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Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

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ABSTRACT

Background
Neonatal hypoglycaemia, a common condition, can be associated with brain injury. It is frequently managed by providing infants with an alternative source of glucose, given enterally with formula or intravenously with dextrose solution. This often requires that mother and baby are cared for in separate environments and may inhibit breast feeding. Dextrose gel is simple and inexpensive and can be administered directly to the buccal mucosa for rapid correction of hypoglycaemia, in association with continued breast feeding and maternal care.

Objectives
To assess the effectiveness of dextrose gel in correcting hypoglycaemia and in reducing long-term neurodevelopmental impairment.

Search methods
We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Web of Science from inception of the database to February 2016. We also searched international clinical trials networks and handsearched proceedings of specific scientific meetings.

Selection criteria
Randomised and quasi-randomised studies comparing dextrose gel versus placebo, no treatment or other therapies for treatment of neonatal hypoglycaemia.

Data collection and analysis
Two review authors independently assessed trial quality and extracted data and did not assess publications for which they themselves were study authors.

Main results
We included two trials involving 312 infants. No data were available for correction of hypoglycaemia for each hypoglycaemic event. We found no evidence of a difference between dextrose gel and placebo gel for major neurosensory disability at two-year follow-up (risk ratio (RR) 6.27, 95% confidence interval (CI) 0.77 to 51.03; one trial, n = 184; quality of evidence very low). Dextrose gel compared
with placebo gel or no gel did not alter the need for intravenous treatment for hypoglycaemia (typical RR 0.78, 95% CI 0.46 to 1.32; two trials, 312 infants; quality of evidence very low). Infants treated with dextrose gel were less likely to be separated from their mothers for treatment of hypoglycaemia (RR 0.54, 95% CI 0.31 to 0.93; one trial, 237 infants; quality of evidence moderate) and were more likely to be exclusively breast fed after discharge (RR 1.10, 95% CI 1.01 to 1.18; one trial, 237 infants; quality of evidence moderate). Estimated rise in blood glucose concentration following dextrose gel was 0.4 mmol/L (95% CI -0.14 to 0.94; one trial, 75 infants).

Authors’ conclusions

Treatment of infants with neonatal hypoglycaemia with 40% dextrose gel reduces the incidence of mother-infant separation for treatment and increases the likelihood of full breast feeding after discharge compared with placebo gel. No evidence suggests occurrence of adverse effects during the neonatal period or at two years’ corrected age. Oral dextrose gel should be considered first-line treatment for infants with neonatal hypoglycaemia.

Plain Language Summary

Oral dextrose gel for treatment of newborn infants with low blood glucose levels

Review question: For hypoglycaemic newborn infants, is oral dextrose gel more effective than placebo, no treatment or other active treatments in correcting hypoglycaemia and reducing long-term neurodevelopmental impairment?

Background: Low blood glucose levels in newborn infants are common and occur frequently in certain at-risk groups (infants of diabetic mothers, preterm infants, small and large infants). Infants with low blood glucose levels are at higher risk for developmental problems later in childhood. Therefore, active treatments are generally used to treat these infants, and such treatments frequently require use of formula milk or admission to the neonatal unit, resulting in temporary separation from the mother.

Study characteristics: Two trials to date have assessed use of dextrose gel to reverse low blood glucose levels while the baby remains in the mother’s care; these studies included a total of 312 infants. Investigators rubbed dextrose gel into the inside of the infant’s cheek; they provided a normal feed for 157 of these infants and placebo gel plus a normal feed, or a normal feed alone, for 155 infants.

Key results: Results suggest that dextrose gel is effective in keeping mothers and infants together and improving the rate of full breast feeding after discharge from hospital. Researchers reported no adverse effects when dextrose gel was given to infants and no effects on development at two years of age.

The review is limited by lack of data for the important outcomes of effectiveness of treatment for individual episodes of low blood glucose levels and effects on brain injury. Further research is required to address these important questions.

Dextrose gel applied to the inside of the cheek is a simple and safe treatment for initial care of infants with low blood glucose levels.

Quality of evidence: Overall the quality of the evidence was moderate to very low. Reasons for downgrading the quality of evidence included imprecision (variation in data), publication bias (evidence based on data from a single trial; one publication in abstract format only), insufficient detail to allow a judgement about risk of bias and/or high levels of disagreement for a particular outcome.
## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

### Dextrose gel versus control

**Patient or population:** newborn infants with hypoglycaemia  
**Intervention:** dextrose gel  
**Comparison:** control (placebo gel)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Risk with control</td>
<td>Risk with dextrose gel</td>
<td></td>
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<tr>
<td>Correction of hypoglycaemia for each hypoglycaemic event - not reported</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>-</td>
<td>No data reported for this outcome</td>
</tr>
<tr>
<td>Major neurosensory disability (2-year follow-up)</td>
<td>Study population</td>
<td>RR 6.27 (0.77 to 51.03)</td>
<td>184 (1 RCT)</td>
<td>⊕⊕⊕⊕ Very low&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<td></td>
<td>11 per 1000</td>
<td>67 per 1000 (8 to 543)</td>
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<tr>
<td>Receipt of intravenous treatment for hypoglycaemia (for each infant)</td>
<td>Study population</td>
<td>RR 0.81 (0.29 to 2.25)</td>
<td>312 (2 RCTs)</td>
<td>⊕⊕⊕⊕ Very low&lt;sup&gt;c,d,e&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>168 per 1000</td>
<td>136 per 1000 (49 to 377)</td>
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<tr>
<td>Adverse effects</td>
<td>Study population</td>
<td>Not estimable</td>
<td>237 (1 RCT)</td>
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<td>No events reported in the dextrose gel nor the placebo gel group</td>
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<tr>
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<td>0 per 1000</td>
<td>0 per 1000 (0 to 0)</td>
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<tr>
<td>Separation from mother for treatment of hypoglycaemia</td>
<td>Study population</td>
<td>RR 0.54 (0.31 to 0.93)</td>
<td>237 (1 RCT)</td>
<td>⊕⊕⊕ Moderate&lt;sup&gt;h&lt;/sup&gt;</td>
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<tr>
<td>Exclusive breast feeding after discharge (WHO definition)</td>
<td>Study population</td>
<td>RR 1.10 (1.01 to 1.18)</td>
<td>237 (1 RCT)</td>
<td>Moderate(^b)</td>
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<tr>
<td>252 per 1000</td>
<td>136 per 1000 (78 to 234)</td>
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<tr>
<td>874 per 1000</td>
<td>961 per 1000 (883 to 1000)</td>
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</table>

\(^a\) Risk in the intervention group (and its 95% confidence interval) is based on assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio; RR: risk ratio; WHO: World Health Organization

**GRADE Working Group grades of evidence**

- **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
- **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different
- **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of 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

- **a** Wide confidence intervals, low event rates and small sample sizes are suggestive of imprecision - downgraded 2 levels
- **b** Evidence is based on a single trial - downgraded 1 level
- **c** One trial showed low risk of bias for all domains, but the other trial showed high risk of attrition bias and unclear risk of bias for all other domains - downgraded 1 level
- **d** One trial has been published in full; the other trial was reported only as a conference abstract - downgraded 1 level
- **e** Heterogeneity was high at \( I^2 = 72\% \) - downgraded 1 level
BACKGROUND

Description of the condition

Neonatal hypoglycaemia is a common condition affecting 5% to 15% of infants in the immediate postnatal period (Cornblath 2000; Hay 2009; McGowan 2006). Neonatal hypoglycaemia is important because it can be associated with brain injury (Kerstjens 2012; Koh 1988; Lucas 1988) and poor later school performance (Kaiser 2015), although these associations are not consistently reported (Tin 2012). The incidence of this disorder is likely to be on the rise, as factors that predispose infants to hypoglycaemia are increasing, including preterm birth (Blencowe 2012), maternal diabetes (Wild 2004) and obesity (Doherty 2006). Risk factors for neonatal hypoglycaemia are known, and specific groups of infants are routinely targeted for screening (infants of diabetic mothers, high or low birthweight babies, preterm infants and those with poor feeding). Less common causes include hyperinsulinism and disorders of fatty acid oxidation. Neonatal hypoglycaemia is reported more commonly at maternity hospitals in resource-poor settings (Anderson 1993). Screening of capillary heel-lance blood samples is usually performed because associated clinical signs are not diagnostically helpful. The accuracy of screening blood tests varies with the method of measurement used; point-of-care testing systems have a greater error range than laboratory systems based on glucose oxidase methods (Beardell 2010). The definition of hypoglycaemia remains controversial (Hay 2009), and different publications have used definition thresholds ranging from 1.7 to 2.6 mmol/L (Agrawal 2000; Anderson 1993; Hol trop 1993; Hume 1999; Lubchenco 1971; Maayan-Metzger 2009; Pildes 1967; Sexson 1984). Several different clinical thresholds for treatment have been suggested (Adamkin 2011; Cornblath 2000; Thornton 2015), but a blood glucose concentration < 2.6 mmol/L is widely accepted as the definition of hypoglycaemia (Harris 2014); observations indicate that concentrations below this may be associated with altered brain function and delayed development (Koh 1988; Lucas 1988).

