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Oral dextrose gel for the prevention of hypoglycaemia in newborn infants (Protocol)


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Oral dextrose gel for the prevention of hypoglycaemia in newborn infants

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Editorial group: Cochrane Neonatal Group.


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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess whether oral dextrose gel in infants at risk of neonatal hypoglycaemia is more effective than placebo or no treatment or other active therapies (such as antenatal expression of colostrum, early initiation of breastfeeding, supplementation or substitution of breastfeeding with formula milk) in:

- preventing hypoglycaemia in newborn infants;
- reducing developmental impairments at childhood follow-up.

BACKGROUND

Description of the condition

Hypoglycaemia is the commonest metabolic disorder of the newborn. It is a common cause of brain damage in newborn infants (Hay 2009), and is the only known cause that is readily preventable (Chertok 2009; Singhal 1991; Singhal 1992). Neonatal hypoglycaemia can cause both brain damage (Burns 2008; Duvanel 1999; Kerstjens 2012; Koh 1988), and death (Achoki 2010; Cornblath 1965; Nadjm 2013; Willcox 2010). Some authors have reported brain abnormalities associated with neonatal hypoglycaemia on magnetic resonance imaging (MRI). Early studies reported that the commonest site of damage is in the occipital cortex (Alkalay 2005; Spar 1994). However, it has been recognised more recently that more widespread MRI changes may also be seen in the temporoparietal region, cerebral cortex and basal ganglia/thalamus (Burns 2008).

Up to 15% of newborn infants will have low blood glucose concentrations (Hay 2009). The rate is much higher in those infants who have additional risk factors: up to 50% in infants of diabetic mothers (Maayan-Metzger 2009), and 66% in preterm infants (Lucas 1988). Those at highest risk of hypoglycaemia are infants of diabetics (Agrawal 2000; Maayan-Metzger 2009), large for gestation (Weissmann-Brenner 2012), small for gestation (Hawdon 2009).
1993), and preterm infants (Kerstjens 2012). Fifty per cent of these infants will develop at least one episode of hypoglycaemia and 20% will have more than one episode (Harris 2012). Additional risk factors for neonatal hypoglycaemia include perinatal asphyxia (Salhab 2004), prolonged labour, hypothermia, sepsis and some maternal medications such as β-agonists (Kurtoglu 2005) and β-blockers (Daskas 2013). The definition of neonatal hypoglycaemia remains controversial, with various definitions used in publications (Agrawal 2000; Burns 2008; Kerstjens 2012; Maayan-Metzger 2009), as well as in those suggested as thresholds for intervention (Adamkin 2011; Cornblath 2000). The use of < 2.6 mmol/L has been widely accepted as a definition of hypoglycaemia (Harris 2009). This was heavily influenced by the description of abnormal sensory evoked potentials in infants who had blood glucose concentrations of < 2.6 mmol/L (Koh 1988), and of a relationship between the number of days on which blood glucose measurements of < 2.6 mmol/L were recorded in preterm infants and neurodevelopmental impairment at 18 months (Lucas 1988), and at seven to eight years (Lucas 1999). Infants who are ‘asymptomatic’ during periods of hypoglycaemia were previously considered to have a better outcome than those who exhibited signs (Hawdon 1993; Kalhan 2000; Koivisto 1972). However, Stenninger et al found that longer-term neurodevelopmental outcomes did not differ between infants who exhibited signs and those who did not (Stenninger 1998).

The effect of transient neonatal hypoglycaemia on longer-term outcomes is not yet well defined. A recent retrospective population study of transient hypoglycaemia (defined as a single initial blood glucose concentration < 2.6 mmol/L, followed by a repeat result above this) demonstrated an association between low first blood glucose concentration and lower academic test scores at 10 years of age (Kaiser 2015). However, in a cohort of babies at risk of neonatal hypoglycaemia, half of whom became hypoglycaemic and were treated to maintain blood glucose concentrations ≥ 2.6 mmol/L, there was no difference in neurodevelopmental outcome at two years between those who did and did not experience neonatal hypoglycaemia (McKinlay 2015).

