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Continuous glucose monitoring for the prevention of morbidity and mortality in preterm infants (Review)

Galderisi A, Bruschettini M, Russo C, Hall R, Trevisanuto D

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Continuous glucose monitoring for the prevention of morbidity and mortality in preterm infants.
Cochrane Database of Systematic Reviews 2020, Issue 12. Art. No.: CD013309.
DOI: 10.1002/14651858.CD013309.pub2.

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TABLE OF CONTENTS

[Intervention Review]

Continuous glucose monitoring for the prevention of morbidity and mortality in preterm infants

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Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 12, 2020.

Citation: Galderisi A, Bruschettini M, Russo C, Hall R, Trevisanuto D. Continuous glucose monitoring for the prevention of morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2020, Issue 12. Art. No.: CD013309. DOI: 10.1002/14651858.CD013309.pub2.

ABSTRACT

Background

Preterm infants are susceptible to hyperglycemia and hypoglycemia, conditions which may lead to adverse neurodevelopment. The use of continuous glucose monitoring devices (CGM) might help keeping glucose levels in the normal range, and reduce the need for blood sampling. However, the use of CGM might be associated with harms in the preterm infant.

Objectives

Objective one: to assess the benefits and harms of CGM alone versus standard method of glycemic measure in preterm infants.

Objective two: to assess the benefits and harms of CGM with automated algorithm versus standard method of glycemic measure in preterm infants.

Objective three: to assess the benefits and harms of CGM with automated algorithm versus CGM without automated algorithm in preterm infants.

Search methods

We adopted the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 9), in the Cochrane Library; MEDLINE via PubMed (1966 to 25 September 2020); Embase (1980 to 25 September 2020); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to 25 September 2020). We also searched clinical trials databases, conference proceedings, and reference lists of retrieved articles for randomized controlled trials and quasi-randomized trials.

Selection criteria

Randomized controlled trials (RCTs) and quasi-RCTs in preterm infants comparing: 1) the use of CGM versus intermittent modalities to measure glycemia (comparison 1); or CGM associated with prespecified interventions to correct hypoglycemia or hyperglycemia versus CGM without such prespecified interventions (comparison 2).

Data collection and analysis

We assessed the methodological quality of included trials using Cochrane Effective Practice and Organisation of Care Group (EPOC) criteria (assessing randomization, blinding, loss to follow-up, and handling of outcome data). We evaluated treatment effects using a fixed-effect

model with risk ratio (RR) for categorical data and mean, standard deviation (SD), and mean difference (MD) for continuous data. We used the GRADE approach to assess the certainty of the evidence.

Main results

Four trials enrolling 138 infants met our inclusion criteria. Investigators in three trials (118 infants) compared the use of CGM to intermittent modalities (comparison one); however one of these trials was analyzed separately because CGM was used as a standalone device, without being coupled to a control algorithm like in the other trials. A fourth trial (20 infants) assessed CGM with an automated algorithm versus CGM with a manual algorithm.

None of the four included trials reported the neurodevelopmental outcome, i.e. the primary outcome of this review. Within comparison one, the certainty of the evidence on the use of CGM on mortality during hospitalization is very uncertain (typical RR 3.00, 95% CI 0.13 to 70.30; typical RD 0.04, 95% CI -0.06 to 0.14; 50 participants; 1 study; very low certainty). The number of hypoglycemic episodes was reported in two studies with conflicting data. The number of hyperglycemic episodes was reported in one study (typical MD -1.40, 95% CI -2.84 to 0.04; 50 participants; 1 study). The certainty of the evidence was very low for all outcomes because of limitations in study design, and imprecision of estimates.

Three studies are ongoing.

Authors' conclusions

There is insufficient evidence to determine if CGM improves preterm infant mortality or morbidities. Long-term outcomes were not reported. Clinical trials are required to determine the most effective CGM and glycemic management regimens in preterm infants before larger studies can be performed to assess the efficacy of CGM for reducing mortality, morbidity and long-term neurodevelopmental impairments. The absence of CGM labelled for neonatal use is still a major limit in its use as well as the absence of dedicated neonatal devices.

PLAIN LANGUAGE SUMMARY

Devices to continuously monitor sugar (glucose) levels in the blood in newborns born preterm

Review questions:

1) What are the benefits and harms of the use of subcutaneous (under the skin) sensors for continuous glucose monitoring (CGM) with or without an algorithm to correct too high or too low levels of blood glucose versus intermittent modalities to measure blood glucose with or without an algorithm to correct too high or too low levels in preterm infants?

2) What are the benefits and harms of the use of of CGM associated with an algorithm to correct too high or too low levels of blood glucose versus CGM without an algorithm to correct too high or too low levels of blood glucose in preterm infants?

Background

Newborns born too early ("preterm") are susceptible to levels of blood glucose that are too high or too low. Most preterm babies with these abnormal concentrations may make a full recovery, or may have only mild problems. For some preterm babies with extremely high or low (or more prolonged) levels of glucose, this may lead to death or to problems later in life.

The aim of this review was to assess whether the use of CGM could improve the long-term development, or reduce mortality in preterm newborns. CGM devices are inserted subcutaneously, and provide data on glucose levels in real time. The standard method of measuring glucose levels consists of withdrawing small amounts of the baby's blood or performing frequent heel pricks.

Study characteristics
We collected and analyzed all relevant studies to answer the review question, and found four studies enrolling 138 babies. Three of those studies compared the use of CGM to intermittent modalities, and one study evaluated CGM combined with an algorithm versus CGM as a standalone tool to correct low and high glucose levels.

Key results

None of the four included studies reported on the long-term neurodevelopmental outcome of preterm infants. The studies were too small to determine if use of CGM has an effect on survival. The number of low blood glucose episodes was reported in two studies with conflicting data. Three studies are ongoing. Further research is needed.

Certainty of evidence:

The certainty of evidence was very low due to the overall limited number of studies, with few babies enrolled.

How up-to-date is this review?

We searched for studies that were available up to 25 September 2020.

