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

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[Intervention Review]

Oral dextrose gel to prevent hypoglycaemia in at-risk neonates

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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 usually involve use of formula milk or admission to the neonatal unit. Dextrose gel is non-invasive, inexpensive and effective for treatment of neonatal hypoglycaemia. Prophylactic dextrose gel can reduce the incidence of neonatal hypoglycaemia, thus potentially reducing separation of mother and baby and supporting breastfeeding, as well as preventing brain injury.

This is an update of a previous Cochrane Review published in 2017.

Objectives

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

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2020, Issue 10) in the Cochrane Library; and Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) on 19 October 2020. We also searched clinical trials databases and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs comparing oral dextrose gel versus placebo, no intervention, or other therapies for the prevention of neonatal hypoglycaemia.

Data collection and analysis

Two review authors independently extracted data and assessed risk of bias. We contacted investigators to obtain additional information. We used fixed-effect meta-analyses. We used the GRADE approach to assess the certainty of evidence.

Main results

We included two studies conducted in high-income countries comparing oral dextrose gel versus placebo in 2548 infants at risk of neonatal hypoglycaemia. Of these, one study was included in the previous version of this review. We judged these two studies to be at low risk of bias, and that the evidence for most outcomes was of moderate certainty.

Meta-analysis of the two studies showed that oral dextrose gel reduces the risk of hypoglycaemia (risk ratio (RR) 0.87, 95% confidence interval (CI) 0.79 to 0.95; risk difference (RD) -0.06, 95% CI -0.10 to -0.02; 2548 infants; high certainty evidence). One study reported that oral dextrose gel probably reduces the risk of major neurological disability at two years' corrected age (RR 0.21, 95% CI 0.05 to 0.78; RD -0.05, 95% CI -0.09 to 0.00; 360 infants; moderate certainty evidence).

Meta-analysis of the two studies showed that oral dextrose gel probably reduces the risk of receipt of treatment for hypoglycaemia during initial hospital stay (RR 0.89, 95% CI 0.79 to 1.00; 2548 infants; moderate certainty evidence) but makes little or no difference to the risk of receipt of intravenous treatment for hypoglycaemia (RR 1.01, 0.68 to 1.49; 2548 infants; moderate certainty evidence). Oral dextrose gel may have little or no effect on the risk of separation from the mother for treatment of hypoglycaemia (RR 1.12, 95% CI 0.81 to 1.55; two studies, 2548 infants; low certainty evidence).

There is probably little or no difference in the risk of adverse events in infants who receive oral dextrose gel compared to placebo gel (RR 1.22, 95% CI 0.64 to 2.33; two studies, 2510 infants; moderate certainty evidence), but there are no studies comparing oral dextrose with other comparators such as no treatment, standard care or other therapies.

No data were available on exclusive breastfeeding after discharge.

Authors' conclusions

Oral dextrose gel reduces the risk of neonatal hypoglycaemia in at-risk infants and probably reduces the risk of major neurological disability at two years of age or greater without increasing the risk of adverse events compared to placebo gel. Additional large follow-up studies at two years of age or older are required. Future research should also be undertaken in low- and middle-income countries, preterm infants, using other dextrose gel preparations, and using comparators other than placebo gel. There are three studies awaiting classification and one ongoing study which may alter the conclusions of the review when published.

PLAIN LANGUAGE SUMMARY

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

Review question

Is oral dextrose gel effective and safe in preventing low blood glucose levels and reducing long-term disability in newborn babies at risk of low blood glucose levels?

Background

Low blood sugar (glucose) levels are important because they are common and are associated with brain injury in newborn babies. Up to 15 of every 100 babies will have low blood glucose levels over the first few days after they are born, and as many as half of babies who are at higher risk (those born preterm, or smaller or larger than usual, or whose mothers have diabetes).

Low blood glucose levels can cause problems with academic achievement and development during childhood. Some evidence suggests that even one episode of low blood glucose or episodes that are undetected can contribute to these problems. Therefore, it would be useful to prevent low glucose levels from occurring. Additionally, treatments for low glucose levels often include formula milk or admission to the neonatal unit, leading to the separation of mother and baby. The treatments and the separation may both impair breastfeeding.

Dextrose (sugar) gel can be rubbed on the inside of a baby's mouth, where the sugar can be absorbed and help raise blood glucose levels, thus potentially helping prevent low glucose levels.

Study characteristics

We identified two studies in high-income countries that compared oral dextrose gel with placebo (inactive) gel for preventing low blood glucose levels in 2548 at-risk infants. The evidence in this Cochrane Review is current to October 2020.

Key results

Two studies showed that preventative oral dextrose gel reduces the risk of low blood glucose levels in newborn infants at risk. A single study reporting two-year outcomes in 360 infants found that oral dextrose gel given to at-risk infants to prevent low blood glucose levels probably reduces the risk of major disability at two years of age, but additional follow-up studies are needed.

Two studies showed that oral dextrose gel probably reduces the chance of receiving any treatment for low blood glucose during initial hospital stay but makes little or no difference to the chance of receiving intravenous treatment for low glucose, or separation from the mother for treatment of low glucose levels.

Evidence from two studies suggests that infants given oral dextrose gel are not at a higher risk of adverse events (harms) such as choking or vomiting compared with infants given placebo gel, but there was no information to assess whether oral dextrose gel is safer than no treatment or other therapies. No data were available on exclusive breastfeeding after discharge.

We assessed the risk of bias in the included studies as low, meaning it is unlikely that there is a systematic error in estimating the effect of the intervention.

Future research should be undertaken in low- and middle-income countries, preterm infants, using other dextrose gel preparations and comparators other than placebo gel. There are three studies awaiting classification and one ongoing study which may alter the conclusions of the review when they are published.

Certainty of evidence

We graded the certainty of the evidence as moderate for all outcomes except risk of low blood glucose levels (assessed as high certainty) and separation from mother (assessed as low certainty).

Summary of findings 1. 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 and Australia
Intervention: dextrose gel
Comparison: placebo gel

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with dextrose gel				
Hypoglycaemia (investigator-defined)	433 per 1000	377 per 1000 (342 to 411)	RR 0.87 (0.79 to 0.95)	2548 (2 RCTs)	⊕⊕⊕⊕ HIGH	
Major neurological disability at 2 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 2 SD below the mean))	60 per 1000	47 per 1000 (3 to 41)	RR 0.21 (0.05 to 0.78)	360 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	Low event rates: 3/277 in dextrose gel group and 7/138 in placebo group.
Receipt of treatment for hypoglycaemia during initial hospital stay (investigator-defined, any treatment - oral dextrose gel, intravenous dextrose, or other drug therapy) during initial hospital stay (yes/no)	316 per 1000	281 per 1000 (249 to 316)	RR 0.89 (0.79 to 1.00)	2548 (2 RCTs)	⊕⊕⊕⊖ MODERATE[b]	
Receipt of intravenous treatment for hypoglycaemia (yes/no)	37 per 1000	37 per 1000 (25 to 55)	RR 1.01 (0.68 to 1.49)	2548 (2 RCTs)	⊕⊕⊕⊖ MODERATE[c]	
Adverse events[#] (e.g. choking or vomiting at time of administration)	10 per 1000	12 per 1000 (6 to 24)	RR 1.22 (0.64 to 2.33)	2510 (2 RCTs)	⊕⊕⊕⊖ MODERATE[c]	Low event rates: 27/1322 in dextrose gel group and

						12/1188 in placebo group.
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))	50 per 1000	56 per 1000 (40 to 77)	RR 1.12 (0.81 to 1.55)	2548 (2 RCTs)	⊕⊕⊖⊖ LOW[c,d]	
Breastfeeding (exclusive after discharge) - not reported (WHO 2008 definition (yes/no))	-	-	-	-	-	No data were reported for this outcome

*__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); #Placebo gel was the comparator.
CI: confidence interval; NICU: neonatal intensive care unit; OR: odds ratio; RR: risk ratio; SD: standard deviations

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level for serious imprecision (due to low event rates)
[b]Downgraded one level for serious imprecision (due to the CI including 1)
[c]Downgraded one level for serious imprecision (due to the CI including possibility of both benefits or harms)
[d]Downgraded one level for serious inconsistency (due to the high I^2 value of 83%)

BACKGROUND

Description of the condition

Hypoglycaemia is the most common metabolic disorder of the newborn (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 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, more recent studies have reported widespread MRI changes 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), born large for gestation (Weissmann-Brenner 2012), small for gestation (Hawdon 1993), or 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 b-agonists (Kurtoglu 2005), and beta-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). A blood glucose concentration of less than 2.6 mmol/L has been widely accepted as a definition of hypoglycaemia (Harris 2014). This was heavily influenced by two studies. One described abnormal sensory evoked potentials among infants with blood glucose concentrations lower than 2.6 mmol/L (Koh 1988). The second reported a relationship between the number of days on which blood glucose measurements lower than 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 exhibit signs (Hawdon 1993; Kalhan 2000; Koivisto 1972). However, Stenninger and colleagues found that longer-term neurodevelopmental outcomes did not differ between infants who exhibited signs and those who did not (Stenninger 1998).

The effects of transient neonatal hypoglycaemia on longer-term outcomes are not yet fully defined. However, some evidence suggests that even transient and undetected episodes may be associated with adverse outcomes (McKinlay 2017). For example, a retrospective population study demonstrated an association between a single initial blood glucose concentration of less than 2.6 mmol/L, followed by a repeat result above this, and lower academic test scores at 10 years of age (Kaiser 2015). Further, a prospective cohort study of infants at risk of neonatal hypoglycaemia, half of whom became hypoglycaemic and were treated to maintain blood glucose concentrations of 2.6 mmol/L or higher, found that clinically undetected low interstitial glucose concentrations were associated with an increased risk of executive dysfunction at four and a half years of age (McKinlay 2017). These findings suggest that even an effective treatment for neonatal hypoglycaemia may not be enough to optimise outcomes of all babies, and that prophylaxis should be considered.