Treatment of neonatal hypoglycaemia commonly requires admission to a newborn intensive care unit (NICU) or special care baby unit (SCBU), separating mothers and infants and interfering with the establishment of breastfeeding, thus incurring a high social and financial cost. The World Health Organization, in its publication on neonatal hypoglycaemia, states “... an approach aimed first at the prevention of hypoglycaemia, second at its reliable detection in newborns at risk and third at appropriate treatment which will not be deleterious to breastfeeding is ... of global importance” (WHO 1997). The American Academy of Pediatrics recommends “... early identification of the at-risk infant and institution of prophylactic measures to prevent neonatal hypoglycaemia” (Adamkin 2011). The widely accepted clinical monitoring of infants at risk of neonatal hypoglycaemia involves:

- early identification of pertinent risk factors;
- early feeding;
- pre-feed blood glucose concentration measurement to determine the blood glucose concentration at the time when it is most at risk of being low;
- monitoring during the highest risk period until the blood glucose concentration is demonstrated to remain above the chosen threshold for intervention (Adamkin 2011; CPSFNC 2004; NICE 2008; WHO 1997).

Despite the recommendations to prevent neonatal hypoglycaemia, there is little evidence of any effective interventions to achieve this. Antenatal expression of colostrum is considered to potentially increase the colostrum supply available for infants following birth, reduce the time taken to establish breastfeeding and decrease formula use (Cox 2006). One small retrospective cohort study of diabetic mothers who expressed colostrum antenatally reported that they gave birth one week earlier, and the rates of admission of their infants to the NICU were increased compared with diabetic mothers who did not express (Soltani 2012). However, the effect of this approach on the incidence of neonatal hypoglycaemia is as yet underdetermined. A small pilot study did not show any improvement in mean blood glucose concentrations for infants whose mothers expressed colostrum antenatally when compared to audit data for infants whose mothers did not express antenatally (Forster 2011). Early initiation of breastfeeding within 30 minutes following birth has no effect on the blood glucose concentration at one hour after birth in infants without risk factors for neonatal hypoglycaemia (Sweet 1999). However, early feeding (within 30 minutes of birth) of infants of diabetic mothers was reported to decrease the incidence of subsequent neonatal hypoglycaemia and these infants maintained a higher mean blood glucose concentration than those who receive their first feed later (Chertok 2009).

Supplementation or substitution of breastfeeding with fluid or foods other than expressed breast milk may reduce the duration of breastfeeding (Becker 2011; Blomquist 1994). Therefore, the commonly accepted practice is to advise exclusive breastfeeding (Eidelman 2012; UNICEF 2013). Healthy newborn infants will usually maintain their blood glucose concentration despite the small-volume, low-energy food source provided by colostrum. However, colostrum alone cannot be relied upon to provide the essential energy needs of infants with additional risk factors for neonatal hypoglycaemia. Thus, infants at high risk of hypoglycaemia frequently receive supplemental or complementary feeding during the establishment of feeding (Blomquist 1994; Harris 2013).

Powdered sugar has been used as an addition to formula in an attempt to prevent neonatal hypoglycaemia. Two randomised controlled studies in India compared formula to formula plus added powdered sugar in the prevention of subsequent hypoglycaemia in infants at risk of hypoglycaemia (small for gestational age - SGA and large for gestational age - LGA). Both studies demonstrated a significant reduction in the subsequent incidence of neonatal hypoglycaemia in the infants who received formula plus powdered sugar.
sugar (Singhal 1991; Singhal 1992). However, as noted above, supplementation with formula milk may reduce longer-term breastfeeding rates (Becker 2011; Blomquist 1994). The ideal intervention would be effective in preventing hypoglycaemia, reduce the need for artificial formula, improve breastfeeding rates and reduce costs, as well as potentially reducing the risk of later adverse outcomes. Oral dextrose gel given as 200 mg/kg (0.5 ml/kg) of 40% dextrose is effective and safe in treating neonatal hypoglycaemia. It is more effective than feeding alone, reduces the use of expressed and formula milk and improves breastfeeding rates at two weeks of age (Harris 2013). A separate Cochrane review, 'Oral dextrose gel for the treatment of hypoglycaemia in newborn infants', is currently being finalised (Weston 2014).

