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Oral dextrose gel to prevent hypoglycaemia in at-risk neonates (Review)

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Oral dextrose gel to prevent hypoglycaemia in at-risk neonates.
Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD012152.
DOI: 10.1002/14651858.CD012152.pub2.

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[Intervention Review]

Oral dextrose gel to prevent hypoglycaemia in at-risk neonates

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Editorial group: Cochrane Neonatal Group
Publication status and date: New, published in Issue 7, 2017.

Citation: Hegarty JE, Harding JE, Crowther CA, Brown J, Alsweiler J. Oral dextrose gel to prevent hypoglycaemia in at-risk neonates. *Cochrane Database of Systematic Reviews* 2017, Issue 7. Art. No.: CD012152. DOI: 10.1002/14651858.CD012152.pub2.

ABSTRACT

Background

Neonatal hypoglycaemia is a common condition that can be associated with brain injury. Current practice usually includes early identification of at-risk infants (e.g. infants of diabetic mothers; preterm, small- or large-for-gestational-age infants), and prophylactic measures are advised. However, these measures often involve use of formula milk or admission to the neonatal unit. Dextrose gel is non-invasive, inexpensive, and effective for treatment of neonatal hypoglycaemia. Use of prophylactic dextrose gel can prevent neonatal hypoglycaemia, thus potentially reducing separation of mother and baby and supporting breastfeeding, as well as preventing brain injury.

Objectives

To assess the effectiveness and safety of oral dextrose gel in preventing hypoglycaemia among newborn infants at risk of hypoglycaemia and in reducing long-term neurodevelopmental impairment.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 12), MEDLINE via PubMed (1966 to 23 January 2017), Embase (1980 to 23 January 2017), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 23 January 2017). We also searched clinical trials databases, conference proceedings, and reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

We included randomised and quasi-randomised studies comparing dextrose gel versus placebo, no intervention, or other therapies for prevention of neonatal hypoglycaemia.

Data collection and analysis

We used standard methodological procedures as expected by the Cochrane Collaboration. Two review authors independently assessed trial quality and extracted data. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the quality of evidence.

Main results

We included one trial comparing oral dextrose gel versus placebo in 416 infants at risk of hypoglycaemia. We judged this trial to be at low risk of bias. Using the GRADE method, we determined that evidence ranged from high quality to moderate quality.

For outcomes selected for the GRADE analysis, we found the following.

• Oral dextrose gel prophylaxis (any dose) is associated with reduced risk of neonatal hypoglycaemia compared with placebo (risk ratio (RR) 0.76, 95% confidence interval (CI) 0.62 to 0.94; one RCT; n = 415 infants; high-quality evidence). The risk difference (RD) is -0.13 (95% CI -0.23 to -0.03), and on average, 8.3 infants would have to receive prophylactic dextrose gel to prevent one additional case of neonatal hypoglycaemia.

• Investigators found no statistically significant differences between dextrose gel and placebo groups in the number of adverse events (RR 1.09, 95% CI 0.55 to 2.17; one RCT; n = 413 infants; moderate-quality evidence); separation from mother for treatment of hypoglycaemia (RR 0.46, 95% CI 0.21 to 1.01; one RCT, n = 415 infants; moderate-quality evidence); exclusive breastfeeding at discharge (RR 1.00, 95% CI 0.86 to 1.15; one RCT; n = 415 women; moderate-quality evidence); or breastfeeding at six weeks postpartum (RR 1.06, 95% CI 0.88 to 1.29; one RCT; n = 386 women; moderate-quality evidence).

• Researchers provided no data for the other prespecified GRADE outcomes for this review (major neurological disability at two years of age or older; receipt of treatment for hypoglycaemia during initial hospital stay; receipt of intravenous treatment for hypoglycaemia).

Authors' conclusions

Oral dextrose gel reduced the risk of neonatal hypoglycaemia in at-risk infants in a single trial. Results showed no statistically significant differences in the number of adverse events or in risk of separation of infant from mother for treatment of hypoglycaemia between babies who received oral dextrose gel and those given placebo. Caution is suggested in interpreting data for the latter two outcomes owing to low event rates.

Available evidence is limited to a cohort of at-risk infants, most of whom were infants of diabetic mothers and were treated on the postnatal ward. Minimal data available for many of the prespecified outcomes of this review showed no long-term neurodevelopmental and disability outcomes. Additional evidence is needed to assess the efficacy and safety of dextrose gel for prevention of neonatal hypoglycaemia.

PLAIN LANGUAGE SUMMARY

Oral dextrose gel for prevention of low blood glucose levels in newborn babies

What is the issue?

Low blood glucose levels are common among newborn babies. Up to 15 of every 100 babies will have low blood glucose levels, and among some babies at higher risk (babies who are born preterm, or smaller or larger than most babies, or whose mothers are diabetic), as many as half will have low blood glucose levels over the first few days after they are born.

Why is this important?

Low blood glucose levels can cause problems with academic achievement and development during childhood. It is possible that even one low level can contribute to these problems in some babies. Therefore, it would be useful to prevent low blood glucose levels from happening. Additionally, treatments for low blood glucose levels often include formula milk or admission to the neonatal unit, leading to separation of mother and baby, and both of these approaches may impair breastfeeding.

What evidence did we find?

During searches updated to January 2017, we found one study (with low risk of bias) that compared oral dextrose gel versus placebo for prevention of low blood glucose levels in 415 at-risk babies. Evidence from this single study suggests that in babies at risk, oral dextrose gel followed by a feed is associated with reduced risk of low blood glucose levels when compared with placebo (high-quality evidence). Results showed no statistically significant differences between oral dextrose gel and placebo in terms of the number of adverse events (moderate-quality evidence), risk of separation of baby from mother for treatment of low glucose levels (moderate-quality evidence), exclusive breastfeeding at discharge (moderate-quality evidence), or continued breastfeeding at six weeks of age (moderate-quality evidence). We must be careful when interpreting the evidence for adverse events and separation of mother and baby, as a small number of events have been reported for these outcomes. Researchers provided no data on long-term outcomes including developmental and disability outcomes.

What does this mean?

Available evidence came from only one study, and no long-term outcome data have been reported. Additionally, this study considers only oral dextrose gel compared with placebo and does not consider other measures that could potentially prevent hypoglycaemia. Therefore, not enough evidence is available at this time to support the routine use of oral dextrose gel for prevention of hypoglycaemia in newborn babies at risk. Childhood follow-up of the single study included here is under way, and an additional ongoing study is seeking to determine the effect of oral dextrose gel on preventing admission to the neonatal intensive care unit (NICU). We advise waiting for data on outcomes of these additional studies to assess the longer-term safety and efficacy of oral dextrose gel for prevention of neonatal hypoglycaemia.