Summary of findings 1. Summary of Findings Table - CGM compared to intermittent modalities for the prevention of morbidity and mortality in preterm infants

CGM compared to intermittent modalities for the prevention of morbidity and mortality in preterm infants

Patient or population: health problem or population **Setting**: neonatal units in France, Italy, the UK **Intervention**: CGM **Comparison**: intermittent modalities

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with intermittent modalities	Risk with CGM				
Death during initial hospitalization (all-cause mortality)	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 3.00** (0.13 to 70.30)	50 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a,b]	
Cerebral palsy - not measured	-	-	-	-	-	
Mental developmental delay - not measured	-	-	-	-	-	
Blindness - not measured	-	-	-	-	-	
Hearing deficit - not measured	-	-	-	-	-	
Neurodevelopmental impairment (composite outcome) - not measured	-	-	-	-	-	
Neonatal seizures - not measured	-	-	-	-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_412522839813175767.

a. Downgraded by one level for performance and detection bias
b. Downgraded by two levels for imprecision: one small study; one event

Summary of findings 2. Summary of Findings Table - CGM vs. intermittent modalities for health problem or population

Patient or population: health problem or population **Setting**: Neonatal unit in the UK **Intervention**: CGM **Comparison**: intermittent modalities

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with intermittent modalities	Risk with CGM				
Death during initial hospitalization (all-cause mortality) - not measured	-	-	-	-	-	
Cerebral palsy - not measured	-	-	-	-	-	
Mental developmental delay - not measured	-	-	-	-	-	
Blindness - not measured	-	-	-	-	-	
Hearing deficit - not measured	-	-	-	-	-	
Neurodevelopmental impairment (composite outcome) - not measured	-	-	-	-	-	
Neonatal seizures - not measured	-	-	-	-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_4152128278688895075.

BACKGROUND

Description of the condition

Glucose homeostasis poses a significant challenge for preterm infants, and there is little evidence for what the optimal target glucose levels should be and the effect of hypoglycemia and hyperglycemia on neurodevelopmental outcome remains controversial (McKinlay 2015; McKinlay 2017a; Tottman 2017). Preterm neonates are susceptible to hypoglycemia (Adamnkin 2017), as a consequence of immature gluconeogenesis and ketogenesis, and to hyperglycemia (Farrag 2000), due to impaired insulin response to glucose variations during the first days of life. Given their high brain-to-body mass ratio, preterm infants have almost double the requirement for glucose (6 to 8 mg/kg/min) of term neonates (2 to 3 mg/kg/day) (Hay 2009). The high oxidative activity of the brain, and consequently the high requirement of glucose and oxygen, contributes to the extreme susceptibility of neuronal tissue to hypoglycemic injury during the first weeks of life (Burns 2008; Ferriero 2016; Wong 2013). In experimental animal models, Hoiland 2016 described a direct effect of glucose on smooth muscle cells of cerebral vessels through the inhibition of K-ATP channels. This mechanism, along with a direct cytotoxic effect of hypoglycemia, would sustain a hypothetical relationship between cerebral blood flow/cerebral oxygenation and glycemic level.

Despite the growing evidence of the effect of prolonged glucose imbalance on brain development, we still lack a consistent recommendation for glucose monitoring in preterm neonates. Traditional strategies are based on point-of-care measures of blood glucose that provide punctual values and largely underestimate the actual prevalence of hypoglycemic events (Uettwiller 2015), and consequently the time of exposure to low blood glucose, which is the main determinant of the neuronal damage. Additionally, point-of-care measures by heel prick test to measure glycemic status is a painful procedure with potential long-term adverse effects on brain development (Ranger 2013)

The use of insulin for prevention (Sinclair 2011) or treatment (Bottino 2011) of neonatal hyperglycemia in very low birth weight infants has been assessed in two Cochrane reviews. The routine use of insulin for hyperglycemia prevention was not supported by current evidence and associated with increased mortality in one trial (Beardsall 2008), in the absence of data on the long term neruodevelopmental effects. (Sinclair 2011) There was also insufficient evidence to determine the benefits and harms of insulin for treatment of hyperglycaemia in very low birth weight infants. (Bottino 2011)

Titration of glucose infusion for hyperglycemia as well as hypoglycemia prevention and treatment has never been assessed.

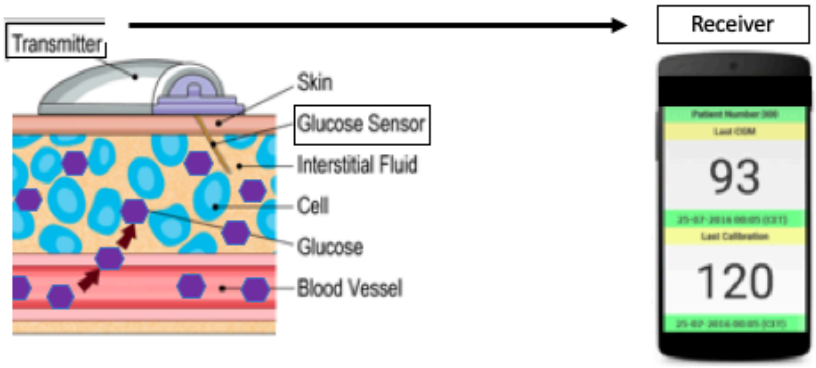
Subcutaneous sensors for continuous glucose monitoring (CGM) are a new area of opportunity for neonatal care. Indeed, CGM has been successfully used for diabetes management in pediatric and adult patients to drive insulin infusion in automated and semi-automated devices that represent a major improvement in the field. Their use in neonatal care holds the potential of providing a continuous measure of subcutaneous glucose, along with the opportunity of providing alerts for hypoglycemia or hyperglycemia and driving therapeutic interventions (Harris 2013).

The accuracy of CGM is comparable to point-of-care blood tests, with a mean absolute relative difference with blood glucose measures below 12% in adults (Fonseca 2016), and is expected to further improve with the use of more recent devices. Despite other technical limits that may limit the sensors' performance in preterm neonates (such as the lack of age-specific sensors and the effect of interstitial fluid composition on sensor readings) (Harris 2013), this tool remains a forefront method to monitor glucose in preterm infants, whose long-term benefits have as yet to be fully explored.

Description of the intervention

The use of CGM is safe in term and preterm neonates (Beardsall 2008), and may represent a paradigm shift in the field of neonatal metabolic studies, offering a continuous measure of glucose values and representing a guide for interventions aimed to improve glycemic control. Real-time CGM consists of a subcutaneous glucose sensor and a non-implantable transmitter that powers the sensor and sends data to a remote monitor via Bluetooth wireless technology (Figure 1). The stream of data provides updated measurements of subcutaneous values every five minutes and real-time display with customizable alerts for low (hereafter referred to as hypoglycemia), or high (hereafter referred to as hyperglycemia) subcutaneous glucose values (Beardsall 2008). The current sensors may remain in place for up to 14 days without needing replacement and need twice daily calibration with blood glucose measurements. Most recent sensors have factory-calibration and do not require additional blood glucose tests during their placement. However, the commercially available devices have been labeled by European and USA regulatory agencies for children aged two years and older, although there is a growing body of data that supports their safe use in a younger population, including term and preterm neonates (Beardsall 2013; Galderisi 2018).

Figure 1. Continuous glucose monitoring: outline of the main components of the sensor



CGM sensors may provide trend information, such as the rate of glucose change, that can guide clinical choices or be integrated in computer-based tools for individualizing the glucose intakes or insulin delivery in the presence of hypoglycemia or hyperglycemia.