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 (WHO) states "… an approach aimed first at the prevention of hypoglycaemia, second at its reliable detection in infants 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 and management of infants at risk of neonatal hypoglycaemia involves:

- early identification of pertinent risk factors;
- early feeding, skin-to-skin contact and ensuring that newborns are kept warm and dry;
- pre-feed blood glucose concentration measurement to determine blood glucose concentrations 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; UNICEF 2013; WHO 1997).

However, despite recommendations to prevent neonatal hypoglycaemia, there is little evidence of effective interventions to achieve this.

Early skin-to-skin contact may reduce the incidence of neonatal hypoglycaemia because it has a protective influence on thermoregulation (UNICEF 2013). A meta-analysis of two randomised trials of low birthweight infants found that compared with standard of care, skin-to-skin contact was associated with a decreased risk of neonatal hypoglycaemia (Boundy 2016). Further, a Cochrane Review of three randomised trials of 144 healthy full-term, low birthweight infants reported that skin-to-skin contact during the establishment of breastfeeding was associated with a 10 mg/dL (0.6 mmol/L) higher blood glucose concentration at 75 to 90 minutes after birth compared with standard contact. However, the evidence was graded as low certainty (Moore 2016). A retrospective pre- and post-intervention study of 561 infants at risk of neonatal hypoglycaemia reported that prolonged skin-to-skin contact for at least 12 hours after birth during blood glucose monitoring was associated with a 4.6% reduction in admission rates to the NICU for neonatal hypoglycaemia and a 3.8% reduction in the number of infants receiving intravenous dextrose (Chiruvolu 2017). However, the small sample sizes and poor quality of some of these studies limit confidence in the findings.

Early feeding is also recommended for prevention of neonatal hypoglycaemia. In infants of diabetic mothers, early feeding (within 30 minutes of birth) was reported to decrease the incidence of

subsequent neonatal hypoglycaemia, and increase mean blood glucose concentration (Chertok 2009). However, two other studies showed that the early initiation of breastfeeding within 30 minutes to one hour after birth does not affect blood glucose concentration at one and two hours in infants without risk factors for neonatal hypoglycaemia (Sweet 1999; Zhou 2017).

Antenatal expression of colostrum may potentially increase the available colostrum supply for infants soon after birth, while reducing the time taken to establish breastfeeding and decreasing the use of formula (Cox 2006). However, the Diabetes and Antenatal Milk Expressing (DAME) study that randomised women with diabetes to antenatal expression of breastmilk or standard care reported no differences between groups for mean blood glucose concentrations (Forster 2011), incidence of neonatal hypoglycaemia, admission to NICU for hypoglycaemia or time until euglycaemic status was achieved (defined as three consecutive blood glucose measurements of 2.6 mmol/L or higher) (Forster 2017). This is consistent with a post hoc analysis of a randomised controlled trial which showed that breastmilk expressed either before or after birth and given to hypoglycaemic infants did not increase glucose concentrations (Harris 2017).

Supplementation or substitution of breastfeeding with fluid or foods other than expressed breast milk may reduce the duration of breastfeeding (Blomquist 1994; Demir 2020; Smith 2016). 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 meet the essential energy needs of infants with additional risk factors for neonatal hypoglycaemia. Thus, infants at 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 trials in India compared formula with formula plus added powdered sugar for prevention of subsequent hypoglycaemia in infants at risk of hypoglycaemia (small or large for gestational age) (Singhal 1991; Singhal 1992). Both studies reported a significant reduction in the incidence of subsequent hypoglycaemia among infants who received formula plus powdered sugar. In contrast, a randomised trial in Thailand of 425 infants at risk of neonatal hypoglycaemia reported no difference in the blood glucose concentrations measured at one, three and six hours after birth of infants who received 200 mg/kg prophylactic oral sucrose solution plus feeding versus infants who received feeding alone (Surachaidungtavil 2020).

The ideal intervention would be effective in preventing hypoglycaemia while reducing the need for artificial formula, improving breastfeeding rates, reducing costs, as well as potentially reducing the risk of later adverse outcomes. Oral dextrose gel is an effective first line treatment for neonatal hypoglycaemia (Harris 2013), that also improves breastfeeding (Weston 2016), reduces costs (Glasgow 2018), and appears safe (Harris 2016). This is an updated review of the previously published Cochrane Review, "Oral dextrose gel to prevent hypoglycaemia in at-risk neonates," which found that oral dextrose gel was reported to be effective and safe in reducing the incidence of neonatal hypoglycaemia in one randomised trial (Hegarty 2017). No longer-term outcomes were available.

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 (US dollars) 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 or admission to the neonatal unit for intravenous dextrose, or both. 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 were found to be effective and safe 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 given to newborn infants at risk of hypoglycaemia in preventing hypoglycaemia and reducing long-term neurodevelopmental impairment.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs, including cluster-randomised trials but not cross-over trials. We included both published and unpublished studies. We included unpublished studies and studies published only as abstracts when 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 beta-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 conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL 2020, Issue 10) in the Cochrane Library; and Ovid MEDLINE(R) and EpubAhead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) (1946 to 19 October 2020). We have included the search strategies for each database in Appendix 1. We did not apply language restrictions.

We searched clinical trial registries for ongoing or recently completed trials. We searched the World Health Organization's International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en/) and the US National Library of Medicine's ClinicalTrials.gov (clinicaltrials.gov) via Cochrane CENTRAL. Additionally, we searched the ISRCTN Registry (www.isrctn.com) and the ANZCTR Registry (www.anzctr.org.au) for any unique trials not found through the Cochrane CENTRAL search.

For the 2020 update, we developed a new search strategy. The previous search methods are available in Appendix 2.

Searching other resources

We searched the reference lists of included studies 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 and GRADE to assess the certainty of evidence.

Selection of studies

Two review authors (TE, GL) independently assessed the eligibility of each study for inclusion. We did not encounter any disagreements.

Data extraction and management

Two review authors (TE, GL) independently extracted data from the eligible studies. We contacted investigators of two studies included in the meta-analysis for additional data (Harding 2020; Hegarty 2016a). We did not encounter any disagreements.

Assessment of risk of bias in included studies

Two review authors (TE, GL) independently assessed the risk of bias (low, high, or unclear) of all included studies using the Cochrane 'Risk of bias' tool (Higgins 2011), for these domains:

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- any other bias.

We resolved any disagreements encountered by discussion or consultation with a third review author. See Appendix 3 for a more detailed description of each domain.

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 for inclusion.

Dealing with missing data

We carried out analyses on an intention-to-treat basis for all outcomes. We contacted the original investigators to request missing data when possible.

Assessment of heterogeneity

We considered whether clinical and methodological characteristics of included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary by assessing statistical heterogeneity using the Chi^2 test and the I^2 statistic, considering an I^2 value of less than 25% to be none, 25% to 49% low, 50% to 74% moderate, and 75% or greater to be 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 2019). If we detected substantial heterogeneity, we planned to explore possible explanations by performing sensitivity or subgroup analyses but we were unable to do this given the small number of eligible trials. We took statistical heterogeneity into account when interpreting results, especially when we noted variation in the direction of effect.

Assessment of reporting biases

Reporting biases arise when dissemination of research findings is influenced by the nature and direction of results. Some types of reporting bias (e.g. publication bias, multiple publication bias, language bias) reduce the likelihood that all studies eligible for a review will be retrieved. If all eligible studies are not retrieved, the review may be biased. We conducted a comprehensive search for eligible studies and were alert for duplication of data. We were unable to assess publication bias by visually inspecting a funnel plot because we did not identify 10 or more trials to make such an inspection valid. Two review authors (TE, GL) examined the methods of each study for prespecified outcomes and if all prespecified outcomes were reported in the results, we considered 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.

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 restricted meta-analysis if bias would be compounded. We used 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 planned to try to explain this on the basis of different study characteristics and subgroup analyses.

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 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 (≤ 200 mg/kg versus > 200 mg/kg).
- Number of dextrose gel doses administered (one versus > one dose).
- Time of administration of first dose of gel (≤ one hour of age versus after one hour of age versus after two hours of age).

Sensitivity analysis

We planned to conduct sensitivity analysis by examining only trials considered to have a low risk of bias across all domains as determined by the Cochrane 'Risk of bias' tool (Higgins 2011). We planned to report results of sensitivity analyses for

primary outcomes only. However, we did not conduct the planned sensitivity analysis because included trials had a low risk of bias.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence for the following (clinically relevant) outcomes: hypoglycaemia; 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; adverse events; separation from the mother for treatment of hypoglycaemia; and exclusive breastfeeding after discharge.

Two review authors (TE, GL) independently assessed the certainty of evidence for each of the outcomes. We considered evidence from randomised controlled trials as high certainty 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 'Summary of findings 1' to report the certainty of evidence.

The GRADE approach results in an assessment of the certainty of a body of evidence as one of four grades.

- High certainty: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low certainty: we are very uncertain about the estimate.

RESULTS

Description of studies

We included two studies in this update: one new study (Harding 2020), that was identified as an ongoing study in the previous Cochrane Review (Hegarty 2017); and one study that was included in the previous review (Hegarty 2016a), that had new follow-up data.

Results of the search

See Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification, and Characteristics of ongoing studies.

Our search, in October 2020, identified 78 records, of which 18 were duplicates. After screening the titles and abstracts of 60 records, we excluded 48 because they were not relevant, and assessed the full text of 12 records (see Figure 1). We excluded four primary and two secondary references (Bourchier 1992; Coors 2018; Retbi 2013; Van Loghum 2014). One study is ongoing (NCT04353713); and three are awaiting classification (CTRI/2017/11/010645; NCT04185766; TCTR20190805003).