Summary of findings for the main comparison. Dextrose gel compared with placebo for prevention of hypoglycaemia in newborn infants

Dextrose gel compared with placebo for prevention of hypoglycaemia in newborn infants

Patient or population: newborn infants at risk of neonatal hypoglycaemia
Setting: New Zealand
Intervention: dextrose gel
Comparison: placebo gel

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with dextrose gel				
Hypoglycaemia	543 per 1000	413 per 1000 (337 to 511)	RR 0.76 (0.62 to 0.94)	415 (1 RCT)	⊕⊕⊕⊕ HIGH	
Major neurological disability at 2 years of age or older - not reported	-	-	-	-	-	No data were reported for this outcome
Receipt of treatment for hypoglycaemia during initial hospital stay - not reported	-	-	-	-	-	No data were reported for this outcome
Receipt of intravenous treatment for hypoglycaemia - not reported	-	-	-	-	-	No data were reported for this outcome
Adverse events (e.g. choking or vomiting at time of administration)	80 per 1000	87 per 1000 (44 to 173)	RR 1.09 (0.55 to 2.17)	413 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	Low event rates: 24/275 in dextrose gel group; 11/138 in placebo group
Separation from mother for treatment of hypoglycaemia (admission to NICU for hypoglycaemia)	87 per 1000	39 per 1000 (18 to 88)	RR 0.46 (0.21 to 1.01)	415 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	Low event rates: 11/277 in dextrose gel group; 12/138 in placebo group
Breastfeeding (exclusive at discharge)	674 per 1000	674 per 1000 (580 to 775)	RR 1.00 (0.86 to 1.15)	415 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	
Breastfeeding (6 weeks postpartum)	535 per 1000	567 per 1000 (471 to 690)	RR 1.06 (0.88 to 1.29)	386 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	

*__The 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

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

[a]Evidence of imprecision with wide confidence intervals, probably attributable to low event rates - downgraded one level
[b]Evidence of imprecision. Evidence is based on a single trial, which, although robust, was not powered to detect differences in breastfeeding at discharge or six weeks postpartum - downgraded one level

BACKGROUND

Description of the condition

Hypoglycaemia is the most common metabolic disorder of the newborn. It can cause brain damage in newborn infants (Hay 2009) and is potentially 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 study authors have reported brain abnormalities associated with neonatal hypoglycaemia on magnetic resonance imaging (MRI). Early studies reported that the most common site of damage is the occipital cortex (Alkalay 2005; Spar 1994). However, it has been recognised more recently that widespread MRI changes may 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). This rate is much higher among infants with 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 diabetic mothers (Agrawal 2000; Maayan-Metzger 2009), large for gestation (Weissmann-Brenner 2012), small for gestation (Hawdon 1993), and preterm (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 maternal medications such as β-agonists (Kurtoglu 2005) and β-blockers (Daskas 2013).

The definition of neonatal hypoglycaemia remains controversial, and various definitions have been proposed (Agrawal 2000; Burns 2008; Kerstjens 2012; Maayan-Metzger 2009) or suggested as thresholds for intervention (Adamkin 2011; Cornblath 2000). Blood glucose concentration < 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 among infants with blood glucose concentrations < 2.6 mmol/L (Koh 1988) and of the relationship between the number of days on which blood glucose measurements < 2.6 mmol/L in preterm infants were recorded 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 exhibit 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).

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

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

Despite recommendations to prevent neonatal hypoglycaemia, little evidence shows that effective interventions can achieve this.

Antenatal expression of colostrum is considered to potentially increase the available colostrum supply for infants following birth, while reducing the time taken to establish breastfeeding and decreasing use of formula (Cox 2006). One small retrospective cohort study of diabetic mothers who expressed colostrum antenatally reported that they gave birth one week earlier than anticipated, and rates of admission of their infants to the NICU were greater than rates among diabetic mothers who did not express (Soltani 2012). However, the effect of this approach on the incidence of neonatal hypoglycaemia is as yet undetermined. A small pilot study did not show improvement in mean blood glucose concentrations among infants whose mothers expressed colostrum antenatally when compared with infants whose mothers did not express antenatally (as determined from audit data) (Forster 2011).

Early initiation of breastfeeding within 30 minutes following birth has no effect on 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 received 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 fulfil the essential energy needs of infants with additional risk factors for neonatal hypo-

glycaemia. Thus, infants at high risk of hypoglycaemia frequently receive supplemental or complementary feeding during 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 versus formula plus added powdered sugar for 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 incidence of subsequent hypoglycaemia among infants who received formula plus powdered 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 while reducing the need for artificial formula, improving breastfeeding rates, and reducing 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 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", has recently been published (Weston 2016).

Description of the intervention

Dextrose gel is a non-proprietary, low-cost, simple carbohydrate in concentrated thickened aqueous solution, which can be administered by direct application to the oral mucosa - 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 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. The difference in effectiveness of various formulations is unknown.

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 contrasts with oral-gastrointestinal administration, whereby the first pass effect of the portal circulation may diminish the systemic blood glucose concentration achieved. Prevention of neonatal hypoglycaemia achieved by providing additional glucose during the neonatal metabolic transition period 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 is associated with brain injury in newborn infants. Risk factors for neonatal hypoglycaemia are known, so specific groups of newborn infants are routinely targeted for screening (i.e. infants of diabetic mothers, those of high or low birth weight, preterm infants, and those with poor feeding). These infants are frequently treated prophylactically with supplemental formula milk and/or admission to the neonatal unit for intravenous dextrose. Supplemental formula may impair establishment of breastfeeding; intravenous treatment is expensive, is not always available in resource-poor settings, and usually requires separation of mother and infant.

Oral dextrose gel is simple to administer and inexpensive. Therefore, if it is found to be effective in preventing neonatal hypoglycaemia, its use would provide many advantages, particularly in low-resource settings.

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 the effectiveness and safety of oral dextrose gel in preventing hypoglycaemia among newborn infants at risk of 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, including cluster-randomised trials but not cross-over trials. We included both published and unpublished studies. We planned to include unpublished studies and studies published only as abstracts, if assessment of study quality was possible, and if other criteria for inclusion were fulfilled.

Types of participants

Newborn infants at risk of hypoglycaemia, including infants of diabetic mothers (all types), large for dates, small for dates, and those born preterm (< 37 weeks) or with other risk factors as determined by investigators (e.g. maternal medication such as β-blockers from birth to 24 hours of age), who had not yet received a diagnosis of hypoglycaemia (blood glucose concentration below normal range, investigator-defined) and had not received 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 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 older, defined as any of the following: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy or developmental delay/intellectual impairment (developmental quotient or intelligence quotient lower than two standard deviations below the mean)

Secondary outcomes

- Hypoglycaemia (any blood glucose concentration < 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 medication for hypoglycaemia, such as glucagon or corticosteroids (yes/no)
- Number of episodes of hypoglycaemia (investigator-defined) (total number per infant)
- Adverse events (e.g. choking or vomiting at time of administration) (yes/no)
- 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)
- 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 older - investigator-defined (yes/no)
- Visual impairment and severity of impairment at two years of age or older.
- Hearing impairment and severity of impairment at two years of age or older.
- Cerebral palsy and severity of disorder at two years of age or older.
- Developmental delay/intellectual impairment and severity of impairment at two years of age or older.
- Executive dysfunction and severity of dysfunction at two years of age or older.
- Behavioural problems and severity of problems at two years of age or older.
- Abnormal MRI of the brain at two years of age or older.

Search methods for identification of studies

Electronic searches

We used criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group (see the Cochrane Neonatal Group search strategy for specialized register).

We conducted a comprehensive search that included the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 12) in the Cochrane Library; MEDLINE via PubMed (1966 to 23 January 2017); Embase (1980 to 23 January 2017); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 23 January 2017) using the following search terms: (hypoglycaemia OR hypogly*) AND ((dextrose OR glucose) AND gel), plus database-specific limiters for RCTs and neonates (see Appendix 1 for full search strategies for each database). We did not apply language restrictions.

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

Searching other resources

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

Data collection and analysis

We used standard methods of the Cochrane Neonatal Review Group.

Selection of studies

Two review authors (JoH and JB) 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 the full text 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 (including requesting missing results, if required).
- Made final decisions on study inclusion and proceeded to data collection.

Review authors encountered no disagreements when selecting studies.

Data extraction and management

We developed a data extraction form before extracting data. To avoid potential conflict of interest, an independent assessor (Tineke Crawford) and one review author (JB) independently extracted data from each selected article. Data collected included source details, eligibility assessment, methodological details, participant characteristics, intervention details, and outcomes reported. Review authors encountered no disagreements when selecting studies. We entered consensus data into Review Manager.