Different commercial brands for CGM tools have distinctive features regarding the necessity (or not) for daily calibration, the connectivity with other devices and the insertion technique. However, the sensing system is similar to the most commonly used manufacturers. Commonly used medications, such as acetaminophen, may affect the sensor performance and the necessity for their use should be evaluated in the choice of a specific sensor.

The commercially available sensors, labeled for diabetes care, can be linked to algorithms for the adjustment of insulin delivery (so called hybrid closed loop) (Galderisi 2017). However, integrated tools are not currently available for neonatal care and we can rely only on investigational devices combining, based on the individual expertise of the researcher group and the study design, commercial CGM with investigational algorithms directly connected to delivery systems or to computer-based platforms that will operate as enhanced advisors for the neonatal intensive care unit (NICU) personnel.

CGM insertion is associated with lower pain scores compared with the heel stick (Galderisi 2018), and its use might reduce daily heel pricks necessary to monitor blood glucose during the first days of life. This represents a clinically relevant outcome as early exposure to pain is associated with a modified cerebral structure studied with diffusion magnetic resonance imaging (MRI) in specific parts of the brain (Brummelte 2012).

How the intervention might work

The effect of neonatal glycemic control on short-term morbidity, as well as long-term neurodevelopmental outcome, is still controversial.

As time spent in hypoglycemia or hyperglycemia is known to play a major role in determining acute brain damage in children and adults (Cryer 2007), we can hypothesize that neonatal measures of glycemic control based on CGM would be more reliable to assess the meaningfulness of such a variable, as well as to drive therapeutic interventions.

Current interventions based on CGM may use the sensor:

- as an isolated monitoring tool to prompt corrective actions for both hypoglycemia and hyperglycemia. This approach is expected to increase the rate of detection of hypoglycemia and hyperglycemia, minimizing the overall time spent out of target range;
- combined with computer-based algorithms to adapt glucose or insulin infusion based on CGM readings;
- combined with computer-based algorithms to adapt glucose or insulin infusion based on alerts for hypoglycemia or hyperglycemia from CGM, after a confirmatory blood glucose test.

Computer-based algorithms suggest changes in glucose or insulin infusion based on the actual CGM with or without confirmatory blood glucose values, the trend values, and the prespecified glycemic target. Three control approaches have been used to optimize glycemic control by means of insulin delivery adjustments, based on CGM: the proportional integrative derivative (PID), the model predictive control (MPC), and the fuzzy logic controller (Steil 2006; Steil 2013). The input to a controller is usually

the glucose level and the outputs can be glucose infusion rate/intakes or insulin delivery. The algorithms or models are meant to reproduce the physiological response to glycemic changes based on a priori assumptions that inform the model and are adjusted over time according to the input.

In neonatal care, differently from the diabetes care these tools were initially developed for, we may observe algorithms designed either to adjust only the glucose infusion rate or both glucose or insulin. The glycemic target (target range or fixed limit), the time in between each adjustment, and the temporary window adopted to feed the algorithm evaluation are the pillars of an algorithm-based approach.

CGM might be used as a stand-alone device too, with caregivers deciding the adjustments based on their own experience or protocols. However, an algorithm-based approach is expected to maximize the benefits deriving from the use of these devices.

Additional advantages may be associated with CGM use. Reducing the frequency of blood sampling may reduce the risk of anemia and the need for blood transfusions. Furthermore, in the absence of a central line, CGM would avoid stressful stimuli due to heel lances, in a fashion similar to what is seen with the use of continuous transcutaneous carbon dioxide monitoring (Bruschettini 2016).

Why it is important to do this review

The lack of long-term studies on CGM constitutes a major gap of knowledge. Although there are narrative reviews on the use of CGM in newborns (McKinlay 2017a; Shah 2018), there is a lack of systematic reviews and meta-analysis on the use of CGM in preterm neonates.

This is a compelling task, due to the growing number of neonatal studies adopting devices for CGM either for detecting hypoglycemia and hyperglycemia or for driving targeted therapeutic interventions (Beardsall 2008; Galderisi 2018).

In this Cochrane Review, we will analyze the available evidence for short- and long-term benefits deriving from CGM use in preterm infants.

OBJECTIVES

1. to assess the benefits and harms of CGM alone versus a standard method of glycemic measure in preterm infants.
2. to assess the benefits and harms of CGM with an automated algorithm versus a standard method of glycemic measure in preterm infants.
3. to assess the benefits and harms of CGM with an automated algorithm versus CGM without an automated algorithm in preterm infants.

METHODS

Criteria for considering studies for this review

Types of studies

We included prospective randomized controlled trials (RCTs), quasi-randomized controlled trials (quasi-RCTs), and cluster-randomized controlled trials (cluster-RCTs). We excluded cross-over trials because the intervention may have a lasting effect that compromises entry to subsequent periods of the trial.

We included published studies, unpublished studies, and studies published only as abstracts if assessment of study quality was possible and other inclusion criteria were fulfilled.

Types of participants

We included preterm infants (i.e. < 37 weeks' gestational age) of any birth weight, any postnatal age, admitted to NICUs or nurseries.

We included infants who had received prior treatment for hypoglycemia or hyperglycemia.

Types of interventions

We included the following comparisons:

- comparison 1: CGM with or without prespecified interventions to correct hypoglycemia (e.g. algorithms; use of automated or strictly defined criteria to perform changes in glucose infusion) or hyperglycemia (e.g. changes in parenteral nutrition: insulin administration) versus intermittent modalities to measure glycemia (e.g. capillary glucose testing; central line sampling or venipuncture) with or without prespecified interventions to correct hypoglycemia or hyperglycemia;
- comparison 2: CGM associated with prespecified interventions to correct hypoglycemia (e.g. algorithms; use of automated or strictly defined criteria to perform changes in glucose infusion) or hyperglycemia (e.g. changes in parenteral nutrition; insulin administration) versus CGM without prespecified interventions to correct hypoglycemia or hyperglycemia.

Prespecified interventions included any automated or semi-automated system driven by the CGM data, as well as mathematical algorithms based on CGM data to calculate the glucose or insulin to be infused; any insulin drift based on CGM; any glucose administration (bolus, change of the infusion rate, oral, or intravenous) administered to correct hypoglycemia based on CGM data.

We planned to address the use of CGM associated with confirmatory glycemia in the 'Subgroup analysis and investigation of heterogeneity' section.

The masked use of CGM (i.e. to preserve blinding) associated with intermittent blood glucose testing was considered as intermittent blood glucose testing.

We considered brief interruption of CGM (e.g. in case of sensor repositioning) as continuous use. Though the target glycemia range could have differed between trials, within each trial the glycemia target range had to be identical in the intervention and control groups.