Figure 1. Study flow diagram

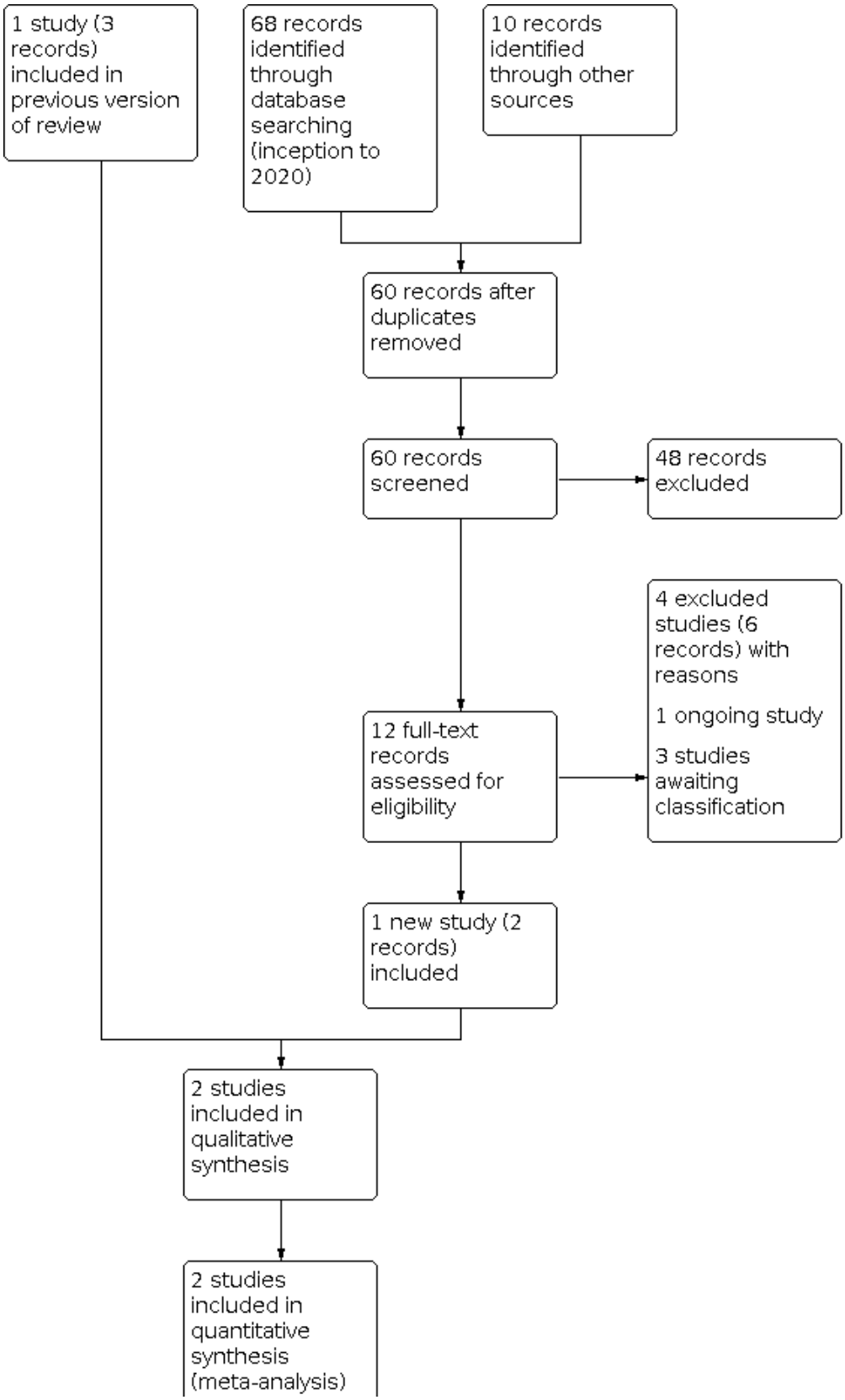


Figure 1. (Continued)

synthesis
(meta-analysis)

Included studies

We identified two eligible randomised, blinded, placebo-controlled trials (Harding 2020; Hegarty 2016a), that enrolled a total of 2548 late preterm and term infants born at risk of neonatal hypoglycaemia (see Characteristics of included studies).

The study by Hegarty 2016a took place in two centres in New Zealand. They randomised 416 infants (including one infant randomised in error) in a 2:1 ratio to one of the following dose regimens of 40% dextrose gel or placebo: 0.5 mL/kg once, 1 mL/kg once, 0.5 mL/kg for four doses, and 1 mL/kg once followed by 0.5 mL/kg for three additional doses. Gel was massaged into the buccal mucosa at one hour after birth, followed by a breastfeed. Blood glucose concentration was checked using the glucose oxidase method at two hours after birth, and subsequent measurements were performed according to local hospital protocol (two to four hours pre-feed for at least the first 12 hours). Of those randomised, 401 infants were eligible for follow-up at two years' corrected age (13 withdrawals, one death) and a total of 360 were assessed.

The study by Harding 2020 recruited from 18 maternity hospitals in New Zealand and Australia. A total of 2149 infants born at risk of neonatal hypoglycaemia but unlikely to require neonatal unit admission for other reasons were randomised to receive a single dose of 40% dextrose gel or placebo gel massaged into the buccal mucosa at one hour after birth followed by a breastfeed. Blood glucose concentration was measured at two hours after birth and then according to hospital standard practice.

Excluded studies

We excluded four studies (six records) for the following reasons:

- Three studies were commentaries which evaluated dextrose gel as a treatment for neonatal hypoglycaemia (Bourchier 1992; Retbi 2013; Van Loghum 2014).
- One study (three records) was a non-randomised study which investigated oral dextrose gel as prophylaxis against transient neonatal hypoglycaemia in at-risk infants (Coors 2018).

See Characteristics of excluded studies for more details.

Risk of bias in included studies

Refer to Figure 2 and Figure 3 for a summary of the 'Risk of bias' assessment and Characteristics of included studies for more details.

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

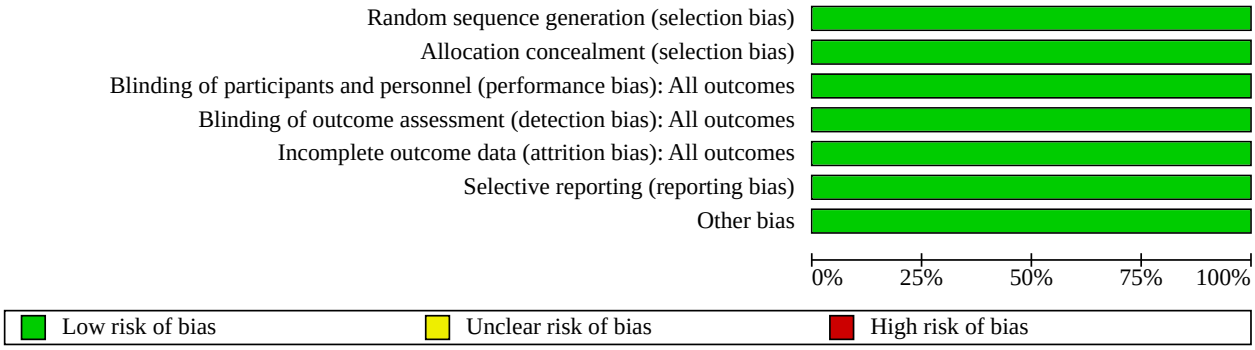
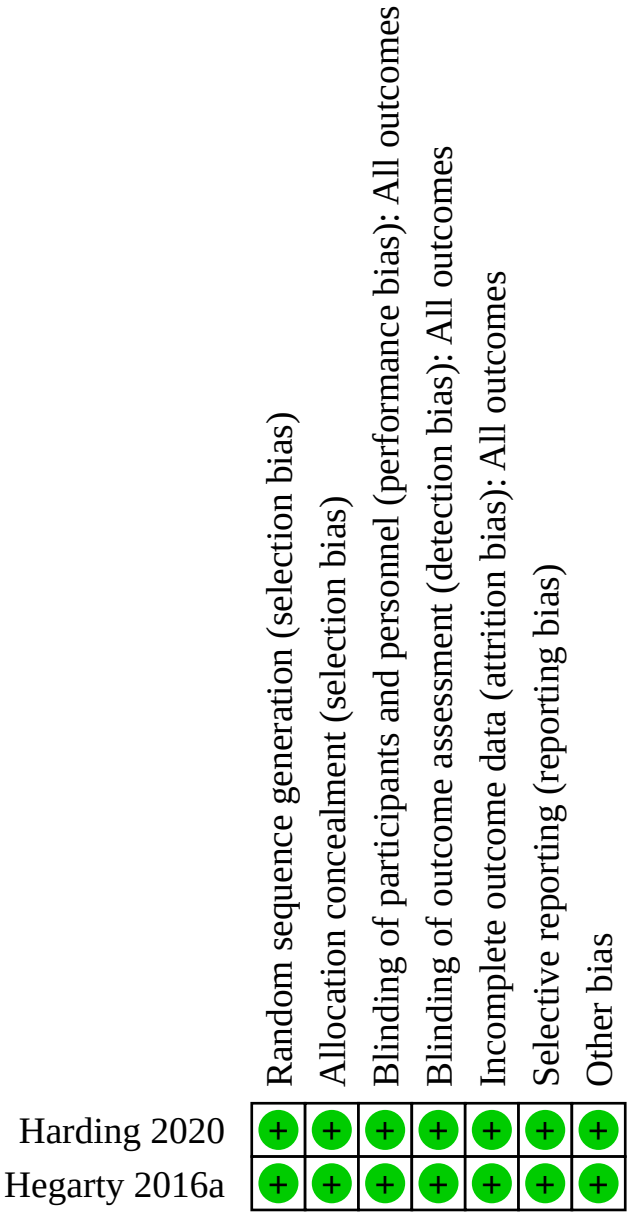


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Both studies reported using computer-generated block randomisation with variable block sizes (Harding 2020; Hegarty 2016a). Allocation was concealed by a central randomisation system which assigned infants to a numbered trial pack containing identical-looking syringes of either dextrose or placebo gel. We judged these studies to be at a low risk of selection bias.

Blinding

Both studies reported that clinicians, families and all study personnel were masked to treatment allocation (Harding 2020; Hegarty 2016a). The two-year follow-up of one study reported that follow-up assessors were unaware of the infant's treatment allocation (Hegarty 2016a). We judged these studies to be at low risk of performance and detection bias.