Upon diagnosis, infants are frequently managed with increased feeding, supplemental infant formula or intravenous (IV) dextrose. Supplemental infant formula may disrupt establishment of breast feeding (Blomquist 1994). Intravenous treatment is expensive, usually requires separation of mother and infant and is not always available in resource-poor settings (Graz 2008), or in settings providing lower levels of perinatal care. The World Health Organization (WHO) recommends breast feeding for all infants up to six months of age (WHO 2008), and the health benefits of breast feeding for both mother and infant are well recognised. Human studies have shown that breast milk volume in the first 24 postpartum hours is low and progressively increases by day 3 (Kulski 1981; Le Huerou-Luron 2010; Saint 1984). The concentration of lactose within breast milk is also low in the first 24 hours (Kulski 1981; Saint 1984) and steadily increases over the first three days. Therefore, at-risk infants may be at increased risk of severe and prolonged episodes of hypoglycaemia if they are solely breast fed.

One prospective study sought to reduce the incidence of neonatal hypoglycaemia by establishing breast feeding within 30 minutes of birth (Chertok 2009). Investigators measured blood glucose concentrations at three hours of age in 84 term infants born to women with gestational diabetes, and noted less hypoglycaemia among infants who were breast fed early. Therefore, early feeding may reduce the incidence of neonatal hypoglycaemia.

Formula milk is often given to hypoglycaemic infants, although no studies have reported on this treatment. The carbohydrate content of breast milk on the first day is low (Saint 1984); therefore, formula milk may be more effective than breast milk as treatment for infants with neonatal hypoglycaemia.

In India, researchers conducted two trials aimed at preventing hypoglycaemia in both small and large for gestational age infants by feeding with extra sugar. Infants with a blood glucose concentration \(\leq 30\) mg/dL (1.6 mmol/L) measured by Dextrostix (Ames Dextrometer; Ames Company, Elkhart, IN, USA) at less than 30 minutes of age were randomised to be fed formula alone or formula plus added powdered sugar (1.5 g/30 mL). Both studies showed that hypoglycaemia was reduced four-fold in the group receiving additional sugar (Singhal 1991; Singhal 1992).

If feeding does not improve the blood glucose concentration, the next step is often admission to the neonatal intensive care unit (NICU) for IV dextrose. A bolus of 200 mg/kg/min of 10% dextrose followed by an IV infusion of 8 mg/kg/min increases the blood glucose concentration within one minute, without causing hyperglycaemia (Lilien 1977; Lilien 1980).

Investigators in a randomised controlled trial assessed intravenous dextrose and glucagon (200 mcg/kg) or intragastric medium chain triglycerides (5 mL/kg) (Hawdon 1993). Both treatments substantially increased the blood glucose concentration among infants already receiving 5 mg/kg/min IV dextrose for hypoglycaemia.

Brain injury resulting from hypoglycaemia may be evident on magnetic resonance imaging (MRI). Whereas early publications focused on the occipital cortex as the prime site of injury (Alkalay 2005), more recent reports have suggested other possible sites of injury (Burns 2008). Injury is particularly evident with co-morbidities of hypoxic ischaemic encephalopathy and sepsis (Caksen 2011).

Description of the intervention

Dextrose gel contains dextrose, a simple carbohydrate, in concentrated aqueous solution, which can be administered by direct application to mucosal surfaces of the mouth, including buccal and lingual surfaces. Absorption from these sites may allow rapid access to the circulation. Some proportion of the dose may be swallowed and absorbed from the gastrointestinal tract.
Commercial preparations of dextrose gel are widely available, as they are commonly used for management of hypoglycaemia in patients with diabetes. Many preparations contain preservatives and flavour additives as well as gelling agents, requiring individual assessment for suitability in neonates. Dextrose gel can be manufactured by hospital pharmacies with appropriate facilities. Costs for neonatal doses are low (a few dollars or less per dose), and adverse effects have not been reported.

In infants with hypoglycaemia, simple treatment with dextrose gel and potential avoidance of more complex treatments, such as IV dextrose or complementary milks, would provide an attractive option, if effective. Dextrose gel is typically available in 40 g/100 mL form (40%) and is administered at doses of 200 to 400 mg/kg. Two observational studies suggest that it may be helpful for treatment of individuals with hypoglycaemia, and these studies report no adverse effects (Ang 1990; Bourchier 1992).

How the intervention might work
Dextrose may be absorbed directly from the oral mucosa, thus bypassing the portal circulation and gaining more rapid access to the circulation. Dextrose is rapidly absorbed by the gastrointestinal mucosa because it does not require digestion; it may then be taken up by the liver via the portal circulation and hence may have a more delayed effect on blood glucose concentrations.

Why it is important to do this review
Treatment of the neonate with hypoglycaemia usually involves additional feeding, often with formula milk, with the potential for an adverse impact on the quality and duration of breast feeding. If feeding is not effective, IV dextrose is usually administered, commonly requiring admission to the NICU and resulting in separation of mother and infant, impaired initiation of breast feeding and increased healthcare costs.

Dextrose gel is inexpensive and simple to administer. It may be effective in treating infants with neonatal hypoglycaemia without adverse effects. Further, dextrose gel can be used in resource-poor settings in which higher levels of neonatal care are unavailable, and it may prevent brain damage caused by untreated neonatal hypoglycaemia.

OBJECTIVES
To assess the effectiveness of dextrose gel in correcting hypoglycaemia and in reducing long-term neurodevelopmental impairment.

METHODS

Criteria for considering studies for this review

Types of studies
Randomised controlled trials (RCTs) and quasi-RCTs comparing dextrose gel versus placebo, no treatment or other therapies for neonatal hypoglycaemia. We planned to include published studies, unpublished studies and studies published only as abstracts, if assessment of study quality was possible and if other inclusion criteria were fulfilled.

Types of participants
We included newborn infants from birth to discharge home who were hypoglycaemic (blood glucose concentrations below the normal range, investigator defined) for any reason. We excluded infants who had received prior IV treatment for maintenance of glucose control at the time of hypoglycaemia.

Types of interventions
Dextrose gel, at any dose, given orally compared with placebo, no treatment or other therapies (including IV bolus), at any postmenstrual or postnatal age. The dextrose gel product could be locally prepared or provided commercially.

Types of outcome measures

Primary outcomes
- Correction of hypoglycaemia (investigator defined) for each event of hypoglycaemia (event outcome).
- Major neurological disability at age two years or older (defined as any of the following: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, developmental delay/intellectual impairment (defined as developmental quotient less than two standard deviations (SDs) below the mean) (child outcome).

Secondary outcomes
- Receipt of intravenous treatment for hypoglycaemia (yes/no) (infant outcome).
- Requirement for any medications for hypoglycaemia such as glucagon or corticosteroids (yes/no) (infant outcome).
- Number of episodes of hypoglycaemia (investigator defined) (infant outcome).
- Improved blood glucose to greater than 2.6 mmol/L (yes/no) (event outcome).
Rebound hypoglycaemia (investigator defined hypoglycaemia occurring within six hours of initial correction) (yes/no) (event outcome).

• Increase in blood glucose after treatment (change in blood glucose concentration 30 to 90 minutes after treatment) (event outcome).

• Duration of hypoglycaemia (time from detection of hypoglycaemia to achievement of blood glucose concentration above the threshold definition, minutes) (event outcome).

• Adverse effects (e.g. choking or vomiting at time of administration) (yes/no) (infant outcome).

• Separation from mother for treatment of hypoglycaemia (infant nursed in an environment that is not in the same room as the mother, e.g. for NICU admission or the like) (yes/no) (infant outcome).

• Neonatal seizures (yes/no) (infant outcome).

• Abnormal MRI of the brain in the neonatal period - investigator defined (yes/no) (infant outcome).

• Duration of initial hospital stay (days) (infant outcome).

• Breast feeding (any) after discharge (yes/no) (infant outcome).

• Exclusive breast feeding after discharge - WHO 2008 definition (yes/no) (infant outcome).

• Exclusive breast feeding at six months of age - WHO 2008 definition (yes/no) (infant outcome).

• Developmental disability at age two years or older - investigator defined (yes/no) (child outcome).

• Cerebral palsy and severity at age two years or older (child outcome).

• Hearing impairment and severity at age two years or older (child outcome).

• Cerebral palsy and severity at age two years or older (child outcome).

• Developmental delay/intellectual impairment and severity at age two years or older (child outcome).

• Executive dysfunction and severity at age two years or older (child outcome).

• Behavioural problems and severity at age two years or older (child outcome).

• Abnormal MRI of the brain at age two years or older (child outcome).

• Visual impairment and severity at age two years or older (child outcome).

• Hearing impairment and severity at age two years or older (child outcome).

• Cerebral palsy and severity at age two years or older (child outcome).

• Developmental delay/intellectual impairment and severity at age two years or older (child outcome).

• Executive dysfunction and severity at age two years or older (child outcome).

• Behavioural problems and severity at age two years or older (child outcome).

• Abnormal MRI of the brain at age two years or older (child outcome).