**Description of the intervention**

This review will assess the use of oral dextrose gel in the prevention of neonatal hypoglycaemia. Dextrose gel is a non-proprietary, low-cost, simple carbohydrate in concentrated aqueous solution, which can be administered by direct application to the oral mucosa - either buccal or sublingual. Administration via these highly vascularised, thin mucous membranes allows rapid access to the circulation. Some of the administered gel may be swallowed and absorbed from the gastrointestinal tract. Commercially manufactured gel costs approximately USD 70 per 100 ml. Alternatively, gel can be prepared in hospital pharmacies (Harris 2013). Ingredients will vary by pharmaceutical manufacturer, but commonly include water, glucose, a gelling agent and preservative(s). Some preparations include flavourings and colourings. Suitability of the gel for use in neonates should be assessed on an individual basis.

**How the intervention might work**

Dextrose gel administered to the oral mucosa will enter the systemic circulation via the lingual vein and the internal jugular vein. This is in comparison to oral-gastrointestinal administration, whereby the first pass effect of the portal circulation may diminish the systemic blood glucose concentration achieved. Prevention of neonatal hypoglycaemia by providing additional glucose during the period of the neonatal metabolic transition may reduce the medical prescription of artificial formula feeds, reduce admission to the NICU for intravenous dextrose and prevent the neurodevelopmental impairment associated with neonatal hypoglycaemia.

**Why it is important to do this review**

Neonatal hypoglycaemia is important because it is common and it is associated with brain injury in newborn infants. There are known risk factors for neonatal hypoglycaemia, so specific groups of newborn infants are routinely targeted for screening (i.e. those who are infants of diabetic mothers, high or low birthweight, preterm and those with poor feeding). These infants are frequently managed prophylactically with supplemental formula milk and/or admission to neonatal units for intravenous dextrose. Supplemental formula may impair the establishment of breastfeeding and intravenous treatment is expensive, not always available in resource-poor settings and usually requires separation of the mother and infant.

Oral dextrose gel is simple to administer and inexpensive. Therefore, if it is effective in preventing neonatal hypoglycaemia it would have many advantages, particularly in low-resource settings. The results of this review may help to inform those preparing clinical practice guidelines, such as those currently available to guide the care of babies at risk of neonatal hypoglycaemia (Adamkin 2011; NICE 2008; UNICEF 2013).

**OBJECTIVES**

To assess whether oral dextrose gel in infants at risk of neonatal hypoglycaemia is more effective than placebo or no treatment or other active therapies (such as antenatal expression of colostrum, early initiation of breastfeeding, supplementation or substitution of breastfeeding with formula milk) in:

- preventing hypoglycaemia in newborn infants;
- reducing developmental impairments at childhood follow-up.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

Randomised controlled trials (RCTs) and quasi-RCTs, including cluster-randomised trials but not cross-over trials. We will include both published and unpublished studies. We will include unpublished studies and studies published only as abstracts, if assessment of study quality is possible and if other criteria for inclusion are fulfilled.

**Types of participants**

Newborn infants who are at risk of hypoglycaemia, including infants of diabetics (all types), large for dates, small for dates and born preterm (< 37 weeks) from birth to 24 hours of age, who...
have not yet been diagnosed with hypoglycaemia (blood glucose concentration below the normal range, investigator-defined) or had treatment for hypoglycaemia.

**Types of interventions**

Dextrose gel, of any concentration and at any dose or number of doses, given orally compared with placebo, no treatment/standard care or other therapies (such as antenatal expression of colostrum, early initiation of breastfeeding, supplementation or substitution of breastfeeding with formula milk), for the prevention of hypoglycaemia at any gestational age and commenced within the first 24 hours following birth.

**Types of outcome measures**

**Primary outcomes**
- Hypoglycaemia (investigator-defined).
- Major neurological disability at two years of age or greater (any of: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy or developmental delay/ intellectual impairment (defined as a developmental quotient or intelligence quotient lower than two standard deviations below the mean).