Assessment of risk of bias in included studies

We assessed the methodological quality of included studies using the criteria specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). One reivew author (JB) and one independent assessor (TC) independently assessed each

study. Review authors encountered no disagreements when selecting studies and entered consensus data into Review Manager.

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 an assessment of whether it should produce comparable groups.

We assessed 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); 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:

- 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); or
- unclear risk of bias.

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

For each included study, we described the method 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:

- 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 method used, if any, to blind outcome assessors from knowledge of which intervention a participant received.

We assessed the method used to blind outcome assessment as:

- low, high, or unclear risk of bias.

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

For each included study, we described the completeness of data, including attrition and exclusions from the analysis. We examined study protocols for discrepancy between intended and reported outcomes. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total number of randomised participants), reasons for attrition or exclusions 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 analysis.

We assessed 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); or
- unclear risk of bias.

Selective reporting (reporting bias)

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

- Low risk of other bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- High risk of other bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- Unclear risk of bias.

Other bias

We described for each included study any important concerns that 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 whether risk of other bias is present.

Measures of treatment effect

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

Unit of analysis issues

We planned to include cluster-randomised trials in analyses along with individually randomised trials, but we did not identify any cluster-randomised trials.

Dealing with missing data

We noted levels of attrition. We carried out analyses on an intention-to-treat basis, when possible, for all outcomes. We analysed all participants when possible in the treatment group to which they were randomised, regardless of the actual treatment received. We planned to contact the original investigators to request missing data when possible. We planned to make explicit the assumptions of any methods used to cope with missing data. We planned to perform sensitivity analyses to assess how sensitive results are to reasonable changes in assumptions made. We planned to address the potential impact of missing data on review findings in the Discussion section.

Assessment of heterogeneity

We planned to consider whether clinical and methodological characteristics of included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary by assessing statistical heterogeneity using the Chi^2 test and the I^2 statistic, considering an I^2 value < 25% to be none, 25% to 49% low, 50% to 74% moderate, and ≥ 75% high heterogeneity. We took an I^2 value greater than 50% and a low P value (< 0.10) from the Chi^2 test for heterogeneity to indicate substantial heterogeneity (Higgins 2011). If we detected substantial heterogeneity, we planned to explore possible explanations by performing sensitivity/subgroup analyses. We planned to take statistical heterogeneity into account when interpreting results, especially if 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 were alert for duplication of data. We planned to assess publication bias by visually inspecting a funnel plot, if we found enough studies (10 or more trials) to make such an inspection valid. Two review authors examined the methods of each study for prespecified outcomes. If all prespecified outcomes were reported in the results, the study carried low risk of bias. If any prespecified outcome was 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 effects of including and excluding these studies in the analysis.

Data synthesis

We evaluated studies for potential clinical diversity and planned to restrict meta-analysis to situations in which clinical consistency was apparent. We evaluated studies for bias, as above, and planned to restrict meta-analysis if bias would be compounded. We planned to use a fixed-effect model to combine data when it was reasonable to assume that studies were estimating the same underlying treatment effect. If we found evidence of clinical heterogeneity, we tried to explain this on the basis of different study characteristics and subgroup analyses.

Quality of evidence

We used the GRADE approach, as outlined in the *GRADE Handbook* (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes.

- Hypoglycaemia (investigator-defined).
- Major neurological disability at two years of age or older, defined as any of the following: 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 events (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 breastfeeding after discharge - WHO 2008 definition.

Two review authors independently assessed the quality of evidence for each of the outcomes above. We considered evidence from RCTs as high quality but downgraded the evidence by one level for serious (or two levels for very serious) limitations on the basis of the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of evidence.

The GRADE approach yields an assessment of the quality of a body of evidence according to 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.

Subgroup analysis and investigation of heterogeneity

We planned 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 vs late preterm 35 to 36 weeks vs moderately preterm 30 to 34 weeks vs extremely preterm < 30 weeks).
- Actual mode of feeding (formula vs breast vs mixed).
- Method of administration of gel (rubbed into buccal mucosa vs sublingual vs other).

- Dose of dextrose gel per administration (≤ 200 mg/kg vs > 200 mg/kg).
- Number of dextrose gel doses administered (1 vs > 1 dose).
- Time of administration of first dose of gel (≤ 1 hour of age vs after 1 hour of age vs after 2 hours of age).

Sensitivity analysis

We planned to conduct sensitivity analysis by examining only trials considered to have low risk of bias. We would report results of sensitivity analyses for primary outcomes only.