Search methods for identification of studies

Electronic searches

We were assisted in a search of the Cochrane Neonatal Review Group Specialised Register. We undertook a search of MEDLINE, EMBASE, the Central Register of Controlled Trials (CENTRAL), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Web of Science from inception of the database to 29 February 2016. We undertook a search of registries of clinical trials for any evidence of work in progress, or prior work planned, for which no results were published. We handsearched proceedings of relevant scientific meetings - American Academy of Pediatrics (2000 to 2014), European Society for Pediatric Research (2006 to 2015), Perinatal Society of Australia and New Zealand (2002 to 2015). We applied no language restrictions.

We used the following key words in our search: hypoglycaemia OR hypogly$, AND neonate OR neonat$, AND dextrose gel. We used “*” as a wild card character when appropriate. We ensured that we searched both American and English spellings.

We permitted the newborn period to refer to the time infants were admitted at or soon after birth and remained in their neonatal admission until first discharge home. We limited our search to potentially eligible randomised clinical trials by using a maximally sensitive method filter (see Appendix 1).

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov, World Health Organization International Trials Registry and Platform www.who.int/ictrp/search/en/ and the ISRCTN Registry).

Selecting other resources

We searched the reference lists of included trials and contacted known researchers in this clinical area to identify unpublished or ongoing research.

Data collection and analysis

Selection of studies

Two review authors (PW, DH) independently undertook the following steps.

• Merged search results using reference management software, and removed duplicate records of the same report.

• Examined titles and abstracts to remove obviously irrelevant reports.

• Retrieved full texts of potentially relevant reports.

• Linked together multiple reports of the same study.

• Examined full-text reports for compliance of studies with eligibility criteria.

• Corresponded with investigators, when appropriate, to clarify study eligibility, and, when possible, to obtain missing results.

• Made final decisions on study inclusion and proceeded to data collection.

Review authors encountered no disagreements in selection of studies.
Data extraction and management
We developed and piloted a data extraction form before gathering data (Appendix 2). We extracted data such as source details, eligibility assessment, methodological features, participant characteristics, intervention details and outcome reports. Two review authors independently extracted data. Two review authors not associated with the study (JB, JHegarty) extracted data from the "Sugar Babies Study" (Harris 2013). We referred discrepancies in data extraction to a third review author (MB) for resolution. We entered data into the statistical software of The Cochrane Collaboration (Review Manager 2013) and checked them for accuracy.

Assessment of risk of bias in included studies
Two review authors independently assessed risk of bias for each study by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Assessors for Troughton 2000 (PW, DH) were different from those for Harris 2013 (JB, JHegarty). We encountered no disagreements.

Random sequence generation (checking for possible selection bias)
For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow assessment of whether it should produce comparable groups. We assessed the method as having:
- low risk of bias (any truly random process, e.g. random number table, computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth, hospital or clinic record number); or
- unclear risk of bias.

Allocation concealment (checking for possible selection bias)
For each included study, we described the method used to conceal allocation to interventions before assignment and assessed whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We assessed the method as having:
- low risk of bias (e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation, e.g. unsealed or non-opaque envelopes, alternation, date of birth); or
- unclear risk of bias.

Blinding of participants and personnel (checking for possible performance bias)
For each included study, we described the methods used, if any, to blind study participants and personnel from which intervention a participant received. We considered studies to be at low risk of bias if they were blinded, or if we judged that lack of blinding would be unlikely to affect results.

We assessed the method as having:
- low, high or unclear risk of bias for participants; and
- low, high or unclear risk of bias for personnel.

Blinding of outcome assessment (checking for possible detection bias)
For each included study, we described the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed methods used to blind outcome assessment as having low, high or unclear risk of bias.

Incomplete outcome data (checking for possible attrition bias due to the quantity, nature and handling of incomplete outcome data)
For each included study, we described completeness of data including attrition and exclusions from analysis. We stated whether attrition and exclusions were reported as well as numbers included in the analysis at each stage (compared with total randomised participants), reasons for attrition or exclusion when reported and whether missing data were balanced across groups or were related to outcomes. When sufficient information was reported, we planned to re-include missing data in the analyses undertaken. We assessed the method as having:
- low risk of bias (e.g. no missing outcome data, missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups, ‘as treated’ analysis done with substantial departure of intervention received from intervention assigned at randomisation); or
- unclear risk of bias.

Other sources of bias
We described for each included study any important concerns we had about other possible sources of bias. We assessed whether each study was free of other problems that could put it at risk of bias.
- Low risk of other bias.
- High risk of other bias.
- Unclear risk of other bias.

Measures of treatment effect
We used the numbers of events in control and intervention groups of each study to calculate risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous data. We calculated mean differences (MDs) between treatment groups when outcomes were measured in the same way for continuous data. We reported 95% CIs for all outcomes and risk differences (RDs); when a significant effect was found, we calculated numbers needed to treat for...
additional beneficial outcomes (NNTBs) or numbers needed to treat for additional harmful outcomes (NNTHs).

**Unit of analysis issues**
For some specific measures (related to correction of hypoglycaemia), the unit analysed was the hypoglycaemic event itself. For other measures that determined outcomes for the infant (such as those related to breast-feeding and developmental outcomes), the unit analysed was the infant.

**Dealing with missing data**
We noted whether levels of attrition applied. When possible, we carried out analyses on an intention-to-treat basis for all outcomes and analysed all participants in the treatment group to which they were randomised, regardless of the actual treatment received. We attempted to contact the original investigators to request missing data, when possible. Sensitivity analyses were permitted to assess how sensitive results were to reasonable changes in assumptions made. We addressed in the Discussion section the potential impact of missing data on review findings, when relevant.

**Assessment of heterogeneity**
We considered whether clinical and methodological characteristics of included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We did this by assessing statistical heterogeneity using the Chi² test and the I² statistic. We classified heterogeneity as none (< 25%), low (25% to 49%), moderate (50% to 74%) or high (> 75%). We considered an I² measurement greater than 50% and a low P value (< 0.10) in the Chi² test for heterogeneity to indicate substantial heterogeneity (Higgins 2011). When we detected substantial heterogeneity, we explored possible explanations in sensitivity/subgroup analyses. We considered statistical heterogeneity when interpreting study results, especially when we noted variation in the direction of effect.

**Assessment of reporting biases**
Reporting biases arise when dissemination of research findings is influenced by the nature and direction of results. Some types of reporting bias (e.g., publication bias, multiple publication bias, language bias) reduce the likelihood that all studies eligible for a review will be retrieved. If all eligible studies are not retrieved, the review may be biased. We aimed to conduct a comprehensive search for eligible studies and remained alert for duplication of data. We planned to assess publication bias by visually inspecting a funnel plot, if we identified enough studies (≥ 10 trials) to make such an inspection valid.

Two review authors examined the methods of each study for pre-specified outcomes. If all pre-specified outcomes were reported in the results, we assigned the study low risk of bias. If any pre-specified outcomes were not reported in the results, we considered the study to carry higher risk of bias. If review authors uncovered reporting bias that could, in their opinion, introduce serious bias, we planned to conduct a sensitivity analysis to determine the effects of including and excluding these studies in the analysis.

**Data synthesis**
We evaluated studies for potential clinical diversity, and we restricted meta-analysis to studies in which clinical consistency was apparent. We evaluated studies for bias, as above, and restricted meta-analysis if bias would be compounded. We used a fixed-effect meta-analysis to combine data when it was reasonable to assume that studies were estimating the same underlying treatment effects. If evidence of clinical heterogeneity was sufficient to suggest that underlying treatment effects differed between trials, or if we detected substantial statistical heterogeneity, we planned to undertake sensitivity and subgroup analyses to attempt to explain the heterogeneity.

**Quality of evidence**
We assessed the quality of evidence for main comparisons at the outcome level by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2011a). This methodological approach considers the quality of evidence from randomised controlled trials as high with the potential for downgrading based on consideration of any of five areas: design (risk of bias), consistency across studies, directness of evidence, precision of estimates and presence of publication bias (Guyatt 2011a). The GRADE approach yields an assessment of the quality of a body of evidence according to the following grades. (1) High: We are very confident that the true effect lies close to that of the estimate of effect. (2) Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect but may be substantially different. (3) Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect. (4) Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect (Schünemann 2013).

Review authors independently assessed the quality of evidence found for outcomes identified as critical or important for clinical decision making. These outcomes include the following.
- Correction of hypoglycaemia (investigator defined) for each hypoglycaemic event.
- Major neurological disability at age two years or older (defined as any of the following: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, developmental delay/intellectual impairment (defined as developmental quotient less than two SDs below the mean)).
- Receipt of intravenous treatment for hypoglycaemia.
Adverse effects of dextrose gel (e.g. choking or vomiting at time of administration).

Separation from mother for treatment of hypoglycaemia (infant nursed in an environment that is not in the same room as the mother, e.g. for NICU admission or the like).

Exclusive breast feeding after discharge - WHO 2008 definition.

