral glucose was compared to water and topical placebo cream in one study[17] and a combination of 10 ml of 25% sucrose, NNS and parental holding was compared to standard care (infants were vaccinated while lying on the examination table with no specific comfort measures provided).[22] These combinations of strategies are dissimilar to the administration of small volumes of sweet solutions alone; therefore, results need to be interpreted with caution.

Widely varying concentrations and volumes of sucrose and glucose were used in studies included in this review. Two studies used 2 ml of a 75% sucrose solution,[16 23] and a larger volume of 10 ml of 25% sucrose was used in another.[22] Both the 10 ml volume of 25% sucrose and the undiluted 75% sucrose concentration exceed the total sucrose dose administered in most other studies and far exceed the 0.24–0.50 g sucrose dose recommended for effective pain management in term newborn infants.[1] Although Reis *et al*[22] did not justify using 10 ml of sucrose, Lewindon *et al*[16] reported that a 50% sucrose solution used in a pilot study failed to demonstrate any observable effects, and Soriano and Gomez[23] stated they used the same sucrose concentration as Lewindon *et al*. These results, along with results of animal studies[28] and those reported in a study comparing three different concentrations of sweet solutions (25% and 50% sucrose and 40% glucose),[34] highlight that, in older infants, there is evidence of a sweet-dose related response, with more concentrated sugar solutions being more effective. However, as previously stated, the results obtained by Dilli *et al*,[13] where 12% sucrose was effective in reducing immunisation pain not only for infants but also for children up to 4 years of age, are contrary to this evidence.

For the four studies which used glucose solutions,[17 18 21 24] glucose effectively reduced pain during immunisation compared to water, highlighting that non-sucrose sweet solutions of sufficient concentration are analgesic. Administration of 30% oral glucose resulted in an RR for crying following immunisation of 0.80 and an NNTB of six infants (albeit with a wide CI of 3 to 20). However, Ramenghi *et al*[21] demonstrated that a sweetness dose response exists in this age group as the concentrated 50% sucrose solution was more effective than both 40% glucose and 25% sucrose. Although sucrose is the sweetest of the sugars (sucrose>fructose>glucose>lactose),[35] either sucrose or glucose could be used depending on availability and organisational preference as long as the solutions are sufficiently sweet (ie, at least 30% glucose or 24% sucrose[1]).

Limitations

The wide variety of concentrations of sucrose or glucose solutions used, outcome measures and differences in the timing of outcome assessments precluded inclusion of most studies in meta-analyses. Four different composite pain assessment tools were used, three of which have undergone various degrees of validity and reliability testing in infants,[36–39] with the exception of the Oucher, which has only been validated for use in children aged 3–7 years.[40 41] The four pain assessment tools have varied scales and maximum scores of 5,[37] 7,[36] 10 and 100.[40] Such variations in scales pose difficulties in conducting appropriate meta-analyses.

In addition, in this review, we did not consider varying pain responses to the type of immunisation administered, the order of immunisations performed or injection techniques, all of which have been shown to impact on pain during immunisation.[42 43]

Implications for practice

Based on extensive evidence of the efficacy of sweet solutions in neonates[1] and the evidence from this systematic review, sucrose or glucose along with other recommended physical or psychological pain reduction strategies, such as NNS, breast feeding or effective means of distraction,[44] should be consistently utilised for immunisation. For multiple immunisations, the total dose of sweet solution should be given prior to and throughout the procedure to ensure sustained effects of sweet tasting analgesia. Further studies are warranted comparing different concentrations of sucrose and glucose and the use of single dosing 2 min prior to painful procedures to multiple dosing over the course of procedures. In addition, sucrose or glucose, depending on the availability of solutions, should be considered for other painful procedures for infants up to 12 months of age. This information is important for healthcare professionals working with infants in both inpatient and outpatient settings, as sweet solutions are readily available, have a very short onset of time to analgesia, are inexpensive and are easy to administer.

CONCLUSION

Sucrose and glucose of various doses and concentrations moderately reduces crying incidence, crying duration and pain scores during or following immunisation, beyond the neonatal period up to 12 months of age. Healthcare professionals responsible for administering immunisations should consider using sucrose or glucose during painful procedures.

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REFERENCES

1. **Stevens B**, Yamada J, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev* 2004;**3**:CD001069.