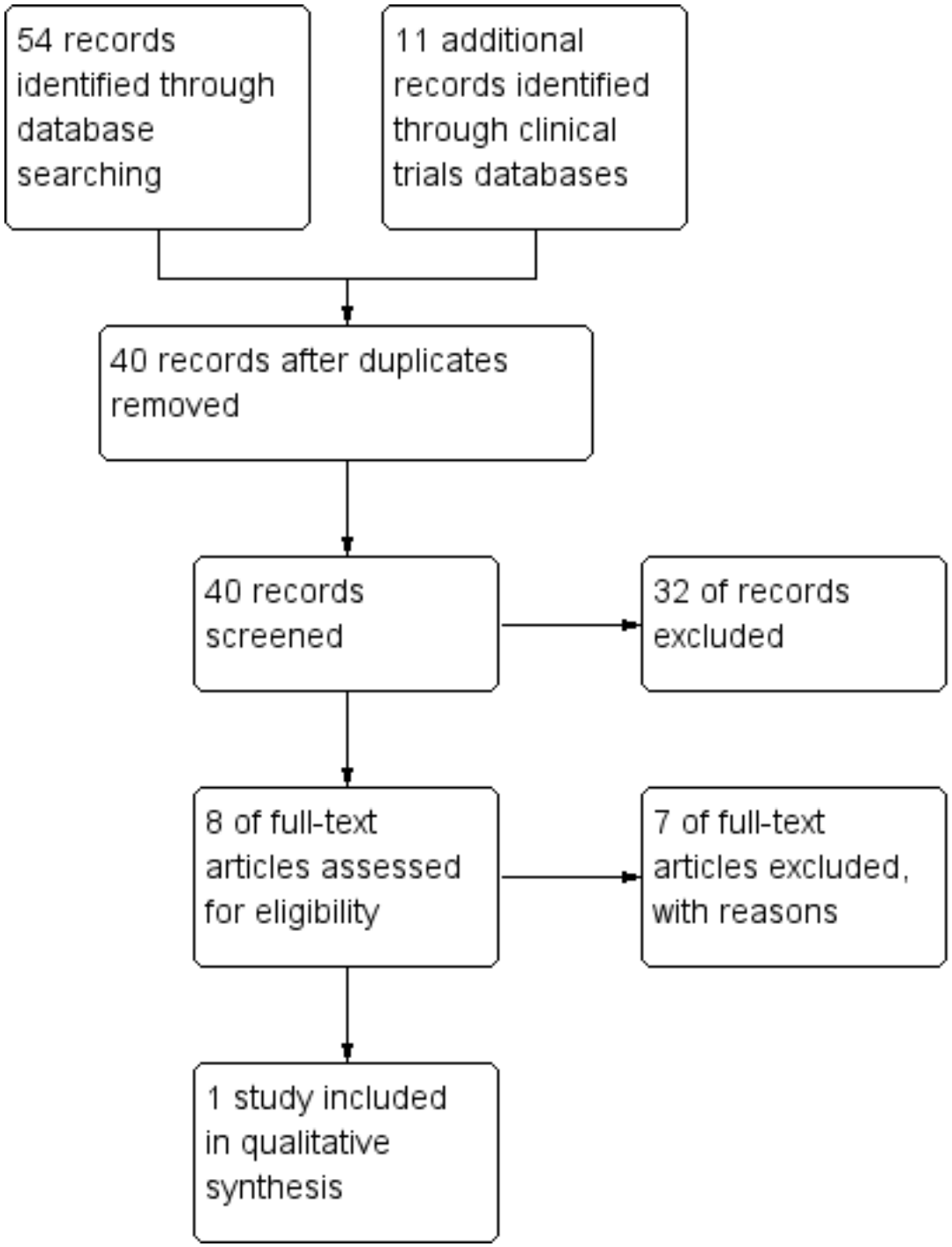
RESULTS

Description of studies

Results of the search

We presented search strategy details in Appendix 1 and results in the study flow diagram (Figure 1). We ran the search on 30 July 2014, 5 October 2016, and 23 January 2017 (for the final update). We identified 65 potential publications through database searching. We removed 25 duplicates and screened 40 potential publications. We excluded 32 publications at this point, as they were not relevant. We assessed the full text of 8 articles for eligibility and excluded 7 full-text articles (2 conference abstracts, 1 commentary on the study, and the trial registration for Hegarty 2016). Two publications (trial registration and trial protocol) described an ongoing trial (Harding 2015); therefore we did not include them in this review. We excluded 1 trial that was not an RCT but was a pilot study of prophylactic dextrose gel (without placebo comparison) on the basis of researcher availability (Hagan 2016).

Figure 1. Study flow diagram.



We did not identify any trials that compared dextrose gel versus no intervention or other therapies for prevention of neonatal hypoglycaemia.

Included studies

We included one study (Hegarty 2016) in this review. This randomised, double-blinded, placebo-controlled study enrolled 416 infants at risk of neonatal hypoglycaemia (infants of diabetic mothers, late preterm (35 or 36 weeks' gestation), small (birth weight < 10th centile or < 2.5 kg), large (birth weight > 90th centile or > 4.5 kg), or other risk factors) but without apparent indication for admission to neonatal intensive care, and of ≥ 35 weeks' gestation and ≥ 2.2 kg birth weight, within one hour after birth. The study was undertaken in two hospitals in New Zealand providing maternity and neonatal services. Primary risk factors for included infants included the following: infant of diabetic mother (301 babies, 73%), preterm (27 babies, 6%), small (49 babies, 12%), and large (38 babies, 9%), with 10 babies (2%) having more than one risk factor. Overall, investigators randomised 277 infants to receive 40% dextrose gel and 138 to receive placebo gel. One additional infant was randomised in error.

Infants were randomised to 40% dextrose or placebo gel (hydroxymethylcellulose) in a 2:1 ratio, and to one of the following dose regimens: 0.5 mL/kg once (66 dextrose, 34 placebo), 1 mL/kg once (73 dextrose, 36 placebo), 0.5 mL/kg for four doses (68 dextrose, 35 placebo), and 1 mL/kg once followed by 0.5 mL/kg for three additional doses (70 dextrose, 33 placebo). Investigators massaged study gel into the buccal mucosa and provided a breastfeed after each dose of gel. Researchers checked blood glucose concentration at two hours after birth, and performed subsequent measurements according to local hospital protocol (two to four hours prefeed for at least the first 12 hours). Investigators used the glucose oxidase method to analyse all blood glucose concentrations and obtained consent before birth. The primary outcome was hypoglycaemia, defined as any blood glucose concentration < 2.6 mmol/L in the first 48 hours after birth.

Excluded studies

We excluded one study (Hagan 2016). This was not an RCT but was a pilot study of prophylactic dextrose gel (without placebo comparison) based on researcher availability.

Risk of bias in included studies

Refer to Figure 2 and Figure 3 for a summary of the risk of bias.

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

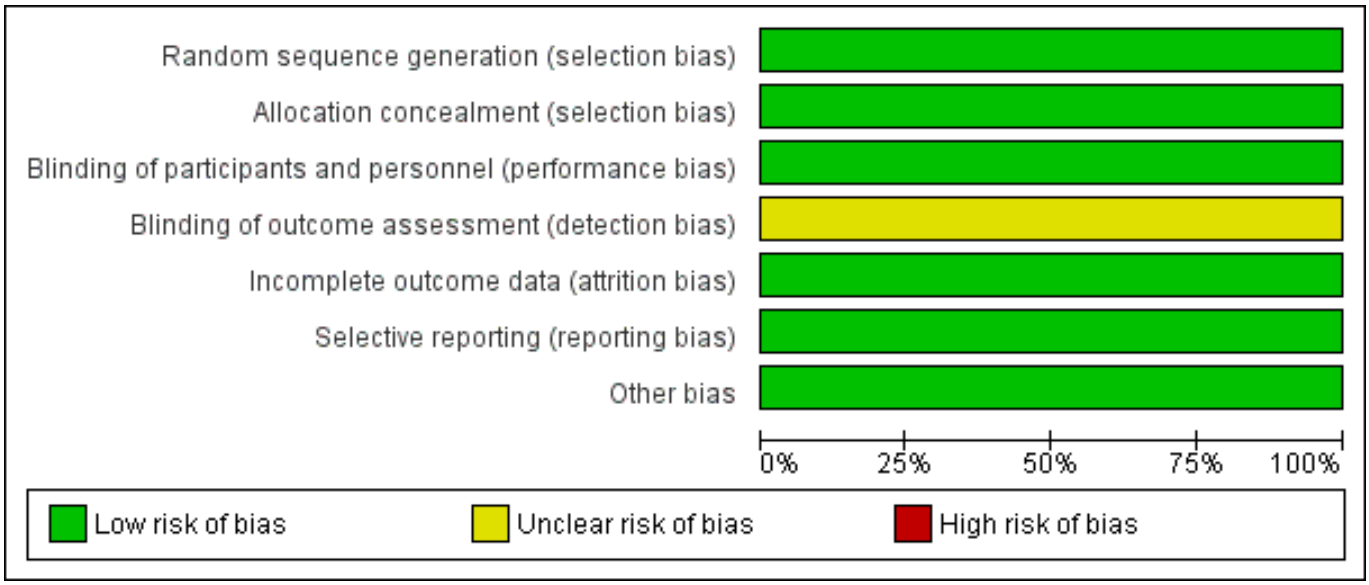
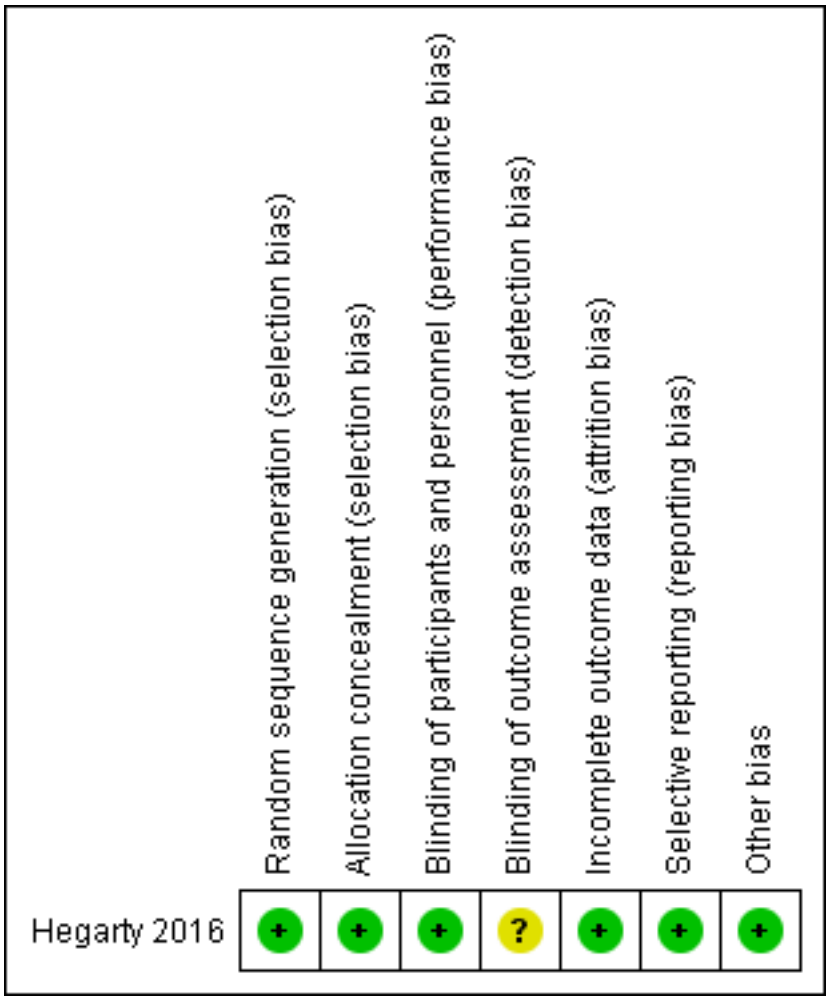


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

Hegarty 2016 reported using computer-generated block randomisation with variable block sizes. We judged this study to be at low risk of selection bias.