**Secondary outcomes**
- Hypoglycaemia (any blood glucose concentration less than 2.6 mmol/l) during initial hospital stay (yes/no).
- Receipt of treatment for hypoglycaemia (investigator-defined, any treatment - oral dextrose gel, intravenous dextrose or other drug therapy) during initial hospital stay (yes/no).
- Receipt of intravenous treatment for hypoglycaemia (yes/no).
- Receipt of oral dextrose gel treatment for hypoglycaemia (yes/no).
- Receipt of any medications for hypoglycaemia, such as glucagon or corticosteroids (yes/no).
- Number of episodes of hypoglycaemia (investigator-defined) (total number per infant).
- Adverse effects, e.g. choking or vomiting at time of administration (yes/no).
- Separation from the mother for treatment of hypoglycaemia (infant being nursed in an environment that is not in the same room as the mother, e.g. for NICU admission or the like) (yes/no).
- Neonatal seizures (yes/no).
- Abnormal MRI of the brain in the neonatal period (yes/no).
- Duration of initial hospital stay (days).
- Breastfeeding (any) after discharge (yes/no).
- Exclusive breastfeeding after discharge - WHO 2008 definition (yes/no).
- Exclusive breastfeeding at six months of age - WHO 2008 definition (yes/no).
- Developmental disability at two years of age or greater - investigator-defined (yes/no).
- Visual impairment and severity at two years of age or greater.
- Hearing impairment and severity at two years of age or greater.
- Cerebral palsy and severity at two years of age or greater.
- Developmental delay/intellectual impairment and severity at two years of age or greater.
- Executive dysfunction and severity at two years of age or greater.
- Behavioural problems and severity at two years of age or greater.
- Abnormal MRI of the brain at two years of age or greater.

**Search methods for identification of studies**

**Electronic searches**
We will request a search from the Cochrane Neonatal Review Group's Specialist Register. We will search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL and Web of Science from the inception of the database to the present. We will search clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov, controlled-trials.com; who.int/ictrp and www.anzctr.org.au). We will search conference abstracts for the Pediatric Academic Societies, European Society of Paediatric Research and Perinatal Society of Australia and New Zealand. We will not apply any language restrictions.

We will search using the following keywords: hypoglycaemia or hypogly$, AND neonate OR neonat$, AND dextrose OR glucose gel. We will use “*” as a wild card where appropriate. We will search using both English and American spelling.

We will limit to potentially eligible randomised controlled trials and neonates using a maximally sensitive methodology filter (see Appendix 1).

**Searching other resources**

We will search the reference lists of included trials. We will approach well-known researchers in this clinical area to identify any unpublished or ongoing research.
Data collection and analysis

We will use the standard methods of the Cochrane Neonatal Group.

Selection of studies

Two authors will independently undertake the following steps:

- Merge search results using reference management software and remove duplicate records of the same report.
- Examine titles and abstracts to remove obviously irrelevant reports.
- Retrieve the full text of potentially relevant reports.
- Link together multiple reports of the same study.
- Examine full-text reports for compliance of studies with the eligibility criteria.
- Correspond with investigators, where appropriate, to clarify study eligibility (including requesting missing results, if required).
- Make final decisions on study inclusion and proceed to data collection.

We will resolve any disagreement by discussion. If necessary, a third author will arbitrate for differences in interpretation. We will produce a study flow diagram to illustrate this process.

Data extraction and management

We will develop a data extraction form prior to data extraction. Two authors will independently extract data from each selected article. Data collected will include source details, eligibility assessment, methodological details, participant characteristics, intervention details and outcomes reported. We will resolve any disagreement by discussion. If necessary, a third author will arbitrate for differences in interpretation. We will keep a record of any consensus made. We will enter consensus data into Review Manager.

Assessment of risk of bias in included studies

We will assess the methodological quality of included studies using the criteria specified in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Two authors will independently assess each study. We will resolve any disagreement by discussion. If necessary, a third author will arbitrate for differences in interpretation. We will keep a record of any consensus made. We will enter consensus data into Review Manager.

Sequence generation (checking for possible selection bias)

For each included study we will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We will assess the method as:

- 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);
- unclear risk of bias.

Allocation concealment (checking for possible selection bias)

For each included study we will describe the method used to conceal allocation to interventions prior to assignment and assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
- unclear risk of bias.