Types of outcome measures

See Primary outcomes and Secondary outcomes.

Primary outcomes

- Neurodevelopmental outcome including: cerebral palsy, significant mental developmental delay (Bayley Scales of Infant Development Mental Developmental Index greater than two standard deviations (SDs) below the mean) (Bayley 1993; Bayley

2006), legal blindness (< 20/200 visual acuity), and hearing deficit (aided or < 60 dB on audiometric testing). The composite outcome 'neurodevelopmental impairment' was defined as having any one of the aforementioned deficits (modified from definitions of moderate to severe developmental delay) (Schmidt 2007). We planned to assess the outcome assessed at 18 to 36 months and three to five years of age.

Secondary outcomes

- Impairment of executive function (BRIEF T-score > 65) at two years and 4.5 to 5 of corrected age (Gioia 2003);
- impairment of communicative skills assessed by caregivers' questionnaires (MacArthur-Bates Communicative Development Inventory score (MB-CDI) at two years and 4.5 to 5 of corrected age (Fenson 2007);
- neonatal death (first 28 days; all-cause mortality);
- death during initial hospitalization (all-cause mortality);
- seizures during neonatal period (yes/no). We planned to report seizures only after study entry;
- hypoglycemia episodes (number from study entry to discontinuation of glucose monitoring; number from study entry to hospital discharge) per patient detected by CGM or masked use of CGM. Though the definition of hypoglycemic episodes (threshold and duration) might differ between trials, within each trial the definition of hypoglycemic episodes must be identical in both study groups;
- hyperglycemia episodes (number from study entry to discontinuation of glucose monitoring; number from study entry to hospital discharge) per patient detected by CGM or masked use of CGM. Though the definition of hyperglycemic episodes (threshold and duration) might differ between trials, within each trial the definition of hyperglycemic episodes must be identical in both study groups;
- requirement for any medications for hypoglycemia (from study entry to discontinuation of glucose monitoring), e.g. glucagon or corticosteroids (yes/no);
- requirement for any medications for hyperglycemia (from study entry to discontinuation of glucose monitoring), e.g. insulin (yes/no);
- need for blood transfusions during initial hospitalization (yes/no);
- any germinal matrix-intraventricular hemorrhage (IVH): any IVH, grades 1 to 4 (according to Papile classification; Papile 1978);
- severe IVH: ultrasound diagnosis grades 3 and 4 (according to Papile classification; Papile 1978);
- cerebellar hemorrhage on brain ultrasound in the first month of life (yes/no; Graça 2013);
- cystic periventricular leukomalacia on brain ultrasound in the first month of life;
- brain MRI abnormalities at term equivalent age (yes/no), defined as white matter lesions (i.e. cavitations (Rutherford 2010) and punctate lesions (Cornette 2002); germinal matrix (GM)-IVH (Parodi 2015); or cerebellar hemorrhage (Fumagalli 2009; Limperopoulos 2007);
- retinopathy of prematurity: any and severe (≥ stage 3; ICROP 1984);
- bronchopulmonary dysplasia/chronic lung disease, defined as:
  - respiratory support or oxygen, or both, at 28 days of life (Ehrenkranz 2005);
  - respiratory support or oxygen, or both, at 36 weeks of postmenstrual age (PMA) (Jobe 2001);
  - physiological definition (Walsh 2004);
- duration of initial hospital stay (days);
- pain during CGM insertion and blood sampling for glucose monitoring, e.g. heel stick, venipuncture. We will include the following pain scales: the Premature Infant Pain Profile (PIPP) scale (Gibbins 2014; Stevens 1996); Neonatal Pain, Agitation, and Sedation Scale (N-PASS) (Hummel 2008; Hummel 2010); Neonatal Infant Pain Scale (NIPS) (Lawrence 1993); Neonatal Facial Coding System (NFCS) (Grunau 1998; Peters 2003); 'Faceless' Acute Neonatal pain Scale (FANS) (Milesi 2010); the "crying, requires increased oxygen administration, increased vital signs, expression, sleeplessness" (CRIES) (Krechel 1995). We planned to report the mean values of each analgesia scale assessed during the procedure and at one to two hours after the procedure;
- number of skin-breaking procedures associated with blood glucose testing: insertion and repositioning of the CGM; intermittent modalities to measure glycemia (e.g. capillary glucose testing; venipuncture).

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register). We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), and reported the date that we performed this in the review.

Electronic searches

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL, Issue 9, 2020) in the Cochrane Library; MEDLINE via PubMed (1996 to 25 September 2020); Embase (1980 to current); and CINAHL (1982 to 25 September 2020) as described in Appendix 1. We did not apply language restrictions. We searched clinical trials registries for ongoing or recently completed trials (ClinicalTrials.gov (clinicaltrials.gov); the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; http://apps.who.int/trialsearch/default.aspx), and the ISRCTN Registry (www.isrctn.com/)).

Searching other resources

We assessed the reference lists of all identified articles for relevant articles not identified by the primary electronic searches.

Data collection and analysis

We used the standard methods of Cochrane Neonatal, as described below.

Selection of studies

Two review authors (AG and CR) independently searched for and identified eligible trials that met the inclusion criteria. We screened the titles and abstracts to identify potentially relevant citations, and retrieved the full texts of all potentially relevant articles; we independently assessed the eligibility of studies by filling out

eligibility forms designed in accordance with the specified inclusion criteria. We excluded studies published only in abstract form unless the final results of the trial were reported and we could ascertain all necessary information - from the abstract or authors, or both - to justify its inclusion according to the inclusion criteria of this review. We reviewed studies for relevance by assessing study design, types of participants, interventions provided, and outcome measures reported. We resolved disagreements by discussion and, when necessary, by consulting a third review author (MB). We contacted trial authors if details of primary trials were not clear. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (AG and CR) independently extracted data using a data extraction form integrated with a modified version of the Cochrane Effective Practice and Organisation of Care (EPOC) Group data collection checklist (Cochrane EPOC 2017).

We extracted the following characteristics from each included study:

- administrative details: study author(s); published or unpublished; year of publication; year in which study was conducted; presence of vested interest; details of other relevant papers cited;
- study details: study design; type, duration, and completeness of follow-up (e.g. > 80%); country and location of study; informed consent; ethics approval;
- participant details: birth weight, gestational age, number of participants;
- intervention details: type, duration, mode of use of CGM;
- details of outcomes as mentioned above under the 'Types of outcome measures' section.

We resolved disagreements by discussion. We described ongoing studies identified by our search, when available, detailing the primary author, research question(s), methods, and outcome measures, together with an estimate of the reporting date.