In cases in which we considered risk of bias arising from inadequate concealment of allocation, randomised assignment, complete follow-up or blinded outcome assessment to reduce our confidence in effect estimates, we downgraded the quality of evidence accordingly (Guyatt 2011b). We evaluated consistency through similarity of point estimates, extent of overlap of confidence intervals and statistical criteria including measurement of heterogeneity ($I^2$). We downgraded the quality of evidence when we detected large and unexplained inconsistency across studies (i.e. some studies suggest important benefit, and others no effect or harm, without a clinical explanation) (Guyatt 2011d). We assessed precision by determining width of the 95% confidence interval (CI) and by calculating the optimal information size (OIS). If the total number of participants included in the pooled effect estimation was less than the number generated by a conventional sample size calculation for a single adequately powered trial, we considered rating down for imprecision (Guyatt 2011c). When trials were conducted in populations other than the target population, we downgraded the quality of evidence because of indirectness (Guyatt 2011e).

We entered data (i.e. pooled estimates of effects and corresponding 95% confidence Interval) and explicit judgements for each of the above aspects assessed into the Guideline Development Tool - the software used to create ‘Summary of findings’ tables (GradePro GDT). We explained in footnotes or in comments included in the ‘Summary of findings’ table all judgements involving assessment of the study characteristics described above.

Subgroup analysis and investigation of heterogeneity
If we identified substantial heterogeneity, we planned to investigate this by using subgroup and sensitivity analyses. We planned to carry out the following subgroup analyses.

Infant factors
- Reason for risk of hypoglycaemia (infant of diabetic mother, preterm, small, large, other).
- Method used to measure blood glucose concentration (reliable instrument using glucose oxidase method vs less reliable cot-side approaches).
- Treatment of first episode of hypoglycaemia versus any subsequent episodes.
- Dextrose gel as the only intervention versus dextrose gel administered as a co-intervention (e.g. in addition to formula feeds).

Event factors
- Method of feeding at the time of the event (formula vs breast feeding vs mixed vs nil vs other).
- Method of administration of gel (buccal mucosa vs lingual mucosa vs other).
- Dose of dextrose per administration ($\leq$ 200 mg/kg vs $>$ 200 mg/kg).
- Maximum number of doses for treatment of a single episode of hypoglycaemia (1 vs $>$ 1).

Sensitivity analysis
We conducted sensitivity analysis by examining only trials considered to have low risk of bias.

RESULTS

Description of studies

Results of the search
We presented search strategy details in Appendix 1. This search was run on 14 June 2014, and an updated search on 29 February 2016. We identified 26 potential publications through database searching and an additional three potential publications through other sources. After we removed duplicates, we screened a total of 13 potential publications. We excluded eight publications at this point, as they were irrelevant; five were abstracted summaries or commentaries of the Harris 2013 paper (Anon 2013; Anon 2014; Badulek 2014; Mosalli 2014; Retbi 2013). We assessed five publications for eligibility - four published trials (Harris 2013; Harris 2014; Harris 2016; Troughton 2000) and one ongoing trial identified from ClinicalTrials.gov (NCT02523222). Three of the publications reported the same trial (Harris 2013) and were also reported as conference abstracts (Harris 2014) and as a two-year follow-up paper (Harris 2016). We had prior knowledge of the Troughton abstract (Troughton 2000), and a subgroup of the authors of this systematic review were involved in the trial (Harris 2013; Harris 2014; Harris 2016). We presented the results of these searches in the study flow diagram (Figure 1).
Figure 1. Study flow diagram.

26 records identified through database searching

3 additional records identified through other sources

13 records after duplicates removed

6 records excluded as irrelevant or not randomised controlled trials

13 records screened

2 full-text articles and 2 abstracts assessed for eligibility.

1 registered randomised trial

2 studies included in qualitative synthesis

2 studies included in quantitative synthesis (meta-analysis)
Included studies
We included two studies in this review (see Characteristics of included studies).

The largest study (Harris 2013) enrolled 514 infants ≥ 35 weeks’ gestation and recognised as being at risk for hypoglycaemia in the first 48 hours after birth. This study was undertaken at a tertiary maternity hospital in New Zealand. Investigators randomised 242 infants who became hypoglycaemic - 118 infants to receive 40% dextrose gel 0.5 mL/kg, massaged into the buccal mucosa followed by a milk feed of maternal choice, and 119 infants to receive placebo gel 0.5 mL/kg with a milk feed of maternal choice (five additional infants were randomised in error). Researchers checked the blood glucose concentration again after 30 minutes and repeated treatment if the blood glucose concentration remained < 2.6 mmol/L. The primary outcome was failure to restore the blood glucose concentration to ≥ 2.6 mmol/L after up to two doses of gel. The main result was that dextrose gel reduced the frequency of treatment failure compared with placebo (14% vs 29%; P value = 0.04). Outcomes at 2 years’ corrected age were reported for infants who had participated in this study (Harris 2014; Harris 2016). Investigators reported a 78% follow-up rate, with neurosensory disability defined as cognitive, language or motor score below -1 SD, or cerebral palsy, blindness or deafness. Processing disorder was a composite outcome defined as clinically assessed executive function or a global motion coherence perception threshold worse than 1.5 SD from the mean.

The earlier study (Troughton 2000) involved 75 infants on day 1 who were ≥ 36 weeks’ gestation. In this single-centre study from Northern Ireland, infants were randomised to receive 1 mL/kg of 40% dextrose gel massaged into the buccal mucosa plus a feed (n = 39), or a feed alone (n = 36). The primary outcome was the change in blood glucose concentration at 15 and 30 minutes after treatment. Results showed an additional increase of 0.4 mmol/L for the dextrose gel group over the control group at both times (P values = 0.1 and 0.2). Secondary outcomes were subsequent requirement for intravenous dextrose and volume of the next feed taken for bottle fed infants. Results showed no differences in the requirement for IV dextrose (33% vs 26%; P value = 0.7), but infants randomised to dextrose gel took a smaller volume of formula at the next oral feed (7.6 mL/kg vs 13.1 mL/kg; P value = 0.001).

Excluded studies
We excluded no studies.

Risk of bias in included studies
We determined that the Harris 2013 study had low risk of bias. Investigators fully described randomisation and blinding and used computer-generated blocked randomisation with variable block sizes. Researchers maintained allocation concealment until data analysis was complete. They excluded from the analysis five infants randomised in error. At two years, investigators followed up on 76% of the original trial cohort (90/118 who had been randomised to the dextrose gel group, and 94/119 to the placebo gel group). They assessed neurosensory and developmental outcomes and confirmed the blinding status of study assessors as satisfactory. The Troughton 2000 abstract provides insufficient detail to reveal any of the components of risk of bias but presents numbers indicating that some unexplained attrition is likely. We summarised bias assessments in Figure 2 and Figure 3.
Effects of interventions

Dextrose gel versus control

See: Summary of findings for the main comparison Dextrose gel versus control (placebo gel)

Primary outcomes
- Correction of hypoglycaemic events - No data were reported for this outcome.
- Major neurological disability at two years of age - No evidence suggests a difference between dextrose gel (6/90) and placebo gel groups (1/94) for major neurological disability at two years of age (RR 6.27, 95% CI 0.77 to 51.03; one study, n = 184 children; quality of evidence very low). Caution is required when these results are interpreted because of the wide confidence intervals, the small sample size and the low event rates indicative of imprecision. The GRADE method suggests that if major neurological disability occurs at two years of age in 11% of infants who received placebo gel, then between 8% and 54% would have a major neurological disability at two years of age after receiving dextrose gel (Summary of findings for the main comparison).