Blinding of participants and personnel (checking for possible performance bias)

For each included study we will describe the methods used, if any, to blind study participants and personnel from which intervention a participant received. We will consider studies to be at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

Blinding of outcome assessment (checking for possible detection bias)

For each included study we will describe the methods used to blind outcome assessors from knowledge of which intervention a participant received. We will assess the methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For each included study, we will describe the completeness of data, including attrition and exclusions from the analysis. We will examine study protocols for discrepancy between intended and reported outcomes. We will state whether attrition and exclusions are reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusions where reported, and whether missing data are balanced across groups or are related to outcomes. Where
sufficient information is reported, we will re-include missing data in the analysis that is undertaken. We will assess the methods as:

- 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 that assigned at randomisation, > 20% loss of follow-up data);
- unclear risk of bias.

Other bias
We will describe for each included study any important concerns we have about other possible sources of bias. We will assess 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 whether there is risk of other bias.

Measures of treatment effect
We will use the numbers of events in the control and intervention groups of each study to calculate risk ratios (RRs) for dichotomous data. We will calculate mean differences (MDs) between treatment groups where outcomes are measured in the same way for continuous data. We will report risk differences (RDs) and where a significant effect is found we will calculate the numbers needed to treat (NNTB) or the numbers needed to treat to harm (NNTH). We will report 95% confidence intervals (CIs) for all outcomes.

Unit of analysis issues
We will include cluster-randomised trials in the analyses along with individually randomised trials. We will make adjustments to the standard errors using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Section 16.3.6) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study with a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. We will consider it reasonable to combine the results from both cluster-randomised trials and individually randomised trials if there is little heterogeneity between the study designs and the interaction between the effect of the intervention and the choice of randomisation unit is considered to be unlikely.

We will acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data
We will note levels of attrition. We will carry out analyses on an intention-to-treat basis, where possible, for all of the outcomes. We will analyse all participants where possible in the treatment group to which they were randomised, regardless of the actual treatment received. We will contact the original investigators to request missing data whenever possible. We will make explicit the assumptions of any methods used to cope with missing data. We may perform sensitivity analyses to assess how sensitive results are to reasonable changes in the assumptions that are made. We will address the potential impact of missing data on the findings of the review in the ‘Discussion’ section.

Assessment of heterogeneity
We will consider whether the clinical and methodological characteristics of the included studies are sufficiently similar for meta-analysis to provide a clinically meaningful summary. This will be done by assessing statistical heterogeneity using the Chi² test and the I² statistic, considering an I² value < 25% to be none, and 25% to 49% low, 50% to 74% moderate and ≥ 75% high heterogeneity. We will take an I² value greater than 50% and a low P value (< 0.10) in the Chi² test for heterogeneity to indicate substantial heterogeneity (Higgins 2011). If substantial heterogeneity is detected, we will explore possible explanations in sensitivity/subgroup analyses. We will take statistical heterogeneity into account when interpreting the results, especially if there is any variation in the direction of effect.

Assessment of reporting biases
Reporting biases arise when the 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 aim to conduct a comprehensive search for eligible studies and we will be alert for duplication of data. We will assess publication bias by visual inspection of a funnel plot, if there are enough studies (10 or more trials) to make such an inspection valid. Two authors will examine the methods of each study for prespecified outcomes. If all pre-specified outcomes are reported in the results, the study will carry a low risk of bias. If any pre-specified outcome is not reported in the results, we will consider the study to carry a higher risk of bias. If the authors uncover reporting bias that could, in the opinion of the authors, introduce serious bias, we plan to conduct a sensitivity analysis to determine the effect of including and excluding these studies in the analysis.
Data synthesis

We will evaluate studies for potential clinical diversity and restrict meta-analysis to situations where clinical consistency is apparent. We will evaluate studies for bias, as above, and restrict meta-analysis if the bias would be compounded. We will use a fixed-effect model to combine data where it is reasonable to assume that studies were estimating the same underlying treatment effect. If there is evidence of clinical heterogeneity we will try to explain this based on the different study characteristics and subgroup analyses.