When queries arose, or in cases for which additional data were required, we contacted study investigators/authors for clarification. Two review authors (RH and MB) used RevMan Web for data entry (RevMan Web 2019).

Assessment of risk of bias in included studies

Two review authors (CR and MB) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following 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 through discussion or by consulting a third review author (RH). See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We used risk ratios (RRs), risk differences (RDs), number needed to treat for an additional beneficial outcome (NNTB), or number needed to treat for an additional harmful outcome (NNTH) for categorical variables, and mean differences (MDs) for continuous variables. We calculated standardized MDs when combining different pain scales. We planned to replace any within-group standard error of the mean (SEM) reported in a trial by its corresponding standard deviation (SD) using the formula SD = SEM x $\sqrt{N}$. We reported 95% confidence intervals (CIs) for each statistic.

Unit of analysis issues

We included all RCTs and quasi-RCTs in which the unit of allocation was the individual infant. In future updates, if we should find any cluster-RCTs, we would adjust the analysis for the designed effect using the method stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We planned to obtain a dropout rate for each study. Should we find a significant dropout rate (e.g. > 20%), we would contact study author(s) to request additional data. We planned to perform a sensitivity analysis to evaluate the overall results with and without inclusion of studies with a significant dropout rate. If a study should report outcomes only for participants completing the trial or only for participants who followed the protocol, we would contact study author(s) to ask them to provide additional information to facilitate an intention-to-treat analysis; in instances when this would not be possible, we would perform a complete-case analysis. We planned to address the potential impact of missing data on the findings of the review in the Discussion section.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of important participant factors between trials and trial factors (randomization concealment, blinding of outcome assessment, loss to follow-up, treatment type, co-interventions). We assessed statistical heterogeneity by examining the I^2 statistic (Higgins 2011), a quantity that describes the proportion of variation in point estimates that is due to variability across studies rather than to sampling error.

We interpreted the I^2 statistic as follows:

- < 25%: no (none) heterogeneity;
- 25% to 49%: low heterogeneity;
- 50% to 74%: moderate heterogeneity;
- ≥ 75%: high heterogeneity.

In addition, we employed the Chi^2 test of homogeneity to determine the strength of evidence that heterogeneity was genuine. We explored clinical variation across studies by comparing the distribution of important participant factors among trials and trial factors (randomization concealment, blinding of outcome assessment, loss to follow-up, treatment types, and co-interventions). We considered a threshold of P value < 0.1 as an

indicator of whether heterogeneity (genuine variation in effect sizes) was present.

Assessment of reporting biases

We examined the possibility of within-study selective outcome reporting for each study included in the review. We searched for trial protocols of included trials on electronic sources such as PubMed, ClinicalTrials.gov, and the who.int/ictrp/en/ in order to assess whether outcome reporting seemed to be sufficiently complete and transparent. We planned to investigate publication by using funnel plots if we would include 10 or more clinical trials in the systematic review (Egger 1997; Higgins 2011).

Data synthesis

We performed statistical analyses according to the recommendations of Cochrane Neonatal (neonatal.cochrane.org/en/index.html), and used RevMan Web (RevMan Web 2019). We analyzed all infants randomized on an intention-to-treat basis. We analyzed treatment effects in the individual trials. We used a fixed-effect model to combine the data. For any meta-analyses, we synthesized data using RR, RD, NNTB, NNTH, MD, and 95% CI. We planned to analyze and interpret individual trials separately when we judged meta-analysis to be inappropriate.

Subgroup analysis and investigation of heterogeneity

We planned to present data from the following subgroups both for hypoglycemia and hyperglycemia:

- gestational age: ≤ 32 weeks; > 32 weeks;
- birth weight: < 1500 g; ≥ 1500 g;
- use of CGM associated with intermittent modalities to measure glycemia versus CGM without intermittent modalities to measure glycemia;
- prevention or treatment of hypoglycemia and hyperglycemia: CGM used to prevent hypoglycemia/hyperglycemia with adjustment preceding the designated threshold values or CGM used to alert for actual hypoglycemia/hyperglycemia;
- glucose levels: euglycemic, hypoglycemic, and hyperglycemic infants;
- control algorithm (MPC, PID, or fuzzy logic).

Sensitivity analysis

We planned to conduct sensitivity analyses to explore the effect of the methodological quality of trials, checking to ascertain whether studies with a high risk of bias would overestimate the effect of treatment. Differences in study design of included trials might affect the results of the systematic review. We planned to perform a sensitivity analysis to compare the effects of CGM in randomized trials as opposed to quasi-randomized trials.

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 the evidence for the following (clinically relevant) outcomes: cerebral palsy, significant mental developmental delay (Bayley Scales of Infant Development Mental Developmental Index greater than two SDs below the mean), legal blindness (< 20/200 visual acuity), hearing deficit, the composite outcome ‘neurodevelopmental impairment' (defined as having any one of the four aforementioned deficits), death during initial hospitalization, and neonatal seizures.

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

The GRADE approach results in an assessment of the certainty of a body of evidence and allocation to one of four grades:

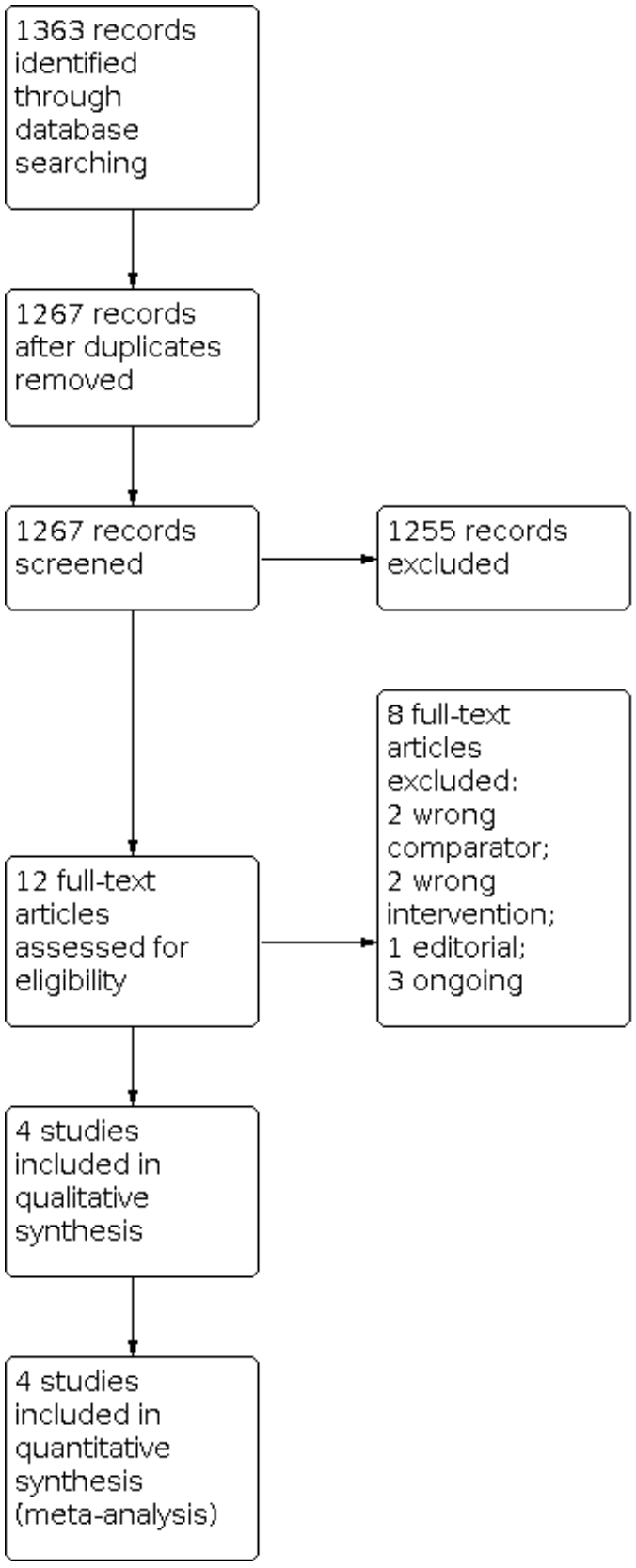
- high certainty: we are very confident that the true effect lies close to that of the estimate of the effect;
- moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially 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.