Allocation concealment

Hegarty 2016 reported, "Research staff entered demographic and entry criteria data into an online randomisation website that provided a number corresponding to a numbered trial pack". We judged this study to be at low risk of selection bias.

Blinding

Performance bias

Hegarty 2016 reported, "Clinicians, families, and all study investigators were masked to treatment group allocation throughout the study and remain so for the planned follow-up". We judged this study to be at low risk of performance bias.

Detection bias

Hegarty 2016 did not report on whether outcome assessors were blinded. We judged this study to be at unclear risk of detection bias.

Incomplete outcome data

Hegarty 2016 included all randomised infants in the intention-to-treat analysis. We judged this study to be at low risk of attrition bias.

Selective reporting

Hegarty 2016 reported data for all prespecified outcomes documented in the trial registration documentation. We judged this study to be at low risk of reporting bias.

Other potential sources of bias

Hegarty 2016 reported that intervention and control groups were balanced at baseline. We did not identify any other potential sources of bias. We judged this study to be at low risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Dextrose gel compared with placebo for prevention of hypoglycaemia in newborn infants

Primary outcomes

1.1 Hypoglycaemia

Oral dextrose gel (any dose) is associated with reduced risk of neonatal hypoglycaemia compared with placebo (risk ratio (RR) 0.76, 95% confidence interval (CI) 0.62 to 0.94; one RCT; n = 415 infants; high-quality evidence). The risk difference (RD) is -0.13 (95% CI -0.23 to -0.03), and on average, 8.3 infants would have to receive prophylactic dextrose gel to prevent one additional case of neonatal hypoglycaemia. Evidence is based on a single robust trial that was appropriately powered to detect differences for this outcome. We found no evidence of imprecision when looking at the confidence intervals, which do not cross the line of no effect. We rated the evidence for this outcome as high quality.

No data were available on the effect of prophylactic dextrose gel on childhood neurodevelopment.

Secondary outcomes

1.2 Receipt of oral dextrose gel treatment for hypoglycaemia

Results showed no statistically significant differences between dextrose gel and placebo for treatment of neonatal hypoglycaemia (RR 0.79, 95% CI 0.56 to 1.12; one RCT; n = 415 infants).

1.3 Receipt of any medication for hypoglycaemia

Additional data received from Hegarty 2016 showed no infants in dextrose gel or placebo groups receiving any medication for hypoglycaemia such as glucagon or corticosteroids.

1.4 Number of episodes of hypoglycaemia per infant

Additional data received from Hegarty 2016 showed that infants in the dextrose gel group had a mean of 1.86 episodes of hypoglycaemia (blood glucose < 2.6 mmol/L, measured by glucose oxidase method; n = 114 infants) and those in the placebo group had a mean of 2.04 episodes per infant (n = 72 infants). The mean difference (MD) was -0.18 episodes (95% CI -0.55 to 0.19; one RCT; n = 186 infants).

1.5 Adverse events

Results showed no statistically significant differences between dextrose gel and placebo groups for the number of adverse events (RR 1.09, 95% CI 0.55 to 2.17; one RCT; n = 413 infants; moderate-quality evidence). We downgraded evidence for imprecision, as the confidence intervals are wide. Imprecision is most likely attributable to low event rates (24/275 for dextrose gel; 11/138 for placebo).

1.6 Separation from mother for treatment of hypoglycaemia

Results showed no statistically significant differences between oral dextrose gel and placebo groups for risk of separation of infant from mother for treatment of hypoglycaemia (RR 0.46, 95% CI 0.21 to 1.01; one RCT; n = 415 infants; moderate-quality evidence). Caution is advised in interpreting these results. The statistical difference is of borderline significance (P = 0.05) in favour of dextrose gel, but event rates are low in both groups, which suggests that power may be insufficient to detect true differences between groups (11/277 events in the dextrose gel group, 12/138 events in the placebo group). Confidence intervals are wide and cross the line of no effect. We therefore rated this evidence as moderate quality.

1.7 Neonatal seizures

Only one event of neonatal seizures was reported in the dextrose gel group (1/277; 0.4%), and no events were reported in the placebo group (RR 1.50, 95% CI 0.06 to 36.58; one RCT; n = 415 infants).

1.8 Duration of initial hospital stay

Additional data received from Hegarty 2016 showed that the mean duration of stay was 3.88 days per infant (n = 275 infants) in the dextrose gel group and 4.07 days per infant (n = 136) in the placebo group (MD -0.19 days, 95% CI -0.66 to 0.28; one RCT; n = 411 infants).

1.9 Exclusive breastfeeding at/after discharge

Results showed no statistically significant differences in exclusive breastfeeding at the time of hospital discharge between oral dextrose gel and placebo groups (RR 1.00, 95% CI 0.86 to 1.15; one RCT; n = 415 women; moderate-quality evidence). We rated this evidence as moderate quality, as it is based on a single trial, which, although robust, was not powered to detect differences for the outcome of exclusive breastfeeding at or after discharge. Therefore, we downgraded the evidence for imprecision.

1.10 Breastfeeding at six weeks postpartum

Results showed no statistically significant differences in breastfeeding at six weeks postpartum between oral dextrose gel and placebo groups (RR 1.06, 95% CI 0.88 to 1.29; one RCT; n = 386 women; moderate-quality evidence). We rated this evidence as moderate quality, as it is based on a single trial, which, although robust, was not powered to detect differences for the outcome of breastfeeding at six weeks postpartum. Therefore, we downgraded the evidence for imprecision.

No data were available for the following secondary outcomes of this review: receipt of treatment for hypoglycaemia; receipt of intravenous treatment for hypoglycaemia; abnormal MRI of the brain in the neonatal period; breastfeeding after discharge; exclusive breastfeeding at six months of age; developmental disability at two years of age or older; visual impairment and severity of impairment at two years of age or older; hearing impairment and severity of impairment at two years of age or older; cerebral palsy and severity of disorder at two years of age or older; developmental delay/intellectual impairment and severity of impairment at two years of age or older; executive dysfunction and severity of dysfunction at two years of age or older; behavioural problems and severity of problems at two years of age or older; and abnormal MRI of the brain at two years of age or older.

DISCUSSION

Summary of main results

The single randomised study of 415 infants that we identified (Hegarty 2016) reported daa on few of the prespecified outcomes for this review.

Evidence suggests that oral dextrose gel is associated with reduced risk of neonatal hypoglycaemia in high-risk infants compared with placebo (Summary of findings for the main comparison). On average, 8.3 at-risk infants would need to be treated with oral dextrose gel to prevent one additional case of neonatal hypoglycaemia. Researchers found no statistically significant difference between dextrose gel and placebo groups for receipt of oral dextrose gel for

treatment of hypoglycaemia, receipt of any medications for hypoglycaemia, number of episodes of hypoglycaemia per patient, adverse events, separation from mother for treatment for hypoglycaemia, neonatal seizures, duration of initial hospital stay, or breastfeeding at six weeks postpartum.