2. **Tsao JCI**, Evans **S**, Meldrum **M**, *et al.* A Review of CAM for Procedural Pain in Infancy: Part I. Sucrose and Non-nutritive Sucking. *Evid Based Complement Alternat Med* 2008;**5**:371–81.
3. American Academy of Pediatrics, Committee on Psychosocial Aspects of Child and Family Health, Task Force on Pain in Infants Children and Adolescents. The assessment and management of acute pain in infants, children, and adolescents. *Pediatrics* 2001;**108**:793–7.
4. **Anand KJ**; International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001;**155**:173–80.
5. Royal Australasian College of Physicians. Guideline Statement: Management of Procedure-related Pain in Neonates. Sydney: Paediatrics & Child Health Division, The Royal Australasian College of Physicians; 2005. http://www.racp.edu.au/page/health-policy-and-advocacy/paediatrics-and-child-health (accessed 19 January 2010).
6. **Harrison D**, Australian College of Neonatal Nurses. Management of pain in sick hospitalised infants. *Neonat Paediatr Child Health Nurs* 2006;**9**:27–9.
7. Henderson-Smart D, Australian & New Zealand Neonatal Network. Evidence Uptake Using Networks - Newborn Pain project. Sydney: National Institute of Clinical Studies, National Health & Medical Research Council. 2007
8. **Harrison D**. Oral sucrose for pain management in the paediatric emergency department; a review. *Australa Emerg Nurs J* 2008;**11**:72–9.
9. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008].* The Cochrane Collaboration, 2008. http://www.cochrane-handbook.org (accessed 6 April 2010).
10. The Nordic Cochrane Centre The Cochrane Collaboration. Review Manager (RevMan) 5.0 ed. Copenhagen; 2008.
11. **Allen KD**, White DD, Walburn JN. Sucrose as an analgesic agent for infants during immunization injections. *Arch Pediatr Adolesc Med* 1996;**150**:270–4.
12. **Barr RG**, Young SN, Wright JH, *et al.* "Sucrose analgesia" and diphtheria-tetanus-pertussis immunizations at 2 and 4 months. *J Dev Behav Pediatr* 1995;**16**:220–5.
13. **Dilli D**, Küçük IG, Dallar Y. Interventions to reduce pain during vaccination in infancy. *J Pediatr* 2009;**154**:385–90.
14. **Hatfield LA**. Sucrose decreases infant biobehavioral pain response to immunizations: a randomized controlled trial. *J Nurs Scholarsh* 2008;**40**:219–25.
15. **Hatfield LA**, Gusic ME, Dyer AM, *et al.* Analgesic properties of oral sucrose during routine immunizations at 2 and 4 months of age. *Pediatrics* 2008;**121**:e327–34.
16. **Lewindon PJ**, Harkness L, Lewindon N. Randomised controlled trial of sucrose by mouth for the relief of infant crying after immunisation. *Arch Dis Child* 1998;**78**:453–6.
17. **Lindh V**, Wiklund U, Blomquist HK, *et al.* EMLA cream and oral glucose for immunization pain in 3-month-old infants. *Pain* 2003;**104**:381–8.
18. **Mörelius E**, Theodorsson E, Nelson N. Stress at three-month immunization: parents' and infants' salivary cortisol response in relation to the use of pacifier and oral glucose. *Eur J Pain* 2009;**13**:202–8.
19. **Mowery B**. Effects of sucrose on immunization injection pain in Hispanic infants. Unpublished thesis. Virginia: University of Virginia; 2007.
20 **Poulsen M**. Cane sugar unsuitable for use as analgesic in paediatric vaccination. *Sygeplejersken/Danish Journal of Nursing* 2009;**106**:54–7.
21. **Ramenghi LA**, Webb AV, Shevlin PM, *et al.* Intra-oral administration of sweet-tasting substances and infants' crying response to immunization: a randomized, placebo-controlled trial. *Biol Neonate* 2002;**81**:163–9.
22. **Reis EC**, Roth EK, Syphan JL, *et al.* Effective pain reduction for multiple immunization injections in young infants. *Arch Pediatr Adolesc Med* 2003;**157**:1115–20.
23. **Soriano Faura J**, Gomez Gil A. Controlled clinical study of sucrose administration to reduce the duration of crying in infants undergoing vaccination. Acta Pediatrica Espanola. 2003 May;**61(5)**:234–8.