Secondary outcomes
- Receipt of intravenous treatment for hypoglycaemia - Dextrose gel did not alter the need for intravenous treatment for hypoglycaemia (RR 0.81, 95% CI 0.29 to 2.25; two studies, 213 infants; quality of evidence very low). This suggests that if receipt of intravenous treatment for hypoglycaemia was required by 17% of infants following placebo gel, then between 5% and 38% would require receipt of intravenous treatment for hypoglycaemia following dextrose gel (Summary of findings for the main comparison). The two included studies provided estimates in opposite directions, but neither study provided findings that showed independent statistical significance. One trial was at low risk of bias for all domains, and one was at high risk of attrition bias and unclear risk of bias for the remaining domains. Heterogeneity was high (I² = 72%), and one trial was published in full (Harris 2013), while one was presented in abstract form (Troughton 2000).
- Receipt of any medications for hypoglycaemia such as glucagon or corticosteroids - No data were reported for this outcome.
- Number of episodes of hypoglycaemia - No data were reported for this outcome.
- Improved blood glucose to greater than 2.6 mM/L - No data were reported for this outcome.
- Rebound hypoglycaemia (occurring within six hours of initial correction) - No data were reported for this outcome.
- Increased blood glucose after treatment - Dextrose gel compared with placebo gel did not result in a significantly different increase in blood glucose concentration 30 to 90 minutes after treatment (MD 0.4 mmol/L, 95% CI -0.1 to 0.94; one study, 75 infants).
- Duration of hypoglycaemia (time from detection of hypoglycaemia to blood glucose concentration above the threshold definition) - No data were reported for this outcome.
- Adverse effects - Harris 2013 reported no adverse effects in the dextrose gel or placebo gel group (Summary of findings for the main comparison).
- Separation from mother for treatment of hypoglycaemia - Dextrose gel compared with placebo gel reduced the incidence of separation of mother and infant for treatment of hypoglycaemia (RR 0.54, 95% CI 0.31 to 0.93; one study, 237 infants; quality of evidence moderate). This suggests that if 25% of infants were separated from mother for treatment of hypoglycaemia after placebo gel, then between 8% and 23% would be separated from mother for treatment of hypoglycaemia after receiving dextrose gel (Summary of findings for the main comparison). The number needed to treat to prevent one such separation was 9, but in this study, the overall incidence of separation for all reasons - not just hypoglycaemia - was not different between the two groups (RR 0.83, 95% CI 0.61 to 1.11).
- Neonatal seizures - No seizures occurred in the dextrose gel or placebo group in the one study that reported this outcome (one study, 237 infants). Therefore, the odds ratio is not estimable.
- Abnormal MRI of the brain in the neonatal period - No data were reported for this outcome.
- Duration of initial hospital stay (days) - No data were reported for this outcome.
- Breast feeding (any) after discharge - No data were reported for this outcome.
- Exclusive breast feeding after discharge (WHO 2008 definition) - Dextrose gel compared with placebo gel increased the likelihood of exclusive breast feeding at two weeks of age (RR 1.10, 95% CI 1.01 to 1.18; one study, 237 infants, NNTB = 12; quality of evidence moderate). This suggests that if 87% of infants were exclusively breast fed after discharge following placebo gel, then between 88% and 100% would be exclusively breast fed after discharge following dextrose gel (Summary of findings for the main comparison).
- Exclusive breast feeding at six months of age (WHO 2008 definition) - No data were reported for this outcome.
- Developmental disability at age two years or older - No evidence revealed a difference between dextrose gel and placebo gel groups for overall developmental disability (including mild, moderate and severe) (RR 1.11, 95% CI 0.75 to 1.63; one study, n = 184 children).
- Visual impairment and severity at age two years or older - No evidence suggested differences between dextrose gel and placebo gel groups for vision problems (RR 1.17, 95% CI 0.72 to 1.89; one study, n = 183 children).
- Hearing impairment and severity at age two years or older - No data were reported for this outcome.
- Cerebral palsy and severity at age two years or older - No evidence revealed a difference between dextrose gel and placebo gel groups for cerebral palsy (RR 5.16, 95% CI 0.25 to 106.12; one study, n = 183). Caution is required when these results are interpreted because of the wide confidence intervals, the small
sample size and the low event rates indicative of imprecision.

- Developmental delay/intellectual impairment and severity at age two years or older - No evidence suggests a difference between dextrose gel (34/90) and placebo gel groups (32/94) for any developmental impairment (including mild, moderate and severe) (RR 1.07, 95% CI 0.71 to 1.61; one study, n = 183 children). No evidence revealed a difference between dextrose gel and placebo gel groups for any of the composite scores of the Bayley III scale.
  - Cognitive (MD -1.00, 95% CI -3.92 to 1.92; one study, n = 183 children).
  - Language (MD 0.00, 95% CI -3.93 to 3.93; one study, n = 182 children).
  - Motor (MD 0.00, 95% CI -2.76 to 2.76; one study, n = 183 children).
  - Social emotional (MD 1.00, 95% CI -3.56 to 5.56; one study, n = 178 children).
  - General adaptive (MD 2.00, 95% CI -1.95 to 5.95; one study, n = 180 children).
- Executive dysfunction and severity at age two years or older - No evidence revealed a difference between dextrose gel and placebo gel groups for executive functioning composite score (MD 0.90, 95% CI -0.29 to 2.09; one study, n = 179 children) and the Behavior Rating Index of Executive Function for Preschool (BRIEF-P Index) - Global Executive Composite score (MD 2.00, 95% CI -1.20 to 5.20; one study, n = 182 children).
- Behavioural problems and severity at age two years or older - No data were reported for this outcome.
- Abnormal MRI of the brain at age two years or older - No data were reported for this outcome.

**DISCUSSION**

**Summary of main results**

Use of dextrose gel compared with placebo or no gel for the treatment of newborn infants with hypoglycaemia reduced maternal-infant separation and improved the rate of exclusive breast feeding after discharge, without altering the rate of developmental impairment at two years (Summary of findings for the main comparison). We found no data regarding effective correction of events of hypoglycaemia.

**Overall completeness and applicability of evidence**

Data were not available for many outcomes of interest; it is expected that these data will become available in the future. However, study findings of reduced maternal-infant separation and improved breast feeding after discharge are important indicators of the utility of dextrose gel, especially in the light of absence of evidence of adverse effects during the neonatal period and at two years of age. These outcomes are sufficient to warrant consideration of dextrose gel as a first-line treatment for infants with neonatal hypoglycaemia. The simplicity of this treatment suggests that it may have wide applicability at various levels of care and in international settings, limited only by the ability of care providers to measure blood glucose concentrations.

**Quality of the evidence**

In the only outcome measure for which data from the two studies could be pooled (receipt of intravenous treatment), estimates of effect were opposite and revealed no statistically significant differences.

Data on the remaining four available outcomes were derived from single studies only (three from Harris 2013, one from Troughton 2000).

**Potential biases in the review process**

Bias associated with Troughton 2000 is uncertain, and we could obtain no further information from the original study authors. We judged bias associated with Harris 2013 to be of low likelihood for the neonatal study and for follow-up of the cohort (Harris 2016). We considered bias associated with non-discovery of published research to be low. Our search did not reveal all of the publications known to the review authors, nor did it identify a key publication (Troughton 2000) that was included in this review. However, the authors of this review consider the likelihood of undiscovered relevant work to be very low.

**Agreements and disagreements with other studies or reviews**

No other reviews have examined this topic. Ang 1990 reported in a non-randomised evaluation that 14/20 infants responded with a mean increase in blood glucose concentration of 1.8 mmol/L at 20 minutes after gel dose 0.5 mL/kg, which was maintained at 30 minutes. Bourchier 1992 reported in a non-randomised evaluation that 88/132 events of hypoglycaemia were satisfactorily treated with dextrose gel 0.5 mg/kg, but investigators included no comparison group.

**AUTHORS’ CONCLUSIONS**
Implications for practice

Only one trial is available to support the finding that dextrose gel given for treatment of neonatal hypoglycaemia is helpful in reducing maternal-infant separation for hypoglycaemia and in supporting breast feeding after discharge. This trial reported no adverse effects during the neonatal period nor at two-year follow-up. Given its simplicity and wide applicability, we considered these outcomes sufficient to support consideration of the use of dextrose gel for initial treatment of infants with neonatal hypoglycaemia during the first 48 hours after birth.

Available evidence derived from a group of at-risk infants born at \( \geq 35 \) weeks' during the first 48 hours after birth does not support extrapolation to circumstances other than this.

Implications for research

Data on the key outcomes of this review are limited. Future studies should use robust methods, report clinically relevant outcomes such as those indicated in this review and ensure that enrolled infants are followed up with standardised tools used to assess beneficial or adverse effects on later neurodevelopment. The potential for improved neurodevelopmental outcomes following rescue treatment is likely to be most pertinent to resource-poor settings, where alternative rescue treatments such as intravenous dextrose may be less available. Future studies should evaluate both event-based and infant-based outcomes, and should examine the use of dextrose gel in a variety of settings and patient groups.

ACKNOWLEDGEMENTS

We acknowledge the support of the editorial base and Professor Caroline Crowther for advice and support provided during preparation of this review.

We acknowledge the expertise of Dr William W Hay, Jr, who served as the external referee for the review.

REFERENCES

References to studies included in this review

Harris 2013 {published data only}


Troughton 2000 {published data only}

References to ongoing studies

NCT02523222 {unpublished data only}

[NCT02523222]

Additional references

Adamkin 2011

Agrawal 2000

Alkalay 2005

Anderson 1993

Ang 1990

Anon 2013

Anon 2014
oral dextrose gel for the treatment of hypoglycaemia in newborn infants (Review)

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17
Oral dextrose gel for the treatment of hypoglycaemia in newborn infants (Review)

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Hay 2009

Higgins 2011

Hol trop 1993

Hume 1999

Kaiser 2015

Kerstjens 2012

Koh 1988

Kulski 1981

Le Huerou-Luron 2010

Lilien 1977

Lilien 1980

Lubchenco 1971

Lucas 1988

Maayan-Metzger 2009

McGowan 2006

Mosalli 2014

Pildes 1967

Rethi 2013

Review Manager 2013 [Computer program]