Overall completeness and applicability of evidence

No data were available for the primary outcome of childhood neurodevelopment at two years, or for the following secondary outcomes of this review: receipt of treatment for hypoglycaemia; receipt of intravenous treatment for hypoglycaemia; abnormal magnetic resonance imaging (MRI) of the brain in the neonatal period; exclusive breastfeeding at six months of age; developmental disability at two years of age or older; visual impairment and severity of impairment at two years of age or older; hearing impairment and severity of impairment at two years of age or older; cerebral palsy and severity of the disorder at two years of age or older; developmental delay/intellectual impairment and severity of impairment at two years of age or older; executive dysfunction and severity of dysfunction at two years of age or older; behavioural problems and severity of problems at two years of age or older; and abnormal MRI of the brain at two years of age or older.

Evidence is based on a single study of a single preparation of dextrose gel compared with placebo in one healthcare setting in which most participants were infants of diabetic mothers; applicability to other healthcare settings and balance of risk factors remain unknown. Evidence for long-term neurodevelopmental and disability outcomes is lacking.

Quality of the evidence

We judged Hegarty 2016 to be at low overall risk of bias, and the quality of evidence as assessed by the GRADE method ranged from high to moderate for selected outcomes with associated data. We advise caution in interpreting some of the data, as event rates were low and may not reflect true differences between treatment and control groups.

Potential biases in the review process

We believe that we have made every effort to minimise bias in the review process. We conducted a systematic search of the literature for randomised controlled trial evidence, not restricted by language or date of publication. When necessary, we attempted to contact authors of primary studies to obtain additional methodological and/or outcome data. We adhered to the Cochrane method of searching and performing data extraction and analysis. Review authors who were also directly involved in the Hegarty 2016 study were not involved in study selection or data extraction associated with this study.

Agreements and disagreements with other studies or reviews

The Cochrane review, "Oral dextrose gel for the treatment of hypoglycaemia in newborn infants" (Weston 2016), reported that treatment of hypoglycaemia with oral dextrose gel was associated with a reduction in separation of mother and infant and increased likelihood of full breastfeeding following discharge. This review also found no evidence of adverse events of dextrose gel during the neonatal period or at two years' corrected age.

AUTHORS' CONCLUSIONS

Implications for practice

We identified one trial that found that use of prophylactic oral dextrose gel was associated with reduced risk of neonatal hypoglycaemia in infants at risk of hypoglycaemia. This trial was designed as a dosage trial for a larger study that will assess effects on neurodevelopment. The authors of this review consider it important to ascertain the effects of prophylactic dextrose gel not only on blood glucose concentration, but also on longer-term outcomes. Furthermore, available evidence is limited to a cohort of at-risk infants, most of whom were infants of diabetic mothers who were treated on the postnatal ward. Therefore, until additional evidence including effects on neurodevelopmental outcomes becomes available, dextrose gel should not be used routinely for prevention of hypoglycaemia in newborn infants.

We suggest that use of oral dextrose gel for prevention of neonatal hypoglycaemia should be limited to research trials pending further learnings about key longer-term outcomes.

Implications for research

Data on key outcomes of this review are limited, especially for long-term neurodevelopmental and disability outcomes. Future research on prevention of hypoglycaemia should include standardised developmental assessment conducted to determine long-term benefits or adverse events. Future studies should seek to include infants with a wide range of risk factors for neonatal hypoglycaemia. Use of oral dextrose gel for prevention of neonatal hypoglycaemia should also be investigated in resource-poor healthcare settings.

ACKNOWLEDGEMENTS

We acknowledge the support of the Cochrane Neonatal Review Group editorial office and contributions of Tineke Crawford (data extraction and risk of bias assessment) and 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".

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Hegarty 2016

Methods	Randomised parallel controlled trial
Participants	416 infants

Hegarty 2016 *(Continued)*

	Inclusion criteria: infants of diabetic mothers or late preterm infants (35 to 36 weeks' gestation) or small-for-gestational age (< 2.5 kg or < 10th percentile) or large-for-gestational age (> 4.5 kg or > 90th percentile) infants **Exclusion criteria:** not stated. **Setting:** 2 hospitals providing maternity and neonatal services (Auckland City Hospital and Waitakere Hospital) in Auckland, New Zealand **Timing:** August 3, 2013, to November 13, 2014
Interventions	40% dextrose gel massaged into the buccal mucosa as a single dose (0.5 mL/kg or 1 mL/kg at 1 hour) or multiple doses (additional 0.5 mL/kg 3 times pre-feed in first 12 hours) (n = 277) vs Placebo gel massaged into the buccal mucosa using same protocol and volume as the intervention (n = 138)
Outcomes	**Primary outcome** Hypoglycaemia, defined as any blood glucose concentration < 2.6 mmol/L in the first 48 hours after birth **Secondary outcomes** • Admission to NICU (defined as admission for > 4 hours) • Admission to NICU for hypoglycaemia • Hyperglycaemia (blood glucose concentration > 10 mmol/L) • Breastfeeding at discharge from hospital (full or exclusive) • Receipt of any formula before discharge from hospital • Formula feeding at 6 weeks of age • Cost of care until discharge home (to be reported separately) • Maternal satisfaction at 6 weeks
Notes	This trial was funded by the A+ Trust (www.adhb.govt.nz; A+5696); Auckland Medical Research Foundation (www.medicalresearch.org.nz; 1113012); Cure Kids (www.curekids.org.nz; 3537); and Lottery Health Research (http://www.communitymatters.govt.nz; 326844), and by philanthropic donations to the University of Auckland Foundation (www.auckland.ac.nz). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript Australian New Zealand Clinical Trials Registry ACTRN12613000322730

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We used computer-generated blocked randomisation with variable block sizes"
Allocation concealment (selection bias)	Low risk	Centralised allocation. "Research staff entered demographic and entry criteria data into an online randomisation website that provided a number corresponding to a numbered trial pack"

Hegarty 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clinicians, families, and all study investigators were masked to treatment group allocation throughout the study and remain so for planned follow-up
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were analysed with no losses
Selective reporting (reporting bias)	Low risk	All prespecified outcomes are reported. Trial registration was viewed
Other bias	Low risk	Groups appear balanced at baseline. No other evidence of bias

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

Study	Reason for exclusion
Hagan 2016	Not a randomised controlled trial, but a pilot study of prophylactic dextrose gel (without placebo comparison) based on researcher availability

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

Harding 2015

Trial name or title	Hypoglycaemia Prevention With Oral Dextrose Gel (hPOD)
Methods	Randomised parallel controlled trial
Participants	2129 infants **Inclusion criteria:** infants of diabetic mothers or late preterm infants (35 to 36 weeks' gestation) or small (< 2.5 kg or < 10th percentile) or large (> 4.5 kg or > 90th percentile) infants **Exclusion criteria:** major congenital abnormality; previous formula feed or intravenous fluids; previous diagnosis of hypoglycaemia; admitted to NICU; imminent admission to NICU **Setting:** multi-centre
Interventions	40% dextrose gel massaged into buccal mucosa as a single dose (0.5 mL/kg) 1 hour after birth vs Placebo gel massaged into buccal mucosa using same protocol as the intervention
Outcomes	**Primary outcome** Admission to NICU - defined as admission to NICU (or special care baby unit (SCBU) for hospitals using that name) for > 4 hours **Secondary outcomes**