Incomplete outcome data

Both studies included all randomised infants in the intention-to-treat analysis of neonatal outcomes (Harding 2020; Hegarty 2016a). Hegarty 2016a assessed 90% of those eligible at two years' corrected age (dextrose 243/271 and placebo 117/130) and 87% of those randomised (dextrose 243/277 and placebo 117/138). Maternal and child characteristics were similar in those who were and were not assessed at two years. We judged these studies to be at low risk of attrition bias.

Selective reporting

Both studies reported data for all outcomes prespecified in the trial registration documentation (Harding 2020; Hegarty 2016a). We judged these studies to be at low risk of reporting bias.

Other potential sources of bias

Both studies reported that the demographic and prognostic characteristics of infants in each trial arm were balanced at baseline (Harding 2020; Hegarty 2016a). We did not identify any other potential sources of bias. We judged these studies to be at low risk of other bias.

Effects of interventions

See: **Summary of findings 1** Dextrose gel compared with placebo for prevention of hypoglycaemia in newborn infants

Primary outcomes

1.1 Hypoglycaemia (investigator-defined)

Meta-analysis showed that oral dextrose gel reduces the risk of neonatal hypoglycaemia (defined as a blood glucose concentration < 2.6 mmol/L) compared with placebo gel (RR 0.87, 95% CI 0.79 to 0.95; two studies, 2548 infants; high certainty evidence; Analysis 1.1). The RD was -0.06 (95% CI -0.10 to -0.02), and on average, 17 infants would have to receive prophylactic dextrose gel to prevent one additional case of neonatal hypoglycaemia.

1.2 Major neurological disability at two years or older

Additional data from one study (Hegarty 2016a) showed that oral dextrose gel probably reduces the risk of major neurological disability at two years' corrected age compared with placebo gel (RR 0.21, 95% CI 0.05 to 0.78; one study, 360 infants; moderate certainty evidence, downgraded for serious imprecision due to low event rates; Analysis 1.2). The RD was -0.05 (95% CI -0.09 to 0.00), and on average, 20 infants would have to receive prophylactic dextrose gel to prevent one additional case of major neurological disability.

Secondary outcomes

1.3 Hypoglycaemia (any blood glucose concentration less than 2.6 mmol/L) during initial hospital stay

No data were available for this outcome.

1.4 Receipt of treatment for hypoglycaemia during initial hospital stay

Meta-analysis showed that oral dextrose gel probably reduces the risk of receipt of treatment for neonatal hypoglycaemia compared with placebo gel (RR 0.89, 95% CI 0.79 to 1.00; two studies, 2548 infants; moderate certainty evidence, downgraded for serious imprecision; Analysis 1.3).

1.5 Receipt of intravenous treatment for hypoglycaemia

Meta-analysis showed that there is probably little or no difference in the risk of receipt of intravenous treatment for hypoglycaemia after oral dextrose gel compared to placebo gel (RR 1.01, 95% CI 0.68 to 1.49; two studies, 2548 infants; moderate certainty evidence, downgraded for serious imprecision; Analysis 1.4). We received additional data from the authors of one study (Harding 2020).

1.6 Receipt of oral dextrose gel treatment for hypoglycaemia

Meta-analysis showed that there is probably little or no difference in receipt of oral dextrose gel for treatment of hypoglycaemia after oral dextrose gel compared to placebo gel (RR 0.90, 95% CI 0.79 to 1.01; two studies, 2548 infants; Analysis 1.5).

1.7 Receipt of any medication for hypoglycaemia

Additional data received from the authors of both studies showed that no infants in either the dextrose gel or placebo groups received any medication for hypoglycaemia, such as glucagon or corticosteroids.

1.8 Number of episodes of hypoglycaemia per infant

Additional data from one study (Hegarty 2016a) showed that there is probably little or no difference in the number of episodes of hypoglycaemia per infant after oral dextrose gel compared to placebo gel (MD -0.18, 95% CI -0.55 to 0.19; one study, 186 infants; Analysis 1.6).

1.9 Adverse events

Meta-analysis showed that there is probably little or no difference in the risk of adverse events from use of oral dextrose gel compared to placebo gel (RR 1.22, 95% CI 0.64 to 2.33; two studies, 2510 infants; moderate certainty evidence, downgraded for serious imprecision; Analysis 1.7). We received additional data from the authors of one study (Harding 2020).

1.10 Separation from mother for treatment of hypoglycaemia

Meta-analysis showed that oral dextrose gel may have little or no effect on the risk of separation of the infant from the mother for treatment of neonatal hypoglycaemia compared to placebo gel (RR 1.12, 95% CI 0.81 to 1.55; two studies, 2548 infants; low certainty evidence, downgraded for imprecision and substantial heterogeneity (I^2 = 83%); Analysis 1.8). We were unable to perform subgroup analysis to further explore sources of heterogeneity as there were insufficient studies.

1.11 Neonatal seizures

Only one event of neonatal seizures was reported in the dextrose gel group (1/1347; 0.1%) in (Hegarty 2016a), and one event of neonatal seizures was reported in the placebo group (1/1201; 0.1%) in (Harding 2020), (RR 0.69, 95% CI 0.08 to 5.69; two studies, 2548 infants; Analysis 1.9). Both studies reported that the seizures were unrelated to neonatal hypoglycaemia.

1.12 Abnormal MRI of the brain in the neonatal period

No data were available for this outcome.

1.13 Duration of initial hospital stay

We received additional data from the authors of both studies which showed that oral dextrose gel makes little or no difference to the mean duration of initial hospital stay (days) (MD 0.06, 95% CI -0.13 to 0.24; two studies, 2537 infants; Analysis 1.10).

1.14 Breastfeeding (any) after discharge

We received additional data from the authors of both studies which showed that there is little or no difference in breastfeeding (any) after discharge after oral dextrose gel compared to placebo gel (RR 1.01, 95% CI 0.98 to 1.05; two studies, 2323 infants; Analysis 1.11). Oral dextrose gel also made no difference to full or exclusive breastfeeding after discharge (RR 1.00, 95% CI 0.98 to 1.03); two studies, 2528 infants).

1.15 Exclusive breastfeeding after discharge – WHO 2008 definition

No data were available for this outcome.

1.16 Exclusive breastfeeding at six months of age – WHO 2008 definition

No data were available for this outcome.

1.17 Developmental disability at two years of age or greater

One study (Hegarty 2016a) reported that oral dextrose gel may have little or no effect on the risk of any developmental disability at two years' corrected age (RR, 0.75, 95% CI 0.49 to 1.17; one study, 359 infants; Analysis 1.12)

1.18 Visual impairment and severity at two years of age or greater

No infants were blind at two years' corrected age (one study, 359 infants).

1.19 Hearing impairment at two years of age or greater

One infant in the placebo group was deaf at two years' corrected age (1/116; 0.01%, RR 0.16, 95% CI 0.01 to 3.89; one study; 359 infants; Analysis 1.12).

1.20 Cerebral palsy at two years of age or greater

No infant had cerebral palsy at two years' corrected age (one study, 359 infants).

1.21 Developmental delay/intellectual impairment and severity at two years of age or greater

Additional data from one study (Hegarty 2016a) reported that oral dextrose gel may have little to no effect on the risk of developmental delay/intellectual impairment at two years' corrected age (RR 0.75, 95% CI 0.49 to 1.17; one study, 359 infants; Analysis 1.12).

1.22 Executive dysfunction and severity at two years of age or greater

Additional data from one study (Hegarty 2016a) reported that oral dextrose gel probably reduces the risk of executive dysfunction at two years' corrected age compared with placebo gel (RR 0.48, 95% CI 0.23 to 0.99; one study, 357 infants; Analysis 1.12). The risk difference (RD) was -0.06 (95% CI -0.12 to 0.01), and on average, 17 infants would have to receive prophylactic dextrose gel to prevent one additional case of executive dysfunction. No severity data were available.

1.23 Behavioural problems and severity at two years of age or greater

No data were available for this outcome.

1.24 Abnormal MRI of the brain at two years of age or greater

No data were available for this outcome.

DISCUSSION

Summary of main results

This updated review included two studies that evaluated oral dextrose gel compared with placebo gel in preventing neonatal hypoglycaemia in 2548 at-risk infants (Harding 2020; Hegarty 2016a).

High certainty evidence from the two studies showed that oral dextrose gel reduces the risk of neonatal hypoglycaemia. On average, 17 at-risk infants would need to be treated with oral dextrose gel to prevent one additional case of neonatal hypoglycaemia (95% CI 10 to 50). There was moderate certainty evidence from one study in 360 infants that oral dextrose gel compared with placebo gel probably reduces the risk of major neurological disability at two years of age or older (NNTB 20, 95% 11 to ∞) (see Summary of findings 1).

Oral dextrose gel probably reduces the risk of receipt of treatment for hypoglycaemia during the initial hospital stay but makes little or no difference to intravenous treatment, may have little or no effect on separation of the mother from the infant for treatment of hypoglycaemia, and probably does not result in increased adverse events compared with placebo gel.

Oral dextrose gel probably also has little or no effect on receipt of oral dextrose gel for the treatment of hypoglycaemia, the number of hypoglycaemic episodes, neonatal seizures, duration of initial hospital stay and whether an infant is breastfed after discharge. The findings from a single study (360 infants) suggest that oral dextrose gel compared with placebo gel may have little or no effect on the risks of any developmental disability, developmental delay/intellectual impairment or hearing impairment, but probably reduces executive dysfunction (NNTB 17, 95% CI 8 to 100). No infants were blind or had cerebral palsy at two years of age or greater.

Overall completeness and applicability of evidence

More data have become available on the long-term neurodevelopmental and disability outcomes since the first version of this review, although this comes from a single small study (Hegarty 2017). No data were available for the following prespecified secondary outcomes: abnormal MRI of the brain in the neonatal period and at two years of age or greater; exclusive breastfeeding after discharge or at six months of age; and behavioural problems and severity at two years of age or greater. Both included studies compared a single preparation of oral dextrose gel with placebo in late preterm and term infants in two high-income countries (Australia and New Zealand) and therefore, the applicability of these findings to other preparations of gel,

extremely and moderately preterm infants and other healthcare settings remains unknown. There were no randomised trials that compared oral dextrose gel with no treatment, standard care or other therapies (such as antenatal expression of colostrum, early initiation of breastfeeding and the supplementation of breastfeeding with formula milk).