Saint 1984

Schünemann 2013

Sexson 1984
Singhal 1991

Singhal 1992

Thornton 2015

Tin 2012

WHO 2008

Wild 2004

* Indicates the major publication for the study
### CHARACTERISTICS OF STUDIES

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

**Harris 2013**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>514 infants ≥ 35 weeks' gestation, &lt; 48 postnatal hours old and at risk for hypoglycaemia. Risk factors included a diabetic mother, small (birthweight &lt; 10th centile, or &lt; 2500 grams) or large (birthweight &gt; 90th centile or &gt; 4500 grams) size, preterm (35 or 36 weeks' gestation) birth and other reasons such as poor feeding.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Infants who became hypoglycaemic (&lt; 2.6 mmol/L) were encouraged to feed (determined by maternal choice) and were randomised to receive 40% dextrose gel (0.5 mL/kg) or placebo gel massaged into the buccal membrane. Blood glucose concentration was measured 30 minutes following gel treatment. Gel was repeated if hypoglycaemia persisted. A maximum of six doses of gel could be given within a 48 hour period.</td>
</tr>
</tbody>
</table>
| Outcomes      | Primary outcome  
  - Treatment failure defined as blood glucose concentration ≤ 2.6 mmol/L, 30 minutes after the second of 2 treatment doses of gel.  
  Secondary outcomes  
  - Admission to the newborn intensive care unit  
  - Frequency of breast feeding  
  - Total volume and frequency of expressed breast milk  
  - Total volume and frequency of infant formula  
  - Total volume and frequency of intravenous dextrose  
  - Total volume and frequency of dextrose gel  
  - Method of feeding 2 weeks after discharge  
  - Incidence of rebound and recurrent hypoglycaemia after successful treatment (defined as blood glucose > 2.6 mmol/L 30 minutes after treatment)  
  - Total duration of interstitial glucose concentrations < 2.6 mmol/L up to 48 hours after birth |
| Notes         | Blood glucose measured using glucose oxidase method. Funding sources included Waikato Medical Research Foundation, Auckland Medical Research Foundation, the Maurice and Phyllis Paykel Trust, the Health Research Council of New Zealand and the Rebecca Roberts Scholarship. Report of 2-year follow-up was published by Harris (2016), for which funding sources also included the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (R01HD0692201). Content of this report is solely the responsibility of study authors and does not necessarily represent the official views of funding bodies. |

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>

*Oral dextrose gel for the treatment of hypoglycaemia in newborn infants (Review)*

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| **Random sequence generation (selection bias)** | Low risk | Computer-generated blocked randomisation with variable block sizes |
| **Allocation concealment (selection bias)** | Low risk | Data entered into a computer, which provided a randomisation number corresponding to the numbered treatment pack |
| **Blinding of participants and personnel (performance bias)** | Low risk | Dextrose and placebo gels were identical in appearance. Clinicians, families and study investigators were masked to group allocation until data analysis was complete |
| **Blinding of outcome assessment (detection bias)** | Low risk | Study investigators were masked to group allocation until data analysis was complete |
| **Incomplete outcome data (attrition bias)** | Low risk | Five infants were randomised in error and were excluded from the analysis, leaving 118 infants in the dextrose gel group and 119 infants in the placebo gel group. Intention-to-treat analysis was conducted |
| **Selective reporting (reporting bias)** | Low risk | The only outcome not listed a priori was acceptability of the intervention. Otherwise all pre-specified outcomes were reported |
| **Other bias** | Low risk | A slightly greater number of mothers in the group allocated to dextrose gel than to placebo gel (114 of 115 vs 109 of 115) intended to breastfeed. Fewer boys were allocated to the dextrose gel group than to the placebo gel group (48 of 118 vs 65 of 119). Groups were otherwise balanced |

**Troughton 2000**

| **Methods** | Randomised controlled trial |
| **Participants** | 75 hypoglycaemic (< 2.5 mmol/L) infants ≥ 36 weeks’ gestation admitted to the newborn intensive care unit |
| **Interventions** | Hypostop (40% dextrose, 1 mL/kg) massaged into the buccal membrane plus a feed vs feeding alone |
| **Outcomes** | Primary outcome  
- Change in blood glucose concentration 15 and 30 minutes after treatment  
Secondary outcomes  
- Subsequent requirement for intravenous dextrose  
- Volume taken at the next feed following randomisation in bottle-fed infants |
Notes
Blood glucose analysed using the Hemocue point-of-care analyser
Funding sources not stated

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information available</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information available</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>No evidence of blinding</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No evidence of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>It seems likely that some attrition occurred, as findings are reported for 26% of control infants, and 26% of 36 infants cannot be resolved as a whole number</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No information available regarding baseline characteristics, risk factors for hypoglycaemia or differential diagnoses</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Available details insufficient for determination of risk of other bias</td>
</tr>
</tbody>
</table>

Characteristics of ongoing studies  [ordered by study ID]

NCT02523222

Trial name or title
Dextrose Gel for Newborn Hypoglycemia

Methods
Randomised placebo-controlled double-blinded study

Participants
Inclusion criteria
- Gestational age > 35 weeks
- Infants < 48 hours of age
- Infants with informed parental consent
- Infants with blood glucose level < 45 mg/dL
- Infants remaining in newborn nursery, Pavilion for Women Neonatal Intensive Care Unit (NICU) or West Tower Level IV NICU

Exclusion criteria
<table>
<thead>
<tr>
<th>Interventions</th>
<th>Dextrose gel (0.5 mL/kg) in the buccal mucosa vs placebo gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Primary outcome measures: treatment failure in hypoglycaemic infants (glucose level &lt; 45 mg/dL after 2 applications of dextrose gel or placebo gel, and admission to the NICU) Treatment failure for at-risk infants, defined as infants of diabetic mothers, late preterm, small for gestational age, large for gestational age, estimated foetal weight &lt; 2.5 kg or &gt; 4.5 kg, intrauterine growth restriction or poor feeding</td>
</tr>
<tr>
<td>Starting date</td>
<td>September 2015</td>
</tr>
<tr>
<td>Contact information</td>
<td>Principal Investigator: Jeffrey R Kaiser, Baylor College of Medicine</td>
</tr>
<tr>
<td>Notes</td>
<td>ClinicalTrials.gov NCT02523222</td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

**Comparison 1. Dextrose gel versus control**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Major neurosensory disability (2-year follow-up)</td>
<td>1</td>
<td>184</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>6.27 [0.77, 51.03]</td>
</tr>
<tr>
<td>2 Receipt of intravenous treatment for hypoglycaemia (for each infant)</td>
<td>2</td>
<td>312</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.81 [0.29, 2.25]</td>
</tr>
<tr>
<td>3 Increased blood glucose 30 to 90 minutes after treatment (by event)</td>
<td>1</td>
<td>75</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.40 [-0.14, 0.94]</td>
</tr>
<tr>
<td>4 Separation from mother for treatment of hypoglycaemia</td>
<td>1</td>
<td>237</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.54 [0.31, 0.93]</td>
</tr>
<tr>
<td>5 Neonatal seizures</td>
<td>1</td>
<td>237</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>6 Exclusive breast feeding after discharge (WHO definition)</td>
<td>1</td>
<td>237</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.10 [1.01, 1.18]</td>
</tr>
<tr>
<td>7 Developmental disability at age 2 years or older</td>
<td>1</td>
<td>184</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.11 [0.75, 1.63]</td>
</tr>
<tr>
<td>8 Visual impairment and severity at age 2 years or older</td>
<td>1</td>
<td>183</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.17 [0.72, 1.89]</td>
</tr>
<tr>
<td>9 Cerebral palsy and severity at age 2 years or older</td>
<td>1</td>
<td>183</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>5.16 [0.25, 106.12]</td>
</tr>
<tr>
<td>10 Developmental delay/intellectual impairment and severity at age 2 years or older</td>
<td>1</td>
<td>183</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.07 [0.71, 1.61]</td>
</tr>
<tr>
<td>11 Developmental impairments - Bayley III scores at 2-year follow-up</td>
<td>1</td>
<td>183</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>11.1 Cognitive</td>
<td>1</td>
<td>183</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-1.0 [-3.92, 1.92]</td>
</tr>
<tr>
<td>11.2 Language</td>
<td>1</td>
<td>182</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [-3.93, 3.93]</td>
</tr>
<tr>
<td>11.3 Motor</td>
<td>1</td>
<td>183</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [-2.76, 2.76]</td>
</tr>
<tr>
<td>11.4 Social emotional</td>
<td>1</td>
<td>178</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>1.0 [-3.56, 5.56]</td>
</tr>
<tr>
<td>11.5 General adaptive</td>
<td>1</td>
<td>180</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>2.0 [-1.95, 5.95]</td>
</tr>
<tr>
<td>12 Executive function (2-year follow-up)</td>
<td>1</td>
<td>179</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>12.1 Executive function composite score (2-year follow-up)</td>
<td>1</td>
<td>179</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.90 [-0.29, 2.09]</td>
</tr>
<tr>
<td>12.2 BRIEF-P Index - Global Executive Composite (2-year follow-up)</td>
<td>1</td>
<td>182</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>2.0 [-1.20, 5.20]</td>
</tr>
</tbody>
</table>
**Analysis 1.1.** Comparison 1 Dextrose gel versus control, Outcome 1 Major neurosensory disability (2-year follow-up).