RESULTS

Description of studies

We have provided results of the search for this review update in the study flow diagram (Figure 2).

Figure 2.



See Summary of findings 1, Summary of findings 2, Characteristics of included studies, Characteristics of excluded studies, Characteristics of ongoing studies.

Results of the search

The literature searches run in September 2020 identified 1267 references. After screening, we assessed nine full-text articles for eligibility and included four trials (Beardsall 2020; Galderisi 2017; Thomson 2019; Uettwiller 2015). We excluded five trials (Beardsall 2007; Beardsall 2008; Galderisi 2018; Hay 2010; Tottman 2018).

We found three relevant ongoing studies by searching clinical trial registries (Beardsall 2018; NCT04347590; UMIN000032812).

Included studies

Four RCTs recruiting 138 infants met the inclusion criteria (Beardsall 2020; Galderisi 2017; Thomson 2019; Uettwiller 2015). We have listed the details of these trials in the Characteristics of included studies section. Three studies compared the use of CGM to intermittent modalities to measure glucose blood levels (Galderisi 2017; Thomson 2019; Uettwiller 2015), however Uettwiller 2015 was analyzed separately because CGM was used as a standalone device, and not coupled to a control algorithm as in Galderisi 2017 and Thomson 2019. In one study, the use of CGM associated with prespecified interventions to correct hypoglycemia or hyperglycemia was compared to CGM without such prespecified interventions (Beardsall 2020).

Beardsall 2020 included 20 preterm infants with a birth weight < 1200 g within 48 hours from birth. All participants were wearing CGM for the first week of life: the intervention group received closed-loop insulin delivery between 48 and 72 hours of age. The median percentage time in tight glycemic target (72 to 144 mg/dL) increased from 26% (6 to 64) with paper algorithm guidance to 91% (78 to 99) during closed loop sessions (P < 0.001) with no serious adverse events. The median time > 180 mg/dL was reduced in the intervention group (0%) versus the control group (16%). There was no difference in the time spent below 47 mg/dL between the two groups.

Galderisi 2017 included 50 preterm infants ≤ 32 weeks' gestation or with birth weight ≤ 1500 g randomly assigned (1:1) within 48 hours from birth to receive computer-guided glucose infusion rate (GIR) with or without CGM. A Proportional Integrative Derivative (PID) algorithm was used to guide continuous GIR adjustments.

In the unblinded CGM group, the GIR adjustments were driven by CGM and rate of glucose change whereas in the blinded CGM group, the GIR was adjusted by using a standard of care glucometer on the basis of blood glucose determinations. The trial aimed to compare the percentage of time spent in euglycemic range (72 to 144 mg/dL) between the two groups (unblinded CGM and blinded CGM). In the unblinded CGM group, they observed a greater median percentage of time spent in euglycemic range (84% vs 68%, P < 0.001) and decreased time spent in mild hypoglycemia (< 72 mg/dL) (P = 0.04) and severe hypoglycemia (< 47 mg/dL) (P = 0.007) and in severe hyperglycemia (> 180 mg/dL) (P = 0.04) compared with the blinded CGM group. Use of CGM also decreased glycemic variability (SD: 21.6 ± 5.4 mg/dL vs 27 ± 7.2 mg/dL, P = 0.01; coefficient of variation: 22.8% ± 4.2% vs 27.9% ± 5.0%; P < 0.001).

Thomson 2019 included 20 very preterm infants within 48 hours from birth. All participants were wearing CGM for the first week of life: the intervention group received insulin delivery combined with a paper guideline to target glucose control (72 to 144 mg/dL) for seven days while the control group wore a blinded CGM and targeted the same glucose range by glucose reduction and insulin adjustment using sliding scale insulin infusion at the discretion of the clinical team. The median percentage of time in target range was greater in the intervention group (77% vs 59%) and percentage of time in hyperglycemia (> 180 mg/dL) was reduced in the intervention group (24% vs 40%, respectively). The use of CGM was perceived as an improvement of clinical care by the staff.

Uettwiller 2015 included 48 very low birth weight infants. During the three first days of life, glucose level was monitored either by real-time continuous glucose monitoring (RT-CGM) (CGM group) or by intermittent capillary glucose testing (IGM group) associated with a blind-CGM to detect retrospectively missed hypoglycemia. CGM was used as a standalone device, i.e. not coupled to a control algorithm. The trial aimed to identify the number and duration of hypoglycemic (50 mg/dL) episodes per patient detected by CGM. Of the 48 included infants, 43 monitorings (IGM n = 21, CGM n = 22) were analyzed. In the IGM group, blind-CGM revealed a significantly higher number of hypoglycemia episodes than capillary blood glucose testing (1.2 ± 0.4 vs 0.4 ± 0.2 episodes/patient, P < 0.01). In the CGM-group, the use of RT-CGM reduced the number of blood samples (CGM 16.9 ± 1.0 vs IGM 21.9 ± 1.0 blood samples/patient, P < 0.001).

We identified three ongoing trials including preterm infants with birth weights ≤ 1200 g (Beardsall 2018) or ≤ 1500 g (NCT04347590; UMIN000032812). The use of real-time CGM will be compared to standard care (with blinded CGM data collection).