Quality of the evidence

We assessed both studies as low risk of bias across all domains. The certainty of evidence assessed by GRADE was moderate for most outcomes, except for the co-primary outcome of hypoglycaemia, which was graded as high certainty, and separation of mother and infant, which was graded as low certainty (see Summary of findings 1). The most common reason for downgrading the evidence was imprecision due to wide confidence intervals and low event rates.

For the co-primary outcome of major neurological disability at two years of age or older, data were available from only one small study with low event rates, so we graded the certainty of this evidence as moderate due to a lack of precision. Additional studies are needed to clarify the certainty of this finding.

We downgraded one outcome (separation from the mother for treatment of hypoglycaemia) to low certainty because of a lack of precision and substantial unexplained heterogeneity. We were unable to further explore this with planned subgroup analyses because there were only two studies. However, it is possible that this heterogeneity may be due to variations between hospitals in policies for admission to the NICU.

We downgraded the outcome of adverse events to moderate certainty because of imprecision due to low event rates. Thus, there is moderate certainty evidence that dextrose gel does not increase the risk of an infant choking or vomiting during administration compared to those who received placebo gel, and that the risk is low (< 1% in both groups), but there is no evidence about whether receipt of oral dextrose gel may increase the risk of these events or other harms compared with no treatment or other therapies such as formula feeding.

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 contacted authors of primary studies to obtain additional outcome data. We adhered to the Cochrane methods of searching and performing data extraction and analysis.

Agreements and disagreements with other studies or reviews

This update agrees with the first version of this review (Hegarty 2017), which reported that oral dextrose gel compared with placebo was associated with a reduced risk of neonatal hypoglycaemia in at-risk infants with no evidence of adverse events. The first version included a single study of 415 at-risk infants. That study was included in this updated version and contributed data to the meta-analysis.

Moreover, 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 the mother and infant and increased likelihood of full breastfeeding after discharge. Weston 2016 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

The available evidence suggests that giving prophylactic oral dextrose gel to 100 at-risk late preterm and term infants will prevent approximately six cases of neonatal hypoglycaemia and probably prevent five cases of major neurological disability at two years' corrected age, without increasing the risk of adverse events.

A cost-utility analysis has also reported that prophylactic oral dextrose gel is likely to be cost-effective, reducing healthcare costs while improving quality of life (Glasgow 2020). Clinicians and policy-makers should now consider whether this evidence from two high-quality trials in high-income countries is sufficient to warrant introduction of prophylactic dextrose gel into clinical practice.

Implications for research

Further research on long-term neurodevelopmental and disability outcomes are required. An update of this review when data become available from an ongoing follow-up study of both the included studies will clarify the certainty of this evidence. Additional data are also required on the effects of prophylactic dextrose gel on exclusive breastfeeding, and if the effects on the separation of mother from infant differ in hospitals with different NICU admission policies.

There is no evidence about the effects of prophylactic oral dextrose gel in low- and middle-income countries, extremely and moderately preterm infants and using other dextrose gel preparations. However, the results of three studies awaiting classification set in India (CTRI/2017/11/010645), Thailand (TCTR20190805003) and Italy (NCT04185766), and an ongoing study in very preterm infants (NCT04353713), may help to address these knowledge gaps. Future research should also compare prophylactic oral dextrose gel with other active therapies and assess adverse events compared with no treatment.

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Nai Ming Lai has peer reviewed and offered feedback for this updated review.

David Osborn reviewed and was the sign-off editor for this updated review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Harding 2020

Study characteristics	
Methods	Randomised parallel controlled trial
Participants	2149 infants (16 infants randomised in error) **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 **Timing:** January 2015 to May 2019
Interventions	40% dextrose gel massaged into buccal mucosa as a single dose (0.5 mL/kg) 1 hour after birth (n = 1070) vs Placebo gel massaged into buccal mucosa using same protocol as the intervention (n = 1063)
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) - no difference between oral dextrose and placebo groups **Secondary outcomes** • Hypoglycaemia (any blood glucose concentration < 2.6 mmol/L in first 48 hours) - lower incidence in oral dextrose gel group • Admission to NICU for hypoglycaemia - no difference between oral dextrose and placebo groups • Hyperglycaemia (any blood glucose concentration > 10 mmol/L) - no cases • Breastfeeding at discharge from hospital (full or exclusive) - no difference between oral dextrose and placebo groups • Receipt of any formula before discharge from hospital - no difference between oral dextrose and placebo groups

Harding 2020 *(Continued)*

	• Formula feeding at 6 weeks of age - no difference between oral dextrose and placebo groups • Cost of care until primary discharge home - reported separately • Maternal satisfaction (via telephone questionnaire at 6 weeks) - high • 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) - follow-up in progress
Notes	Trials registration: ACTRN12614001263684

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Babies will be assigned randomly via an internet randomisation service to the dextrose or placebo group with priority stratification for collaborating centre and risk factor"
Allocation concealment (selection bias)	Low risk	Quote: "Staff at the study site accessed a centralised internet based randomisations service within the first hour after birth to receive a study number which corresponded to a study treatment pack containing a single pre-packaged syringe of 40% dextrose gel or identical appearing 2% hydroxymethylcellulose placebo gel (1:1 ratio)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote. "Families, study and site staff and investigators were all blinded to treatment allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...study and site staff and investigators were all blinded to treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All analyses were pre-specified and carried out using a modified intention-to-treat approach in which babies randomised in error (did not meet eligibility criteria at randomisation) were excluded, but all other babies were analysed in the groups which they were allocated".
Selective reporting (reporting bias)	Low risk	Yes all outcomes mentioned in the protocol were published
Other bias	Low risk	Groups were well balanced for maternal and demographic variables. We conclude that the study is not at risk of other bias.

Hegarty 2016a

Study characteristics	
Methods	Two centre randomised, double-blind, placebo-controlled trial
Participants	416 infants (one infant randomised in error) **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

Hegarty 2016a *(Continued)*

	Exclusion criteria: major congenital abnormality, previously fed by formula or received intravenous fluid, previous diagnosis of hypoglycaemia, admission to NICU or imminent admission to NICU **Setting:** 2 hospitals providing maternity and neonatal services (Auckland City Hospital and Waitakere Hospital) in Auckland, New Zealand **Timing:** Recruitment: August 2013 to November 2014 Follow-up: August 2015 to February 2017
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 - lower incidence in any dextrose group **Secondary outcomes** • Admission to NICU (defined as admission for > 4 hours) - no difference between any dextrose and placebo groups • Admission to NICU for hypoglycaemia - reduced admission in any dextrose group • Hyperglycaemia (blood glucose concentration > 10 mmol/L) - no cases • Breastfeeding at discharge from hospital (full or exclusive) - no difference between any dextrose and placebo groups • Receipt of any formula before discharge from hospital - no difference between any dextrose and placebo groups • Formula feeding at 6 weeks of age - no difference between any dextrose and placebo groups • Cost of care until discharge home (to be reported separately) • Maternal satisfaction at 6 weeks - no difference between any dextrose and placebo groups • Neurosensory disability at two years' corrected age (defined as any of: legal blindness; sensorineural deafness requiring hearing aids; cerebral palsy; Bayley-III cognitive, language or motor score > two standard deviations below the mean) - these data were received from the study authors because the publication used a cut-off on the Bayley-III of more than one standard deviation below the mean. • Developmental delay (defined as Bayley-III cognitive, language or motor composite score > one standard deviation below the mean) measured at two years' corrected age - additional data received from the study authors showed no difference between any dextrose and placebo groups • Executive function z score below -1.5 within the cohort measured at two years' corrected age - unadjusted model showed a reduced risk of low executive function in any dextrose group (RR 0.48, 95% 0.23 to 0.99), but no difference in the adjusted model (aRR 0.50, 95% CI 0.24 to 1.06). • Cerebral palsy measured at two years' corrected age - no cases • Deafness defined as requiring hearing aids measured at two years' corrected age - not estimable as only one case • Blindness defined as visual acuity < 3/60 or > 1.3 logMAR measured at two years' corrected age - no cases
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.

Hegarty 2016a *(Continued)*

Australian New Zealand Clinical Trials Registry ACTRN12613000322730

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used computer-generated blocked randomisation with variable block sizes"
Allocation concealment (selection bias)	Low risk	Centralised allocation. Quote: "Research staff entered demographic and entry criteria data into an online randomisation website that provided a number corresponding to a numbered trial pack"
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	Low risk	At 24 months' corrected age, children underwent a comprehensive assessment of neurodevelopment, growth and general health by doctors trained in all assessments who were unaware of the child's randomisation group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Except for the one infant randomised in error, all infants had primary outcome data available and were included in the intention-to-treat analysis. The follow-up rate at two years' corrected was high (87% of those randomised and 90% of those eligible for follow-up) and maternal and child characteristics were similar between those who were and were not assessed at two years of age.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes are reported. Trial registration was viewed
Other bias	Low risk	Demographic and baseline characteristics were similar for all randomisation groups. Primary risk factors for hypoglycaemia were similar across all treatment groups. The authors concluded that the study is not at risk of other bias.