Review: Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

Comparison: 1 Dextrose gel versus control

Outcome: 1 Major neurosensory disability (2-year follow-up)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dextrose gel</th>
<th>Control</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris 2013</td>
<td>6/90</td>
<td>1/94</td>
<td>100.0 %</td>
<td>6.27 [ 0.77, 51.03 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>90</strong></td>
<td><strong>94</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>6.27 [ 0.77, 51.03 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 6 (Dextrose gel), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.72 (P = 0.086)
Test for subgroup differences: Not applicable

**Analysis 1.2.** Comparison 1 Dextrose gel versus control, Outcome 2 Receipt of intravenous treatment for hypoglycaemia (for each infant).

Review: Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

Comparison: 1 Dextrose gel versus control

Outcome: 2 Receipt of intravenous treatment for hypoglycaemia (for each infant)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dextrose gel</th>
<th>Control</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris 2013</td>
<td>8/118</td>
<td>17/119</td>
<td>100.0 %</td>
<td>48.5 %</td>
<td>0.47 [ 0.21, 1.06 ]</td>
</tr>
<tr>
<td>Troughton 2000</td>
<td>13/39</td>
<td>9/36</td>
<td>100.0 %</td>
<td>51.5 %</td>
<td>1.33 [ 0.65, 2.74 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>157</strong></td>
<td><strong>155</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.81 [ 0.29, 2.25 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 21 (Dextrose gel), 26 (Control)
Heterogeneity: \( \tau^2 = 0.39; \chi^2 = 3.61, \text{df} = 1 (P = 0.06); I^2 = 72\%
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable
Analysis 1.3. Comparison 1 Dextrose gel versus control, Outcome 3 Increased blood glucose 30 to 90 minutes after treatment (by event).

Review: Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

Comparison: 1 Dextrose gel versus control

Outcome: 3 Increased blood glucose 30 to 90 minutes after treatment (by event)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dextrose gel</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)[mmol/l]</td>
<td>N Mean(SD)[mmol/l]</td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
<td></td>
</tr>
<tr>
<td>Troughton 2000</td>
<td>39 1.8 (1.2)</td>
<td>36 1.4 (1.2)</td>
<td>100.0 % 0.40 [-0.14, 0.94]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>39</td>
<td>36</td>
<td>100.0 % 0.40 [-0.14, 0.94]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 1.44 (P = 0.15)

Test for subgroup differences: Not applicable
### Analysis 1.4. Comparison 1 Dextrose gel versus control, Outcome 4 Separation from mother for treatment of hypoglycaemia.

Review: Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

Comparison: 1 Dextrose gel versus control

Outcome: 4 Separation from mother for treatment of hypoglycaemia

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dextrose gel</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Harris 2013</td>
<td>16/118</td>
<td>30/119</td>
<td>100.0 %</td>
<td>0.54 [ 0.31, 0.93 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>118</strong></td>
<td><strong>119</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.54 [ 0.31, 0.93 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 16 (Dextrose gel), 30 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 2.21 (P = 0.027)

Test for subgroup differences: Not applicable

### Analysis 1.5. Comparison 1 Dextrose gel versus control, Outcome 5 Neonatal seizures.

Review: Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

Comparison: 1 Dextrose gel versus control

Outcome: 5 Neonatal seizures

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dextrose gel</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Harris 2013</td>
<td>0/118</td>
<td>0/119</td>
<td>Not estimable</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>118</strong></td>
<td><strong>119</strong></td>
<td></td>
<td></td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Total events: 0 (Dextrose gel), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable
### Analysis 1.6. Comparison 1 Dextrose gel versus control, Outcome 6 Exclusive breast feeding after discharge (WHO definition)

**Review:** Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

**Comparison:** 1 Dextrose gel versus control

**Outcome:** 6 Exclusive breast feeding after discharge (WHO definition)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dextrose gel</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Harris 2013</td>
<td>113/118</td>
<td>104/119</td>
<td>1.10 [ 1.01, 1.18 ]</td>
<td>100.0%</td>
<td>1.10 [ 1.01, 1.18 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>118</td>
<td>119</td>
<td>100.0%</td>
<td>1.10 [ 1.01, 1.18 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 113 (Dextrose gel), 104 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 2.30 (P = 0.022)

Test for subgroup differences: Not applicable

#### Analysis 1.7. Comparison 1 Dextrose gel versus control, Outcome 7 Developmental disability at age 2 years or older

**Review:** Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

**Comparison:** 1 Dextrose gel versus control

**Outcome:** 7 Developmental disability at age 2 years or older

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dextrose gel</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Harris 2013</td>
<td>34/90</td>
<td>32/94</td>
<td>1.11 [ 0.75, 1.63 ]</td>
<td>100.0%</td>
<td>1.11 [ 0.75, 1.63 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>90</td>
<td>94</td>
<td>100.0%</td>
<td>1.11 [ 0.75, 1.63 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 34 (Dextrose gel), 32 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.53 (P = 0.60)

Test for subgroup differences: Not applicable
Analysis 1.8. Comparison 1 Dextrose gel versus control, Outcome 8 Visual impairment and severity at age 2 years or older.

Review: Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

Comparison: Dextrose gel versus control

Outcome: Visual impairment and severity at age 2 years or older

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dextrose gel</th>
<th>Placebo gel</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Harris 2013</td>
<td>26/90</td>
<td>23/93</td>
<td>1.17 [ 0.72, 1.89 ]</td>
<td>100.0 %</td>
<td>1.17 [ 0.72, 1.89 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>90</td>
<td>93</td>
<td>100.0 %</td>
<td>1.17 [ 0.72, 1.89 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 26 (Dextrose gel), 23 (Placebo gel)

Heterogeneity: not applicable

Test for overall effect: Z = 0.63 (P = 0.53)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Dextrose gel versus control, Outcome 9 Cerebral palsy and severity at age 2 years or older.

Review: Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

Comparison: Dextrose gel versus control

Outcome: Cerebral palsy and severity at age 2 years or older

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dextrose gel</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Harris 2013</td>
<td>2/90</td>
<td>0/93</td>
<td>5.16 [ 0.25, 106.12 ]</td>
<td>100.0 %</td>
<td>5.16 [ 0.25, 106.12 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>90</td>
<td>93</td>
<td>100.0 %</td>
<td>5.16 [ 0.25, 106.12 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 2 (Dextrose gel), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.06 (P = 0.29)

Test for subgroup differences: Not applicable
Analysis 1.10. Comparison 1 Dextrose gel versus control, Outcome 10 Developmental delay/intellectual impairment and severity at age 2 years or older.

Review: Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

Comparison: 1 Dextrose gel versus control

Outcome: 10 Developmental delay/intellectual impairment and severity at age 2 years or older

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dextrose gel</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed, 95% CI</td>
<td></td>
<td>M-H,Fixed, 95% CI</td>
</tr>
<tr>
<td>Harris 2013</td>
<td>31/90</td>
<td>30/93</td>
<td>100.0 %</td>
<td>1.07 [ 0.71, 1.61 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>90</strong></td>
<td><strong>93</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.07 [ 0.71, 1.61 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 31 (Dextrose gel), 30 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.31 (P = 0.75)
Test for subgroup differences: Not applicable
Analysis 1.11. Comparison 1 Dextrose gel versus control, Outcome 11 Developmental impairments - Bayley III scores at 2-year follow-up.

Review: Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

Comparison: Dextrose gel versus control

Outcome: Developmental impairments - Bayley III scores at 2-year follow-up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cognitive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harris 2013</td>
<td>90</td>
<td>93</td>
<td>100.0 %</td>
<td>-1.00</td>
<td>[-3.92, 1.92]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>90</td>
<td>93</td>
<td>100.0 %</td>
<td>-1.00</td>
<td>[-3.92, 1.92]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harris 2013</td>
<td>89</td>
<td>96</td>
<td>100.0 %</td>
<td>0.0</td>
<td>[-3.93, 3.93]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>89</td>
<td>93</td>
<td>100.0 %</td>
<td>0.0</td>
<td>[-3.93, 3.93]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harris 2013</td>
<td>90</td>
<td>99</td>
<td>100.0 %</td>
<td>0.0</td>
<td>[-2.76, 2.76]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>90</td>
<td>93</td>
<td>100.0 %</td>
<td>0.0</td>
<td>[-2.76, 2.76]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Social emotional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harris 2013</td>
<td>88</td>
<td>105</td>
<td>100.0 %</td>
<td>1.00</td>
<td>[-3.56, 5.56]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>88</td>
<td>90</td>
<td>100.0 %</td>
<td>1.00</td>
<td>[-3.56, 5.56]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 General adaptive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harris 2013</td>
<td>89</td>
<td>101</td>
<td>100.0 %</td>
<td>2.00</td>
<td>[-1.95, 5.95]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>89</td>
<td>91</td>
<td>100.0 %</td>
<td>2.00</td>
<td>[-1.95, 5.95]</td>
</tr>
</tbody>
</table>

Test for subgroup differences: Chi² = 1.59, df = 4 (P = 0.81), I² =0.0%

-20 -10 0 10 20
Favours dextrose gel  Favours placebo gel
### Analysis 1.12. Comparison 1 Dextrose gel versus control, Outcome 12 Executive function (2-year follow-up).