Quality of evidence

We will assess the quality of the evidence for the main comparison at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2011a). This methodological approach considers evidence from randomised controlled trials as high quality, but they may be downgraded based on consideration of any of five areas: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. (Guyatt 2011a). The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades:

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

The review authors will independently assess the quality of the evidence found for outcomes identified as critical or important for clinical decision-making. These outcomes will include the following:

- Hypoglycaemia (investigator-defined).
- Major neurological disability at two years of age or greater (defined as any of: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy or developmental delay/intellectual impairment (defined as a developmental quotient lower than two standard deviations below the mean)).
- Receipt of treatment for hypoglycaemia (investigator-defined, any treatment - oral dextrose gel, intravenous dextrose or other drug therapy) during initial hospital stay.
- Receipt of intravenous treatment for hypoglycaemia.
- Adverse effects, e.g. choking or vomiting at time of administration.
- Separation from the mother for treatment of hypoglycaemia (infant being nursed in an environment that is not in the same room as the mother, e.g. for NICU admission or the like).
- Exclusive breastfeeding after discharge - WHO 2008 definition.

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

We will enter data (i.e. pooled estimates of the effects and corresponding 95% confidence intervals) and make explicit judgements for each of the above aspects assessed in the Guideline Development Tool, the software used to create ‘Summary of findings’ tables (GRADEpro). We will explain all judgements involving the assessment of the study characteristics described above in footnotes or comments in the ‘Summary of findings’ table.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses using a fixed-effect model:

- Reason for risk of hypoglycaemia (infant of diabetic mother, preterm, small, large, other).
- Gestation at birth (term and post-term versus late preterm 35 to 36 weeks versus moderately preterm 30 to 34 weeks versus extremely preterm < 30 weeks).
- Actual mode of feeding (formula versus breast versus mixed).
- Method of administration of gel (rubbed into buccal mucosa versus sublingual versus other).
- Dose of dextrose gel per administration ($\leq$ 200 mg/kg versus $>200$ mg/kg).
- Number of dextrose gel doses administered (1 versus > 1 dose).
- Time of administration of first dose of gel ($\leq$ 1 hour of age versus after 1 hour of age versus after 2 hours of age).
**Sensitivity analysis**

We will conduct sensitivity analysis by examining only those trials considered to have a low risk of bias. We will report sensitivity analyses for the primary outcomes only.

**ACKNOWLEDGEMENTS**

We acknowledge the support of the Cochrane Neonatal Group editorial office and the contribution of Tineke Crawford and of Dr Phil Weston, Dr Deborah Harris and Dr Malcolm Battin with whom Jo Hegarty, Julie Brown and Jane Harding are co-authors of the Cochrane Review 'Dextrose gel for the treatment of hypoglycaemia in newborn infants'.
Oral dextrose gel for the prevention of hypoglycaemia in newborn infants (Protocol)

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**Eidelman 2012**

**Forster 2011**

**GRADEpro [Computer program]**
McMaster University. GRADEpro [wwwGRADEpro.org]. McMaster University, 2014.

**Guyatt 2011a**

**Guyatt 2011b**

**Guyatt 2011c**

**Guyatt 2011d**

**Guyatt 2011e**

**Harris 2009**

**Harris 2012**

**Harris 2013**

**Hawdon 1993**

**Hay 2009**

**Higgins 2011**

**Kaiser 2015**

**Kalhan 2000**

**Kerstjens 2012**

**Koh 1988**

**Koivisto 1972**

**Kurtoglu 2005**
Lucas 1988

Lucas 1999

Maayan-Metzger 2009

McKinlay 2015

Nadjm 2013

NICE 2008

Salhab 2004

Schniemann 2013

Singhal 1991

Singhal 1992

Soltani 2012

Spar 1994

Stenninger 1998

Sweet 1999

UNICEF 2013

Weissmann-Brenner 2012

Weston 2014

WHO 1997

WHO 2008

Willcox 2010
Willcox ML, Forster M, Dicko MI, Graz B, Mayon-White R, Barennes H. Blood glucose and prognosis in children with presumed severe malaria: is there a threshold for
Appendix I. Standard search methodology


Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

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Contributions of Authors

Jo Hegarty wrote the first draft of the protocol and co-ordinated subsequent drafts, with significant editorial assistance by JB. All review authors contributed to subsequent drafts and approved the final version.

Declarations of Interest

Jo Hegarty, Jane Alsweiler, Caroline Crowther and Jane Harding have designed and are steering committee members of a randomised controlled trial comparing dextrose gel with placebo in the prevention of neonatal hypoglycaemia.

There is no other conflict and in particular no benefits in cash or kind have been received by the authors in relation to any element of the proposed review.
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