NICU: neonatal intensive care unit; SCBU: special care baby unit; vs: versus; aRR: adjusted risk ratio

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

Study	Reason for exclusion
Bourchier 1992	The intervention was oral dextrose gel as a treatment for neonatal hypoglycaemia
Coors 2018	Not a randomised controlled trial
Retbi 2013	The intervention was oral dextrose gel as a treatment for neonatal hypoglycaemia
Van Loghum 2014	The intervention was oral dextrose gel as a treatment for neonatal hypoglycaemia

Characteristics of studies awaiting classification *[ordered by study ID]*

CTRI/2017/11/010645

Methods	Randomised parallel controlled trial
Participants	611 infants **Inclusion criteria:** infants of diabetic mothers, > 35 weeks' gestation and birthweight > 2 kg **Exclusion criteria:** major congenital malformation or requiring admission to NICU before randomisation for any of the following: < 35 weeks' gestation, birthweight < 2 kg, respiratory distress, major lethal congenital malformation, antenatal ultrasound findings with absent/reversal of diastolic mesenteric flow, Rh negative mother with DCT positive baby and indication suggested by consultants. **Setting:** India
Interventions	40% dextrose gel (0.5 ml/L) massaged into the buccal mucosa after birth followed by a breastfeed within 30 minutes after birth vs Breastfeed within 30 minutes after birth
Outcomes	**Primary outcome** • Incidence of hypoglycaemia until 24 hours after birth **Secondary outcomes** • Reduction in admission rate due to hypoglycaemia until 24 hours after birth • Formulation of scoring system to predict the responder and non-responder to oral dextrose gel based on prespecified risk factors at 1.5 hours after birth • Rate of exclusive breastfeeding until discharge • Rate of exclusive breastfeeding up to 6 months of age • Maternal satisfaction at discharge • Incidence of sepsis without antenatal risk of sepsis until discharge • Reduction in admission rate due to hypoglycaemia until 24 hours after birth • Maximum requirement of glucose infusion rate until 24 hours after birth • Incidence of rebound hypoglycaemia until 24 hours after birth • Incidence of hyperglycaemia until 24 hours after birth • Incidence of late hyperglycaemia until 24 hours after birth • Incidence of feed intolerance until 24 hours after birth • Incidence of necrotising enterocolitis until 24 hours after birth • Number needed to treat until 24 hours after birth • Compliance of care until 24 hours after birth • Onset of action and duration of action of oral dextrose gel until 24 hours after birth • Rate of rise of glucose due to oral dextrose gel until 24 hours after birth • Duration of hospital stay within 28 days after birth
Notes	Trial registration: CTRI/2017/11/010645. Trial completed but unpublished - authors contacted in August 2020 for additional information

NCT04185766

Methods	Randomised parallel controlled trial
Participants	172 infants

NCT04185766 *(Continued)*

	Inclusion criteria: late preterm and term infants (34 to 42 weeks' gestation), small (< 10th centile) or large-for-gestational age (> 90thcentile), natural birth, rooming-in and body temperature between 36.5 to 37.5 degrees. Mother intends to breastfeed and has a BMI between 19 and 24. **Exclusion criteria:** major congenital malformations, blood glucose concentration < 47 mg/dL (2.6 mmol/L), NICU admission, milk intake in formula, intravenous infusion of 10% glucose solution, metabolic and respiratory acidosis (pH: 7.28 to 7.38) or mother taking medications during pregnancy. **Setting:** Poliambulanza Foundation Hospital Institute, Brescia, Italy.
Interventions	40% Destrogel as a single dose (0.5 mL/kg or 1 mL/kg) massaged into the buccal mucosa at one hour after birth (n = 86) vs Placebo gel massaged into the buccal mucosa using the same protocol and volume as the intervention (n = 86)
Outcomes	**Primary outcome** • The incidence of hypoglycaemia until 48 hours after birth **Secondary outcomes** • Incidence of the use of formula milk until 48 hours after birth • Incidence of the administration of 10% intravenous glucose solution until 48 hours after birth • Reducing artificial breastfeeding until 48 hours after birth • Reducing the pain of the infant during the execution of peripheral venous access for the administration of hypoglycaemia therapy until 48 hours after birth
Notes	Trial registration: NCT04185766. Trial completed but unpublished - authors contacted in August 2020 for additional information

TCTR20190805003

Methods	Randomised double-blind, placebo-controlled trial
Participants	600 infants **Inclusion criteria:** late preterm (34 to 37 weeks' gestation), small (< 10th centile) or large-for-gestational age (> 90th centile), infants of diabetic mothers, low birthweight (< 2500 g) or macrosomia (> 4000 g). **Exclusion criteria:** received oral feed or intravenous treatment for hypoglycaemia, congenital abnormality, admission to NICU, birthweight < 1800 grams. **Setting:** Thailand
Interventions	40% dextrose gel (0.5 ml/L) applied into the buccal mucosa within 48 hours after birth vs arboxymethyl cellulose placebo gel massaged into the buccal mucosa using the same protocol as the intervention
Outcomes	**Primary outcome** • Admission to Special Care Nursery due to treatment failure (within 30 minutes after intervention)

TCTR20190805003 *(Continued)*

	Secondary outcomes • Length of hospital stay
Notes	Trial registration: TCTR20190805003. Trial completed but unpublished - authors contacted in October 2020 for additional information

BMI: body mass index; DCT: Direct Coombs Test; NICU: neonatal intensive care unit; Rh: rhesus; vs: versus.

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

NCT04353713

Study name	Gel for early hypoglycaemia prevention in preterm infants
Methods	Multicentre, randomised double-blind, placebo-controlled trial
Participants	534 infants **Inclusion criteria:** Infants ≤ 32 weeks' gestation **Exclusion criteria:** planned comfort care (palliative approach) after delivery **Setting:** Ireland
Interventions	40% oral dextrose gel (0.5 ml/L) massaged into the buccal mucosa immediately after stabilisation or resuscitation at birth prior to in-house transport from delivery ward to the NICU vs 2% hydroxymethylcellulose placebo gel massaged into the buccal mucosa using the same protocol and volume as the intervention
Outcomes	**Primary outcome** • Proportion of infants with initial hypoglycaemia defined as a glucose concentration < 1.8 mmol/L at 30 to 60 minutes after birth **Secondary outcomes** • Proportion of infants with any hypoglycaemia episode within 24 hours after birth • Proportion of infants with a hypoglycaemia episode within 24 hours after birth • Number of episodes of hypoglycaemia within 24 hours after birth • Proportion of infants with a hyperglycaemia episode within 24 hours after birth • Proportion of infants who received rescue intravenous dextrose within 24 hours after birth • Tolerance of buccal gel in delivery room • Incidence of symptomatic hypoglycaemia within 24 hours after birth • Proportion of infants who died within 12 hours after birth • Proportion of infants who died > 12 hours after birth but prior to discharge home • Incidence of early bacterial sepsis and/or meningitis within 3 days after birth • Incidence of necrotising enterocolitis within 6 months after birth • Proportion of infants with severe retinopathy of prematurity requiring treatment within 6 months after birth • Proportion of infants with severe (grade III/IV) intraventricular-germinal matrix haemorrhage within 6 months after birth • Proportion of infants with periventricular leukomalacia within 6 months after birth
Starting date	1 July 2020

NCT04353713 *(Continued)*

Contact information	jkelleher@coombe.ie
Notes	Trial registration: NCT04353713

NICU: neonatal intensive care unit; vs: versus

DATA AND ANALYSES

Comparison 1. Dextrose gel versus control

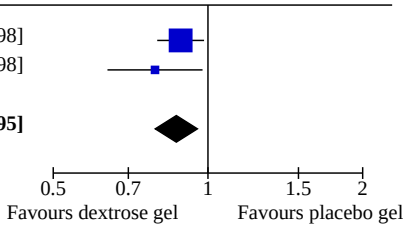
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Hypoglycaemia	2	2548	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.79, 0.95]
1.2 Major neurological disability at two years of age or older	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.05, 0.78]
1.3 Receipt of treatment for hypoglycaemia during initial hospital stay	2	2548	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.79, 1.00]
1.4 Receipt of intravenous treatment for hypoglycaemia	2	2548	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.68, 1.49]
1.5 Receipt of oral dextrose gel treatment for hypoglycaemia	2	2548	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.79, 1.01]
1.6 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]
1.7 Adverse effects (e.g. choking or vomiting at time of administration)	2	2510	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.64, 2.33]
1.8 Separation from mother for treatment of hypoglycaemia (admission to NICU for hypoglycaemia)	2	2548	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.81, 1.55]
1.9 Neonatal seizures	2	2548	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.08, 5.69]
1.10 Duration of initial hospital stay (days)	2	2537	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.13, 0.24]
1.11 Breastfeeding (any) after discharge	2	2323	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.98, 1.05]
1.12 Neurodevelopmental and disability outcomes at two years of age or greater	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.12.1 Developmental disability at two years of age or greater	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.49, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12.2 Hearing impairment at two years of age or greater	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 3.89]
1.12.3 Developmental delay/intellectual impairment at two years of age or greater	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.49, 1.17]
1.12.4 Executive dysfunction at two years of age or greater	1	357	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.23, 0.99]

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

Study or Subgroup	Dextrose gel Events	Dextrose gel Total	Placebo gel Events	Placebo gel Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Harding 2020	399	1070	448	1063	82.4%	0.88 [0.80 , 0.98]
Hegarty 2016a	114	277	72	138	17.6%	0.79 [0.64 , 0.98]
Total (95% CI)		**1347**		**1201**	**100.0%**	**0.87 [0.79 , 0.95]**
Total events:	513		520			

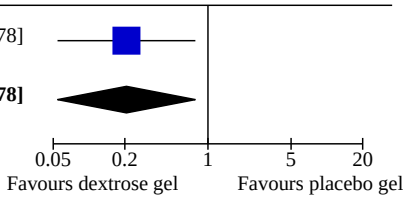
Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 2.95 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Dextrose gel versus control, Outcome 2: Major neurological disability at two years of age or older

Study or Subgroup	Dextrose gel Events	Dextrose gel Total	Placebo gel Events	Placebo gel Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hegarty 2016a (1)	3	243	7	117	100.0%	0.21 [0.05 , 0.78]
Total (95% CI)		**243**		**117**	**100.0%**	**0.21 [0.05 , 0.78]**
Total events:	3		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.32 (P = 0.02)
Test for subgroup differences: Not applicable

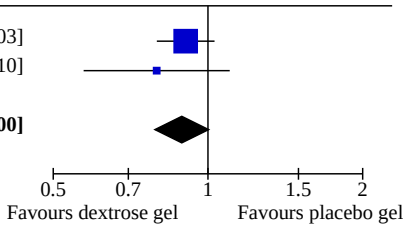


Footnotes
(1) Additional data received from authors

Analysis 1.3. Comparison 1: Dextrose gel versus control, Outcome 3: Receipt of treatment for hypoglycaemia during initial hospital stay