The REACT study (Beardsall 2018) [Real time continuous glucose monitoring in the newborn] is the largest ongoing study consisting of three steps: a feasibility study, a multi-site RCT comparing standard of care vs real-time CGM to guide glucose and insulin adjustment for glucose management in neonates with a birth weight equal or lower than 1200 g, and a final small study aimed to test how a computer-based algorithm combined to real time CGM could improve glycemic control in preterm neonates. The multi-site RCT has completed the enrollment. The REACT trial is not powered to assess clinically relevant outcomes other than glycemic control, although other clinically relevant outcomes will be evaluated during the intervention period.

NCT04347590, started in April 2020, will include neurodevelopmental assessment up to five years of age. In addition, infants will be monitored with near-infrared diffuse optical tomography during the first five days from enrollment.

UMIN000032812 has completed the recruitment at the time of the current Review. Investigators powered the study to detect changes in glycemic outcomes in very low birth weight infants in the absence of other longitudinal outcomes or other clinical outcomes.

Excluded studies

We excluded five trials. We excluded four of the trials because of the different methodology used to monitor glucose concentrations as compared to the inclusion criteria of this review. (Beardsall 2007;

Beardsall 2008; Galderisi 2018; Tottman 2018). We excluded the fifth study because it was an editorial (Hay 2010).

Risk of bias in included studies

The overall quality of the studies was limited (Figure 3; Figure 4). The included studies had no high risk of bias for any of the items Cochrane 'Risk of bias' tool except for blinding (performance bias and detection bias). Most studies had unclear risk of bias for selection bias and reporting bias.

Figure 3.

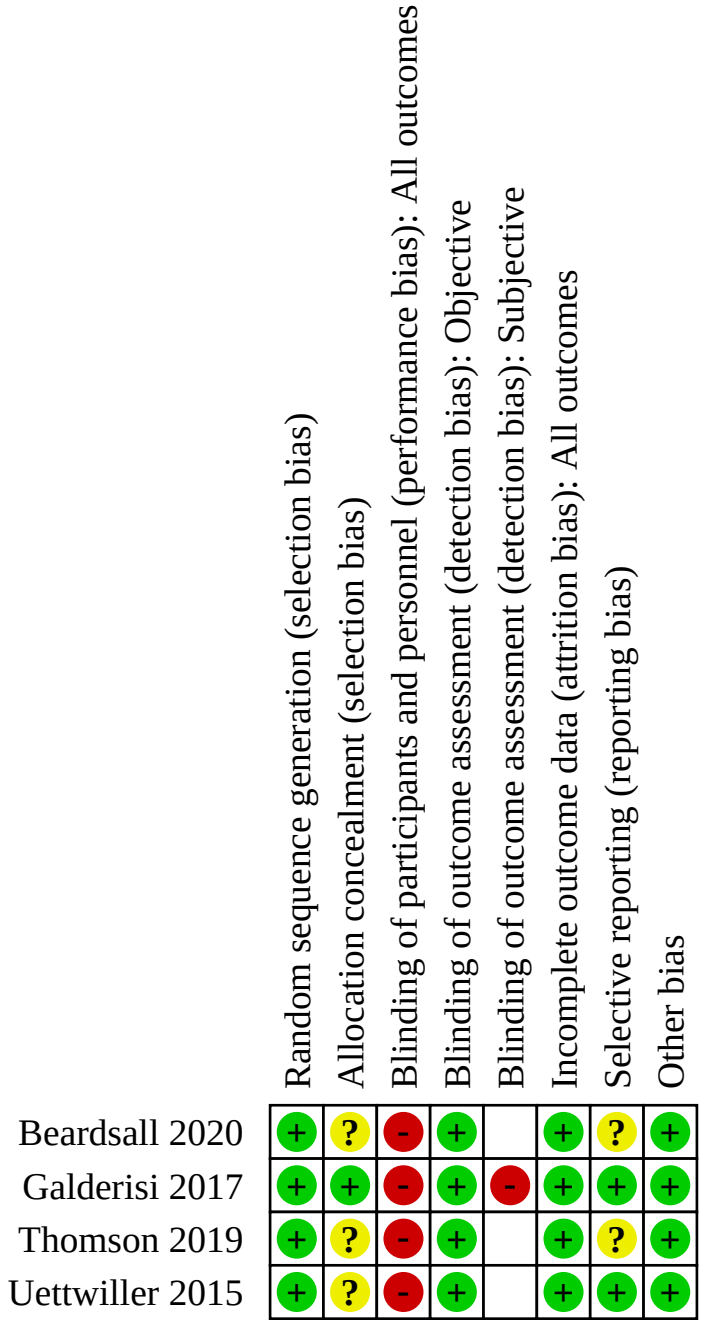
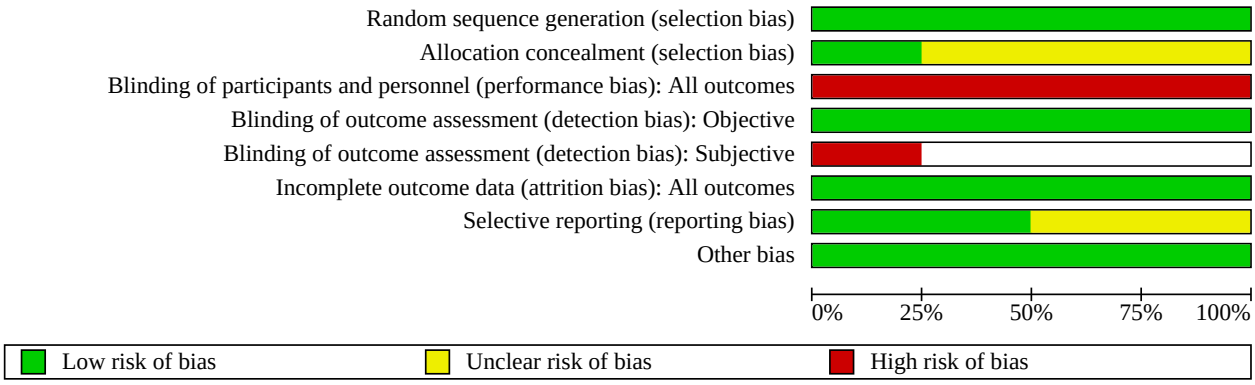


Figure 4.



Details of the methodological quality of each study are described in the Characteristics of included studies table.

Allocation

Random sequence generation was judged to be adequate in all four included studies (Beardsall 2020; Galderisi 2017; Thomson 2019; Uettwiller 2015). Only one study had low risk of bias for allocation concealment (Galderisi 2017). Two studies provided no information on allocation concealment (Beardsall 2020; Thomson 2019). In one study, sequentially numbered sealed envelopes were used, however, it was not specified whether they were opaque (Uettwiller 2015).