Harding 2015 *(Continued)*

	• Hypoglycaemia (any blood glucose concentration < 2.6 mmol/L in first 48 hours) • Admission to NICU for hypoglycaemia • Hyperglycaemia (any blood glucose concentration > 10 mmol/L) • Breastfeeding at discharge from hospital (full or exclusive) • Receipt of any formula before discharge from hospital • Formula feeding at 6 weeks of age • Cost of care until primary discharge home • Maternal satisfaction (via telephone questionnaire at 6 weeks) • Neurosensory disability at 2 years' corrected age (any of the following: legal blindness; sensorineural deafness requiring hearing aids; cerebral palsy; Bayley Scale of Infant Development Version III cognitive, language or motor score < 1 standard deviation below the mean)
Starting date	January 2015
Contact information	j.harding@auckland.ac.nz
Notes	Trials registration: ACTRN12614001263684

DATA AND ANALYSES

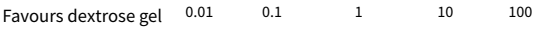
Comparison 1. Dextrose gel versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hypoglycaemia	1	415	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.62, 0.94]
2 Receipt of oral dextrose gel treatment for hypoglycaemia	1	415	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.56, 1.12]
3 Receipt of any medications for hypoglycaemia, such as glucagon or corticosteroids	1	415	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Number of episodes of hypoglycaemia (glucose oxidase method) (total number per infant)	1	186	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.55, 0.19]
5 Adverse events (e.g. choking or vomiting at time of administration)	1	413	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.55, 2.17]
6 Separation from mother for treatment of hypoglycaemia (admission to NICU for hypoglycaemia)	1	415	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.21, 1.01]
7 Neonatal seizures	1	415	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.06, 36.58]
8 Duration of initial hospital stay (days)	1	411	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.66, 0.28]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
9 Exclusive breastfeeding at discharge	1	415	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.15]
10 Breastfeeding (6 weeks)	1	386	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.88, 1.29]

Analysis 1.1. Comparison 1 Dextrose gel versus control, Outcome 1 Hypoglycaemia.

Study or subgroup	Dextrose gel n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hegarty 2016	115/277	75/138		100%	0.76[0.62,0.94]
Total (95% CI)	**277**	**138**		**100%**	**0.76[0.62,0.94]**
Total events: 115 (Dextrose gel), 75 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.55(P=0.01)					

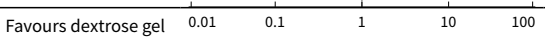


Analysis 1.2. Comparison 1 Dextrose gel versus control, Outcome 2 Receipt of oral dextrose gel treatment for hypoglycaemia.

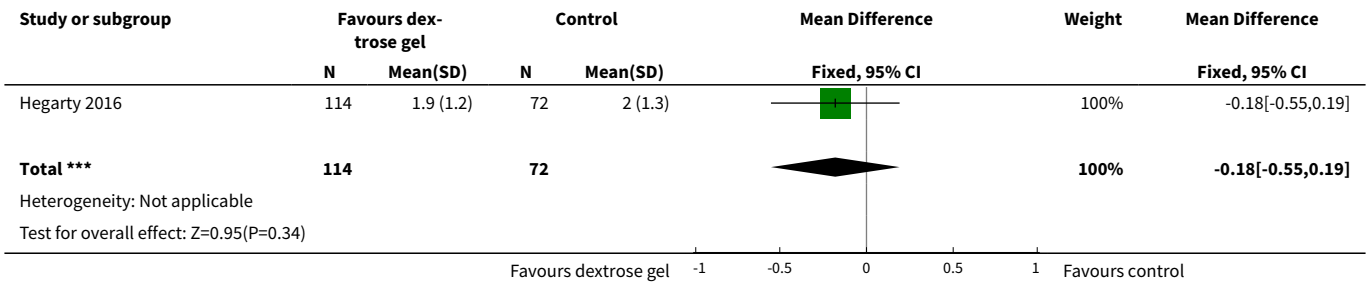
Study or subgroup	Dextrose gel n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hegarty 2016	62/277	39/138		100%	0.79[0.56,1.12]
Total (95% CI)	**277**	**138**		**100%**	**0.79[0.56,1.12]**
Total events: 62 (Dextrose gel), 39 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.33(P=0.18)					

Analysis 1.3. Comparison 1 Dextrose gel versus control, Outcome 3 Receipt of any medications for hypoglycaemia, such as glucagon or corticosteroids.

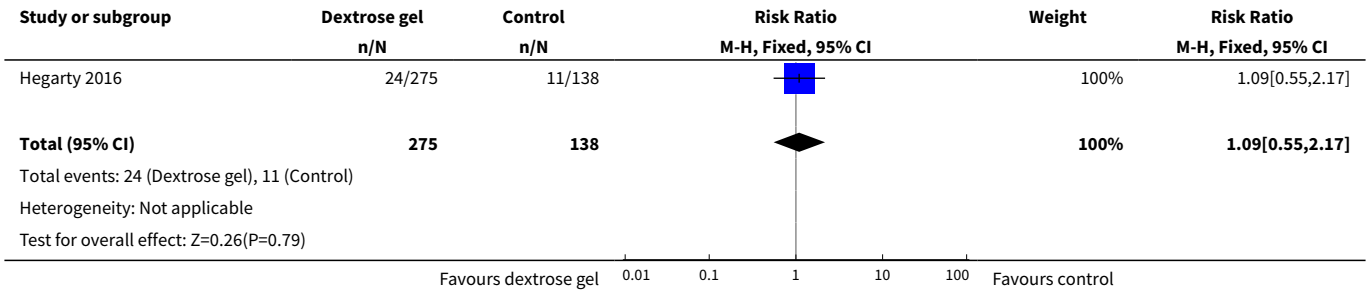
Study or subgroup	Dextrose gel n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hegarty 2016	0/277	0/138			Not estimable
Total (95% CI)	**277**	**138**			**Not estimable**
Total events: 0 (Dextrose gel), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



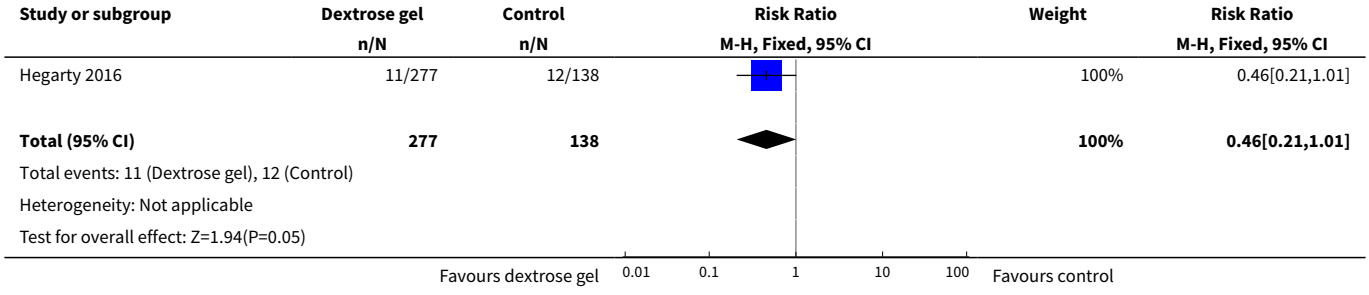
Analysis 1.4. Comparison 1 Dextrose gel versus control, Outcome 4 Number of episodes of hypoglycaemia (glucose oxidase method) (total number per infant).