Study or Subgroup	Dextrose gel Events	Dextrose gel Total	Placebo gel Events	Placebo gel Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Harding 2020	307	1070	337	1063	85.8%	0.91 [0.80 , 1.03]
Hegarty 2016a	67	277	42	138	14.2%	0.79 [0.57 , 1.10]
Total (95% CI)		**1347**		**1201**	**100.0%**	**0.89 [0.79 , 1.00]**
Total events:	374		379			

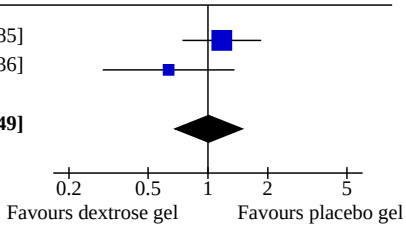
Heterogeneity: Chi² = 0.52, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Dextrose gel versus control, Outcome 4: Receipt of intravenous treatment for hypoglycaemia

Study or Subgroup	Dextrose gel Events	Dextrose gel Total	Placebo gel Events	Placebo gel Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Harding 2020 (1)	39	1070	33	1063	69.3%	1.17 [0.74 , 1.85]
Hegarty 2016a	14	277	11	138	30.7%	0.63 [0.30 , 1.36]
Total (95% CI)		**1347**		**1201**	**100.0%**	**1.01 [0.68 , 1.49]**
Total events:	53		44			

Heterogeneity: Chi² = 1.85, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable

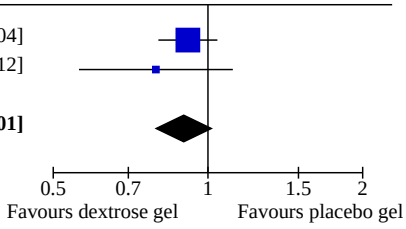


Footnotes
(1) Additional data provided by authors

Analysis 1.5. Comparison 1: Dextrose gel versus control, Outcome 5: Receipt of oral dextrose gel treatment for hypoglycaemia

Study or Subgroup	Dextrose gel Events	Dextrose gel Total	Placebo gel Events	Placebo gel Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Harding 2020	299	1070	325	1063	86.2%	0.91 [0.80 , 1.04]
Hegarty 2016a	62	277	39	138	13.8%	0.79 [0.56 , 1.12]
Total (95% CI)		**1347**		**1201**	**100.0%**	**0.90 [0.79 , 1.01]**
Total events:	361		364			

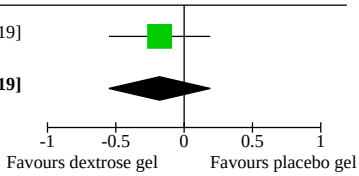
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Dextrose gel versus control, Outcome 6: Number of episodes of hypoglycaemia (glucose oxidase method) (total number per infant)

Study or Subgroup	Dextrose gel Mean	SD	Total	Placebo gel Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hegarty 2016a (1)	1.86	1.22	114	2.04	1.28	72	100.0%	-0.18 [-0.55 , 0.19]
Total (95% CI)			**114**			**72**	**100.0%**	**-0.18 [-0.55 , 0.19]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable

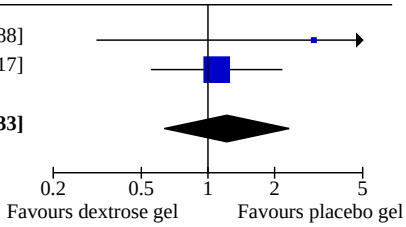


Footnotes
(1) Additional data provided by authors

Analysis 1.7. Comparison 1: Dextrose gel versus control, Outcome 7: Adverse effects (e.g. choking or vomiting at time of administration)

Study or Subgroup	Dextrose gel Events	Total	Placebo gel Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Harding 2020 (1)	3	1047	1	1050	6.4%	3.01 [0.31 , 28.88]
Hegarty 2016a	24	275	11	138	93.6%	1.09 [0.55 , 2.17]
Total (95% CI)		**1322**		**1188**	**100.0%**	**1.22 [0.64 , 2.33]**
Total events:	27		12			

Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)
Test for subgroup differences: Not applicable

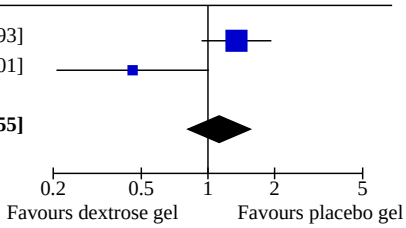


Footnotes
(1) Additional data provided by authors

Analysis 1.8. Comparison 1: Dextrose gel versus control, Outcome 8: Separation from mother for treatment of hypoglycaemia (admission to NICU for hypoglycaemia)

Study or Subgroup	Dextrose gel Events	Total	Placebo gel Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Harding 2020	65	1070	48	1063	75.0%	1.35 [0.94 , 1.93]
Hegarty 2016a	11	277	12	138	25.0%	0.46 [0.21 , 1.01]
Total (95% CI)		**1347**		**1201**	**100.0%**	**1.12 [0.81 , 1.55]**
Total events:	76		60			

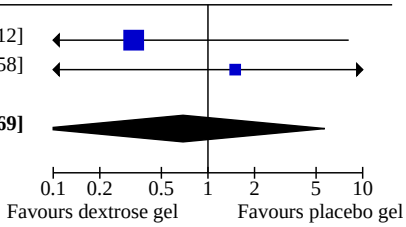
Heterogeneity: Chi² = 5.91, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Dextrose gel versus control, Outcome 9: Neonatal seizures

Study or Subgroup	Dextrose gel Events	Dextrose gel Total	Placebo gel Events	Placebo gel Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Harding 2020	0	1070	1	1063	69.3%	0.33 [0.01 , 8.12]
Hegarty 2016a	1	277	0	138	30.7%	1.50 [0.06 , 36.58]
Total (95% CI)		**1347**		**1201**	**100.0%**	**0.69 [0.08 , 5.69]**
Total events:	1		1			

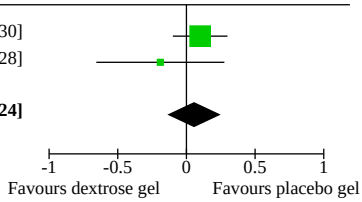
Heterogeneity: Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Dextrose gel versus control, Outcome 10: Duration of initial hospital stay (days)

Study or Subgroup	Dextrose gel Mean	Dextrose gel SD	Dextrose gel Total	Placebo gel Mean	Placebo gel SD	Placebo gel Total	Weight	Mean Difference IV, Fixed, 95% CI
Harding 2020 (1)	3.14	2.13	1068	3.04	2.53	1058	84.6%	0.10 [-0.10 , 0.30]
Hegarty 2016a (1)	3.88	2.44	275	4.07	2.18	136	15.4%	-0.19 [-0.66 , 0.28]
Total (95% CI)			**1343**			**1194**	**100.0%**	**0.06 [-0.13 , 0.24]**

Heterogeneity: Chi² = 1.26, df = 1 (P = 0.26); I² = 20%
Test for overall effect: Z = 0.59 (P = 0.55)
Test for subgroup differences: Not applicable

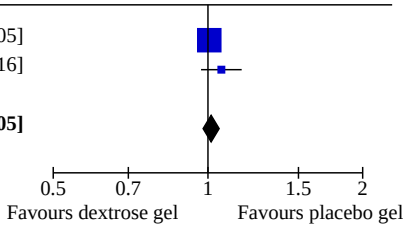


Footnotes
(1) Additional data provided by authors

Analysis 1.11. Comparison 1: Dextrose gel versus control, Outcome 11: Breastfeeding (any) after discharge

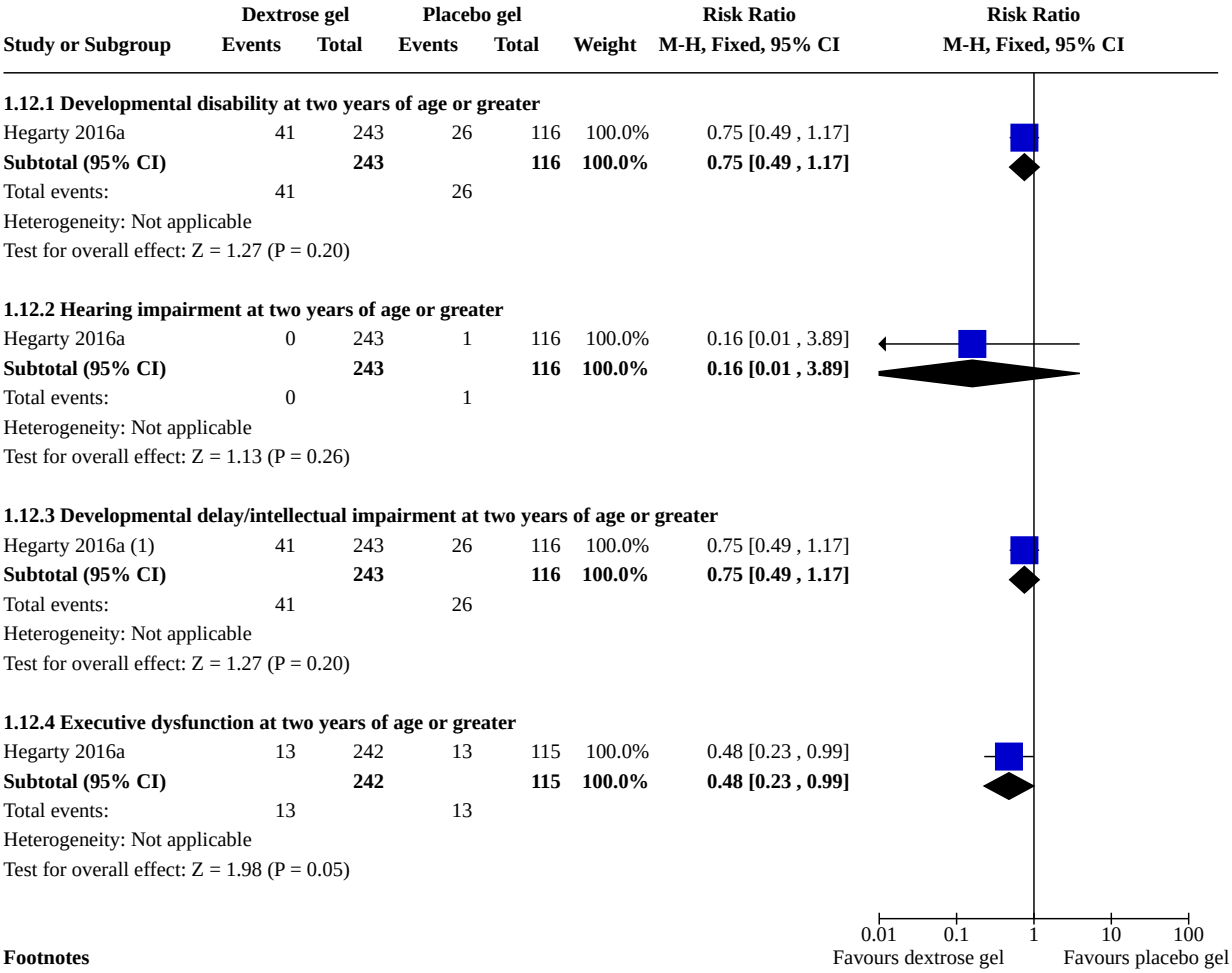
Study or Subgroup	Dextrose gel Events	Dextrose gel Total	Placebo gel Events	Placebo gel Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Harding 2020 (1)	826	981	801	957	85.1%	1.01 [0.97 , 1.05]
Hegarty 2016a (1)	226	257	106	128	14.9%	1.06 [0.97 , 1.16]
Total (95% CI)		**1238**		**1085**	**100.0%**	**1.01 [0.98 , 1.05]**
Total events:	1052		907			