Review: Oral dextrose gel for the treatment of hypoglycaemia in newborn infants

Comparison: 1 Dextrose gel versus control

Outcome: 12 Executive function (2-year follow-up)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dextrose gel</th>
<th>Placebo gel</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>1 Executive function composite score (2-year follow-up)</td>
<td>87 10.9 (4.1)</td>
<td>92 10 (4)</td>
<td>100.0 %</td>
<td>0.90 [-0.29, 2.09]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>87 92</td>
<td>100.0 %</td>
<td>0.90 [-0.29, 2.09]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.49 (P = 0.14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 BRIEF-P Index - Global Executive Composite (2-year follow-up)</td>
<td>89 58 (11)</td>
<td>93 56 (11)</td>
<td>100.0 %</td>
<td>2.00 [-1.20, 5.20]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>89 93</td>
<td>100.0 %</td>
<td>2.00 [-1.20, 5.20]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.23 (P = 0.22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² =0.0%

### Appendices

#### Appendix 1. Search strategy results

**MEDLINE: Hypogly* AND dextrose gel AND neonat***
Date 14 June 2014
Search Results: 1 - 2 of 2
Mosalli 2014, Harris 2013

**CINAHL: Hypogly* AND dextrose gel AND infant, newborn**
Date 14 June 2014
Search Results: 1 - 2 of 2
Harris 2014, Harris 2013

**CINAHL: Hypogly* AND dextrose gel AND neonat**
Date 14 June 2014
Search Results: 1 - 2 of 2
Harris 2013, Anon 2013

**CINAHL: Hypogly* AND dextrose gel AND infant, newborn**
Date 14 June 2014
Search Results: 1 - 2 of 2
Anon 2014, Harris 2013

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Oral dextrose gel for the treatment of hypoglycaemia in newborn infants (Review) 32
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Appendix 2. Data extraction form

<table>
<thead>
<tr>
<th>Review ID:</th>
<th>Study ID:</th>
<th>Reference ID:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person extracting data:</td>
<td>Date of date extraction:</td>
<td>Year of study publication:</td>
</tr>
</tbody>
</table>

Title:

Author:

Reference:

Study design

Type of RCT study design (simple; cluster; block randomisation; stratified randomisation; multi-arm; factorial; quasi-randomisation, etc.)

Unit of randomisation:

Participants and setting
Describe setting:

Inclusion criteria:

Exclusion criteria:

Method used to analyse blood glucose concentration (reliable instrument using glucose oxidase method vs less reliable cot-side analysers)

- Laboratory analyser
- Blood gas machine - glucose oxidase
- i-STAT
- Hemocue
- Advantage
- Dextrostix
- Super Glucocard II
- Precision G
- Other analyser (please state)
- Not stated

Tick reason/s for risk of hypoglycaemia

- Infant of diabetic mother
- Preterm
- Small
- Large
- Other maternal obesity
- Poor feeding
- Blood glucose screening requested by clinical team (e.g. maternal medications)
- Other (please state)
- Not stated
### Type/s of feeding at the time of the hypoglycaemic episode
- Breast feeding
- Infant formula
- Combination feeding
- Other (please state)
- No feeds
- Not stated

### Intervention

#### Experimental intervention:

#### Comparison

#### Comparison intervention:

#### Outcomes:

### Primary outcomes
1. 
2. 
3. 

### Secondary outcomes
1. 
2. 
3. 
4. 
5. 
6. 
7. 
8. 

### Study methods

#### Risk of bias
### Adequate sequence generation
Was the allocation sequence adequately generated?  
Yes/Unclear/No

### Allocation concealment
Was allocation concealment adequate?  
Yes/Unclear/No

### Blinding
Was knowledge of the allocated intervention adequately prevented during the study?  
Yes/Unclear/No
**Participant:** Yes/Unclear/No  
**Clinician:** Yes/Unclear/No  
**Outcome assessor:** Yes/Unclear/No

### Incomplete outcome data addressed
Were complete outcome data adequately addressed?  
Yes/Unclear/No
**Describe any loss of participants to follow-up at each data collection point:**
Describe any exclusion of participants after randomisation: none
Was the analysis intention-to-treat? If not, could the data be re-included?  
**ITT analysis conducted**

### Free of selective reporting bias
Are reports of the study free of suggestions of selective reporting bias?  
Yes/Unclear/No
**Describe:**

### Free of other bias
Was the study apparently free of other problems that could put it at high risk of bias?  
Yes/Unclear/No
**If the study was stopped early, explain the reasons:**
**Describe any baseline in balance:**
**Describe any differential diagnosis:**

### Sample size calculation conducted

### Additional information requested

#### Outcomes for main analysis

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Total number of participants in study =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group</td>
<td>Total no. in study =</td>
</tr>
<tr>
<td>Comparison group</td>
<td>Total no. in study =</td>
</tr>
<tr>
<td>Events</td>
<td>Total</td>
</tr>
</tbody>
</table>

Primary: event (dichotomous)
Correction of hypoglycaemia (yes/no) (investigator defined)

Major neurosensory disability (yes/no) (investigator defined)

**Secondary outcomes:** infant (dichotomous)

Intravenous treatment for hypoglycaemia (yes/no)

Requirement for any medications for hypoglycaemia such as glucagon or corticosteroids (yes/no)

Neonatal seizures (yes/no)

Separation from mother for treatment of hypoglycaemia (yes/no)

Exclusive breast feeding at discharge (WHO definition) (yes/no)

Exclusive breast feeding at 6 months of age (WHO definition) (yes/no)

Breast feeding after discharge (yes/no)

Major neurological disability at age 2 years or older (legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cere-
<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Abnormal MRI of the brain in the neonatal period - investigator defined (yes/no)</td>
</tr>
<tr>
<td>12</td>
<td>Developmental disability at age 2 years or older - investigator defined (yes/no)</td>
</tr>
<tr>
<td>13</td>
<td>Visual impairment and severity at age 2 years or older (yes/no)</td>
</tr>
<tr>
<td>14</td>
<td>Hearing impairment and severity at age 2 years or older (yes/no)</td>
</tr>
<tr>
<td>15</td>
<td>Cerebral palsy and severity at age 2 years or older</td>
</tr>
<tr>
<td>16</td>
<td>Developmental delay/intellectual impairment and severity at age 2 years or older</td>
</tr>
<tr>
<td>17</td>
<td>Executive dysfunction and severity at age 2 years or older</td>
</tr>
<tr>
<td>18</td>
<td>Behavioural problems and severity at age 2 years or older</td>
</tr>
<tr>
<td>19</td>
<td>Abnormal MRI of the brain at age 2 years or older - investigator defined (yes/no)</td>
</tr>
<tr>
<td>20</td>
<td>Rebound hypoglycaemia (investigator defined hypoglycaemia occurring within 6 hours of initial correction) (yes/no) (event outcome)</td>
</tr>
<tr>
<td>----</td>
<td>--------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>21</td>
<td>Adverse effects (e.g. choking or vomiting at time of administration) (yes/no)</td>
</tr>
</tbody>
</table>

**Secondary outcomes:** event (dichotomous)

| 12 | Improvement in blood glucose to > 2.6 mmol/L (yes/no) |

**Secondary outcomes (continuous):**

<table>
<thead>
<tr>
<th>Infant outcomes</th>
<th>Total number of participants in study =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group</td>
<td>Total no. in study =</td>
</tr>
<tr>
<td>Control group</td>
<td>Total no. in study =</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant outcomes</td>
<td>Median</td>
<td>IQR</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>13</th>
<th>Number of episodes of hypoglycaemia/baby</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>14</th>
<th>Duration of initial hospital stay</th>
</tr>
</thead>
</table>

**Event outcomes**

<table>
<thead>
<tr>
<th>15</th>
<th>Increased blood glucose after treat-</th>
</tr>
</thead>
</table>
Additional information

General conclusions

Very brief summary of study authors’ main findings/conclusions:

Notes

Exclusion after data extraction

Reasons for exclusion (study design? participants? interventions/outcomes? attrition? bias?)

Dates:
Date entered into RevMan and by whom?
Date checked and by whom?
Date copy sent to editorial base and by whom?
CONTRIBUTIONS OF AUTHORS

PW and DH extracted data from the Troughton study, and JB and JHegarty from the Harris studies. MB resolved discrepancies in data extraction. JHarding provided assistance in determining study inclusion. PW prepared the first draft, and JB and JHarding provided major editorial assistance.

DECLARATIONS OF INTEREST

Deborah Harris, Phil Weston and Jane Harding have designed and conducted a randomised controlled trial called the “Sugar Babies Study” (Harris 2013) to compare dextrose gel with placebo for treatment of infants with neonatal hypoglycaemia. Deborah Harris was a member of the Steering Group for the follow-up study designed and led by Jane Harding.

SOURCES OF SUPPORT

Internal sources
- Waikato District Health Board, New Zealand.
  Clinical salaries for Phil Weston and Deborah Harris
- Auckland District Health Board, New Zealand.
  Clinical salaries for Malcolm Battin and Jo Hegarty
- Liggins Institute, University of Auckland, New Zealand.
  University appointments for Julie Brown and Jane Harding

External sources
- Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA.
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added methods, the plan for 'Summary of findings' tables and GRADE recommendations, which were not included in the original protocol.