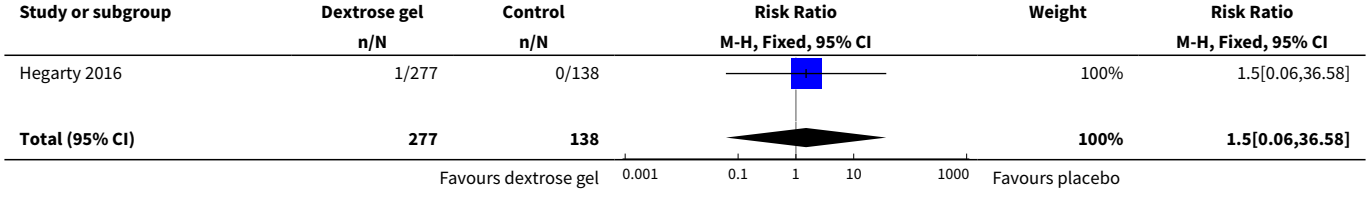
Analysis 1.5. Comparison 1 Dextrose gel versus control, Outcome 5 Adverse events (e.g. choking or vomiting at time of administration).

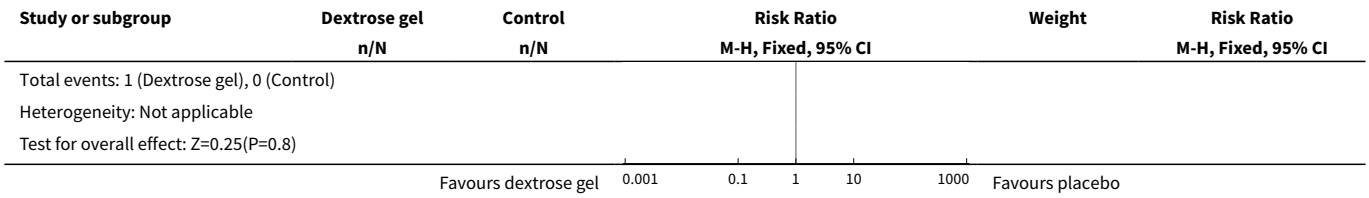


Analysis 1.6. Comparison 1 Dextrose gel versus control, Outcome 6 Separation from mother for treatment of hypoglycaemia (admission to NICU for hypoglycaemia).

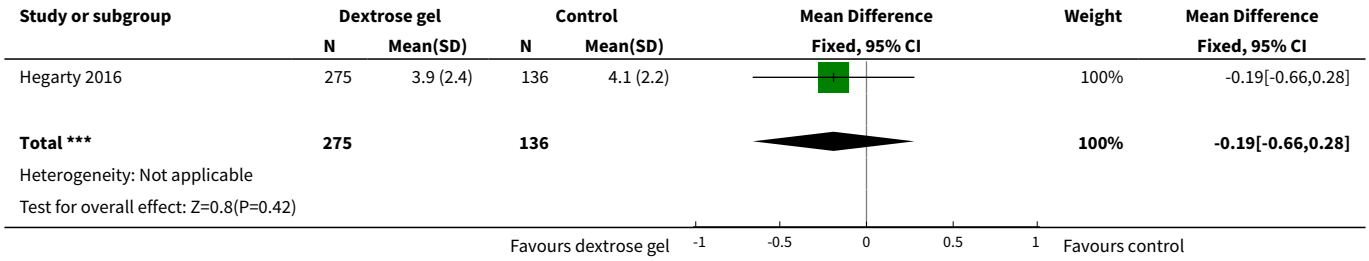


Analysis 1.7. Comparison 1 Dextrose gel versus control, Outcome 7 Neonatal seizures.

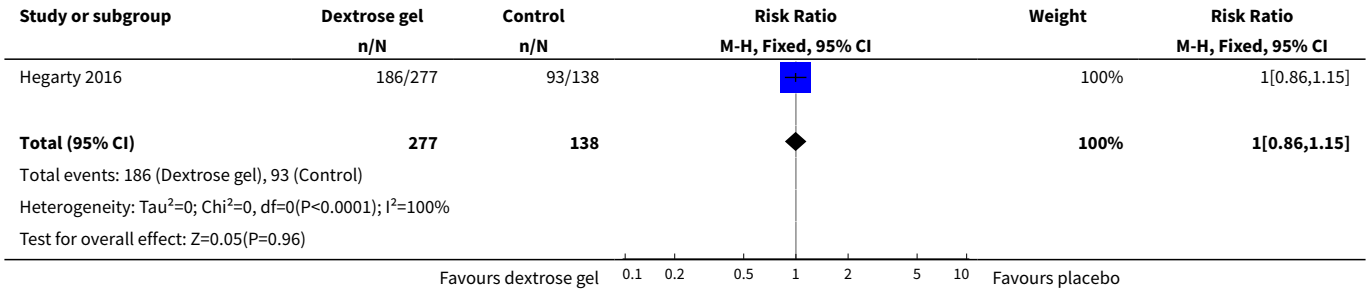




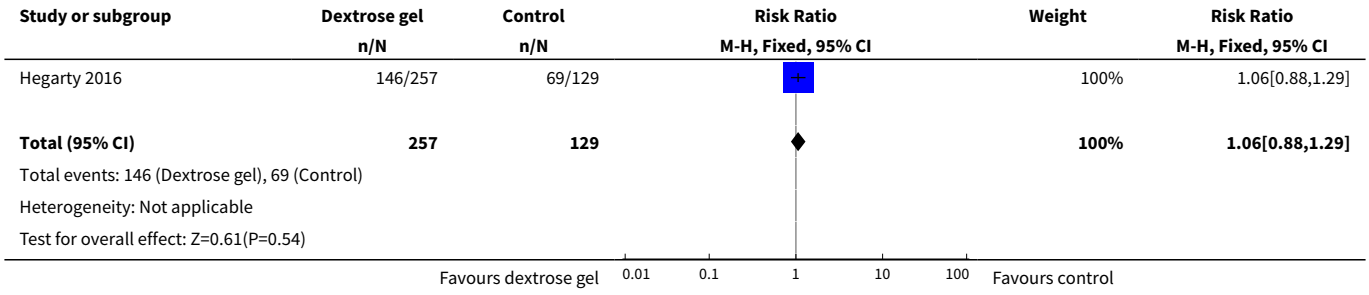
Analysis 1.8. Comparison 1 Dextrose gel versus control, Outcome 8 Duration of initial hospital stay (days).



Analysis 1.9. Comparison 1 Dextrose gel versus control, Outcome 9 Exclusive breastfeeding at discharge.



Analysis 1.10. Comparison 1 Dextrose gel versus control, Outcome 10 Breastfeeding (6 weeks).



APPENDICES

Appendix 1. Standard search methods

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomised [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

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 (randomised controlled trial or controlled clinical trial or randomised 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 (randomised controlled trial OR controlled clinical trial OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

CONTRIBUTIONS OF AUTHORS

Jo Hegarty wrote the first draft of the protocol and co-ordinated and wrote subsequent drafts, with significant editorial assistance provided 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 are authors of the included study (Hegarty JE, Harding JE, Gamble GD, Crowther, CA, Edlin R, Alsweiler JM. Preventing neonatal hypoglycaemia with oral dextrose gel: a randomised controlled trial. PLOS Medicine 2016;13(10):e1002155) and investigators on the large ongoing study (Harding JE, Hegarty JE, Crowther CA, Edlin R, Gamble G, Alsweiler JM. Randomised trial of neonatal hypoglycaemia prevention with oral dextrose gel (hPOD): study protocol. BMC Pediatrics 2015;15(120)).

Review authors report no other conflict and in particular have received no benefits in cash or kind in relation to any element of the proposed review.

SOURCES OF SUPPORT

Internal sources

- Gravida: National Research Centre for Growth and Development, New Zealand.

  PhD Scholarship for Jo Hegarty
- Auckland District Health Board, New Zealand.

  Clinical Salary for Jo Hegarty
- Liggins Institute, University of Auckland, New Zealand.

  University appointments for Jane Harding, Caroline Crowther, Jane Alsweiler, and Julie Brown

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA.

  Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201600005C