Heterogeneity: Chi² = 1.15, df = 1 (P = 0.28); I² = 13%
Test for overall effect: Z = 0.78 (P = 0.44)
Test for subgroup differences: Not applicable



Footnotes
(1) Additional data provided by authors

Analysis 1.12. Comparison 1: Dextrose gel versus control, Outcome 12: Neurodevelopmental and disability outcomes at two years of age or greater



Footnotes

(1) Additional data provided by authors

APPENDICES

Appendix 1. 2020 Search methods

The RCT filters have been created using Cochrane's highly sensitive search strategies for identifying randomised trials (Higgins 2019). The neonatal filters were created and tested by the Cochrane Neonatal Information Specialist.

CENTRAL via CRS Web:

Terms:

1. MESH DESCRIPTOR Hypoglycemia EXPLODE ALL AND CENTRAL:TARGET
2. hypogly* AND CENTRAL:TARGET
3. #2 OR #1 AND CENTRAL:TARGET
4. MESH DESCRIPTOR Glucose EXPLODE ALL AND CENTRAL:TARGET
5. MESH DESCRIPTOR Sweetening Agents EXPLODE ALL AND CENTRAL:TARGET
6. dextrose* or glucose* or sweetening agent* AND CENTRAL:TARGET
7. #6 OR #5 OR #4 AND CENTRAL:TARGET
8. MESH DESCRIPTOR Gels EXPLODE ALL AND CENTRAL:TARGET
9. gel or gels AND CENTRAL:TARGET

10. #9 OR #8 AND CENTRAL:TARGET
11. MESH DESCRIPTOR Infant, Newborn EXPLODE ALL AND CENTRAL:TARGET
12. infant or infants or infant's or "infant s" or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU AND CENTRAL:TARGET
13. #12 OR #11 AND CENTRAL:TARGET
14. #3 AND #7 AND #10 AND #13 AND CENTRAL:TARGET

# of results: 41

MEDLINE via Ovid:

Terms:

1. exp Hypoglycemia/
2. hypogly*.mp.
3. 1 or 2
4. exp Glucose/
5. exp Sweetening Agents/
6. (dextrose* or glucose* or sweetening agent*).mp.
7. 4 or 5 or 6
8. exp Gels/
9. (gel or gels).mp.
10. 8 or 9
11. exp infant, newborn/
12. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or 'infant s' or infant's or infantile or infancy or neonat*).ti,ab.
13. 11 or 12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. drug therapy.fs.
19. randomly.ab.
20. trial.ab.
21. groups.ab.
22. or/14-21
23. exp animals/ not humans.sh.
24. 22 not 23
25. 13 and 24
26. randomi?ed.ti,ab.
27. randomly.ti,ab.
28. trial.ti,ab.
29. groups.ti,ab.
30. ((single or doubl* or tripl* or treb*) and (blind* or mask*)).ti,ab.
31. placebo*.ti,ab.
32. 26 or 27 or 28 or 29 or 30 or 31
33. 12 and 32
34. limit 33 to yr="2018 -Current"
35. 25 or 34
36. 3 and 7 and 10 and 35

# of results: 27

ISRCTN:

Terms:
(Interventions: Dextrose* or glucose* or sweetening agent* AND Participant age range: Neonate)
"Dextrose* or glucose* or sweetening agent* AND (Participant age range: Neonate)"
Dextrose* within Participant age range: Neonate
Condition: hypoglycaemia AND Interventions: Dextrose
Condition: hypoglycaemia AND Interventions: Glucose

# of results: 5

ANZCTR:

Terms:

(hypoglycaemia AND dextrose AND randomised)

Description of intervention(s) / exposure: dextrose* OR glucose* OR “sweetening agent” AND hypoglycaemia

Allocation to intervention: randomised

Age group: under 18yrs

# of results: 4

Appendix 2. Previous search methods

Review authors 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) and did not apply language restrictions.

The following search strategy was used:

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)

Review authors also 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).

Appendix 3. Risk of Bias tool

Sequence generation (checking for possible selection bias). *Was the allocation sequence adequately generated?*

For each included study, we categorised the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

Allocation concealment (checking for possible selection bias*). Was allocation adequately concealed?*

For each included study, we categorised the method used to conceal the allocation sequence as:

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

Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

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

Blinding of outcome assessment (checking for possible detection bias)

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed

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

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk.

Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified 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); or
- unclear risk.

Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

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

- low risk;
- high risk; or
- unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
19 October 2020	New search has been performed	The literature was searched in October 2020 using a new search strategy which we ran without date limits. One new published

Date	Event	Description
		study, one ongoing study and three studies awaiting classification were identified.
19 October 2020	New citation required but conclusions have not changed	There has been a change in authorship. One trial reported on long-term neurodevelopmental and disability outcomes at two years of age or greater.

HISTORY

Protocol first published: Issue 4, 2016
Review first published: Issue 7, 2017

CONTRIBUTIONS OF AUTHORS

2020 update

TE:

- screened studies for eligibility and extracted data;
- prepared the first draft and revised subsequent drafts under the supervision of Jane Harding;
- contributed to subsequent drafts and approved the final version.

JEHegarty:

- contributed to subsequent drafts and approved the final version.

JEHarding:

- supervised the first draft and revised subsequent drafts; and
- approved the final version.

CAC:

- contributed to subsequent drafts and approved the final version.

JA:

- contributed to subsequent drafts and approved the final version.

GL:

- screened studies for eligibility and extracted data;
- contributed to subsequent drafts and approved the final version.

DECLARATIONS OF INTEREST

TE has no interest to declare. TE independently screened studies for eligibility, extracted data and performed risk of bias assessment of included studies.

JEHegarty is an author of the included studies (Hegarty 2016a; Harding 2020).

JEHarding is an author of the included studies (Hegarty 2016a; Harding 2020).

CAC is an author of the included studies (Hegarty 2016a; Harding 2020).

JA is an author of the included studies (Hegarty 2016a; Harding 2020).

GL has no interest to declare. GL independently screened studies for eligibility, extracted data and performed risk of bias assessment of included studies.

SOURCES OF SUPPORT

Internal sources

- Liggins Institute, University of Auckland, New Zealand

  PhD Scholarship for Taygen Edwards
- 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, and Jane Alsweiler
- Aotearoa Foundation, New Zealand

  Undergraduate Clinical Research Internship for Gordon Liu

External sources

- Vermont Oxford Network, USA

  Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The original protocol was published in 2016 (Hegarty 2016b), and informed the first version of this Cochrane Review titled “Oral dextrose gel to prevent hypoglycaemia in at-risk neonates” (Hegarty 2017). For the 2020 update, we developed a new search strategy, which we ran without date limits (Appendix 1).
- As of July 2019, Cochrane Neonatal no longer searches Embase for its reviews. RCTs and controlled clinical trials (CCTs) from Embase are added to the Cochrane Central Register of Controlled Trials (CENTRAL) via a robust process (see how CENTRAL is created). Cochrane Neonatal has validated their searches to ensure that relevant Embase records are found while searching CENTRAL. Further, Cochrane Neonatal no longer searches for RCTs and CCTs from ClinicalTrials.gov or from The World Health Organizationís International Clinical Trials Registry Platform (ICTRP) , as records from both platforms are added to CENTRAL on a monthly basis (see how CENTRAL is created). Comprehensive search strategies are executed in CENTRAL to retrieve relevant records. The ISRCTN (at http://www.isrctn.com formerly controlled-trials.com), is searched separately. Starting in September 2020, Cochrane Neonatal no longer searches CINAHL for reviews, as records are identified and added to CENTRAL on a monthly basis through Cochrane's Centralised Search Service Project (see how CENTRAL is created).
- The term 'adverse effects' has been changed to 'adverse events'.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Gels; Glucose [*administration & dosage] [adverse effects]; Hypoglycemia [complications] [*prevention & control]; Neurodevelopmental Disorders [etiology] [prevention & control]; Randomized Controlled Trials as Topic; Sweetening Agents [*administration & dosage] [adverse effects]

MeSH check words

Humans; Infant; Infant, Newborn