24. **Thyr M**, Sundholm A, Teeland L, *et al.* Oral glucose as an analgesic to reduce infant distress following immunization at the age of 3, 5 and 12 months. *Acta Paediatr* 2007;**96**:233–6.
25. **Morelius E**, Nelson N, Theodorsson E. Salivary cortisol and administration of concentrated oral glucose in newborn infants: improved detection limit and smaller sample volumes without glucose interference. *Scand J Clin Lab Invest* 2004;**64**:113–8.
26. **Curtis SJ**, Jou H, Ali S, *et al.* A randomized controlled trial of sucrose and/or pacifier as analgesia for infants receiving venipuncture in a pediatric emergency department. *BMC Pediatr* 2007;**7**:27.
27. **Rogers AJ**, Greenwald MH, Deguzman MA, *et al.* A randomized, controlled trial of sucrose analgesia in infants younger than 90 days of age who require bladder catheterization in the pediatric emergency department. *Acad Emerg Med* 2006;**13**:617–22.
28. **Blass E**, Fitzgerald E, Kehoe P. Interactions between sucrose, pain and isolation distress. *Pharmacol Biochem Behav* 1987;**26**:483–9.
29. **Blass EM**, Shah A. Pain-reducing properties of sucrose in human newborns. *Chem Senses* 1995;**20**:29–35.
30. **Barr RG**, Quek VS, Cousineau D, *et al.* Effects of intra-oral sucrose on crying, mouthing and hand-mouth contact in newborn and six-week-old infants. *Dev Med Child Neurol* 1994;**36**:608–18.
31. **Harrison D**, Loughnan P, Manias E, *et al.* Repeated doses of sucrose in infants continue to reduce procedural pain during prolonged hospitalizations. *Nurs Res* 2009;**58**:427–34.
32. **Harrison D**, Johnston L, Loughnan P. Oral sucrose for procedural pain in sick hospitalized infants: a randomized-controlled trial. *J Paediatr Child Health* 2003;**39**:591–7.
33. **Johnston CC**, Stremler R, Horton L, *et al.* Effect of repeated doses of sucrose during heel stick procedure in preterm neonates. *Biol Neonate* 1999;**75**:160–6.
34. **Ramenghi LA**, Griffith GC, Wood CM, *et al.* Effect of non-sucrose sweet tasting solution on neonatal heel prick responses. *Arch Dis Child Fetal Neonatal Ed* 1996;**74**:F129–31.
35. **Blass EM**, Smith BA. Differential effects of sucrose, fructose, glucose, and lactose on crying in 1- to 3-day-old human infants: qualitative and quantitative considerations. *Dev Psychol* 1992;**28**:804–10.
36. **Lawrence J**, Alcock D, McGrath P, *et al.* The development of a tool to assess neonatal pain. *Neonatal Netw* 1993;**12**:59–66.
37. **Soetenga D**, Frank J, Pellino TA. Assessment of the validity and reliability of the University of Wisconsin Children's Hospital Pain scale for Preverbal and Nonverbal Children. *Pediatr Nurs* 1999;**25**:670–6.
38. **Duhn LJ**, Medves JM. A systematic integrative review of infant pain assessment tools. *Adv Neonatal Care* 2004;**4**:126–40.
39. **Taddio A**, Nulman I, Koren BS, *et al.* A revised measure of acute pain in infants. *J Pain Symptom Manage* 1995;**10**:456–63.
40. **Beyer JE**, Denyes MJ, Villarruel AM. The creation, validation, and continuing development of the Oucher: a measure of pain intensity in children. *J Pediatr Nurs* 1992;**7**:335–46.
41. **Stinson J**, Yamada J, Dickson A, *et al.* Review of systematic reviews on acute procedural pain in children in the hospital setting. *Pain Res Manag* 2008;**13**:51–7.
42. **Ipp M**, Cohen E, Goldbach M, *et al.* Effect of choice of measles-mumps-rubella vaccine on immediate vaccination pain in infants. *Arch Pediatr Adolesc Med* 2004;**158**:323–6.
43. **Ipp M**, Taddio A, Sam J, *et al.* Vaccine-related pain: randomised controlled trial of two injection techniques. *Arch Dis Child* 2007;**92**:1105–8.
44. **Uman LS**, Chambers CT, McGrath PJ, *et al*. Psychological interventions for needle-related procedural pain and distress in children and adolescents. *Cochrane Database Syst Rev*. 2006;**4**:CD005179.