Blinding

The assigned intervention could not be blinded due to its nature.

Most outcomes could not be affected by the lack of blinding of outcome assessment. Subjective assessment of outcomes such as pain were reported separately in this review. In Galderisi 2017, data were electronically anonymized by using an individual alphanumeric code and analyzed by investigators not involved in patient enrollment or data collection. In the 3 other trials subjective outcomes were not measured and thus were not scored.

Incomplete outcome data

Follow-up was almost complete for all studies (low risk for attrition bias).

Selective reporting

Two studies had low risk of bias for reporting bias (Galderisi 2017; Uettwiller 2015). In two studies, the protocol was not available (Beardsall 2020; Thomson 2019).

Other potential sources of bias

Not identified.

Effects of interventions

See: **Summary of findings 1** Summary of Findings Table - CGM compared to intermittent modalities for the prevention of morbidity and mortality in preterm infants; **Summary of findings 2** Summary of Findings Table - CGM vs. intermittent modalities for health problem or population

Comparison 1: CGM with or without prespecified interventions to correct hypoglycemia (e.g. algorithms; use of automated or strictly defined criteria to perform changes in glucose infusion) or hyperglycemia (e.g. changes in parenteral nutrition; insulin administration) versus intermittent modalities to measure glycemia (e.g. capillary glucose testing; central line sampling or venipuncture) with or without prespecified interventions to correct hypoglycemia or hyperglycemia;

Three trials (Galderisi 2017; Thomson 2019; Uettwiller 2015), with a total of 118 infants, met the eligibility criteria (see Summary of findings 1).

All outcomes, where rated, had very-low certainty evidence, downgraded for risk of bias and imprecision by one and two levels, respectively. The test for heterogeneity was not applicable as no trials were pooled in any analyses.

Primary outcomes

Neurodevelopmental outcome

None of the included trials reported this outcome.

Secondary outcomes

Neonatal mortality (Outcome 1.1)

One study (Galderisi 2017) reported on this outcome. No infants died in either group in the neonatal period (RR 3.00, 95% CI 0.13 to 70.30; RD 0.04, 95% CI -0.06 to 0.14; 50 participants; 1 study; Analysis 1.1). The certainty of the evidence (GRADE) for this outcome was very low due to imprecision (downgraded by two levels) and limitations in study design (see Summary of findings table 1).

Mortality before discharge (Outcome 1.2)

One study (Galderisi 2017) reported on this outcome. One infant died in the CGM group (RR not estimable; RD 0.00, 95% CI -0.07 to 0.07; 50 participants; 1 study; Analysis 1.2). The certainty of the evidence (GRADE) for this outcome was very low due to imprecision (downgraded by two levels) and limitations in study design (see Summary of findings 1).

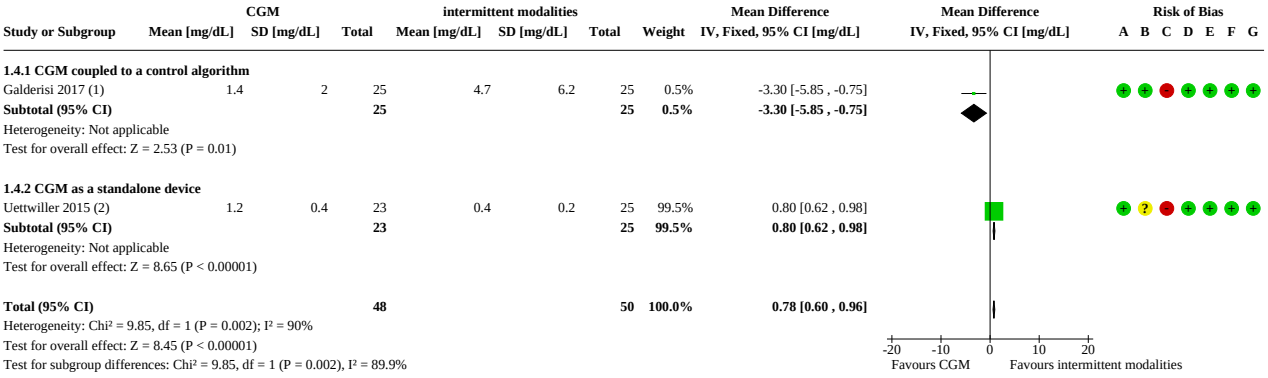
Hypoglycemia episodes (yes/no) (Outcome 1.3)

One study (Thomson 2019) reported on this outcome (RR 0.50, 95% CI 0.05 to 4.67; RD -0.10, 95% CI -0.41 to 0.21; 20 participants; 1 study; Analysis 1.3).

Hypoglycemia episodes per patient (Outcome 1.4)

Two studies (Galderisi 2017; Uettwiller 2015) reported on this outcome, however, they were not pooled because CGM was coupled to a control algorithm only in Galderisi 2017. In Galderisi 2017, there were fewer hypoglycemic events in the CGM group (MD -3.30, 95% CI -5.85 to -0.75; 50 participants; 1 study; Analysis 1.4) whereas in Uettwiller 2015 there were fewer events in the control group (MD 0.80, 95% CI 0.62 to 0.98; 48 participants; 1 study; Analysis 1.4) (Figure 5).

Figure 5.



Footnotes
(1) events defined as <47mg/dL
(2) episode per patient. SD not available for the CGM group; hypoglycemia defined as <=50mg/dL

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Objective
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Hyperglycemia episodes per patient (Outcome 1.5)

One study (Galderisi 2017) reported on this outcome (MD -1.40, 95% CI -2.84 to 0.04; 50 participants; 1 study; Analysis 1.5).

Severe intraventricular hemorrhage (Outcome 1.6)

One study (Galderisi 2017) reported on this outcome (RR 5.00, 95% CI 0.25 to 99.16; RD 0.08, 95% CI -0.05 to 0.21; 50 participants; 1 study; Analysis 1.6).

Bronchopulmonary dysplasia (Outcome 1.7)

One study (Galderisi 2017) reported on this outcome (RR 3.00, 95% CI 0.13 to 70.30; RD 0.04, 95% CI -0.06 to 0.14; 50 participants; 1 study; Analysis 1.7).

Duration of initial hospital stay (days)

One study (Galderisi 2017) reported on this outcome. Median duration was 46 days (interquartile range 40 to 74) and 51 days (37 to 63) in the CGM and control group, respectively (P = 0.59).

Pain during CGM insertion and blood sampling for glucose monitoring

One study (Galderisi 2017) reported on this outcome. Median PIPP was 5 (interquartile range 4 to 6) and 8 (7 to 9) in the CGM and control group (heel stick procedure), respectively (P < 0.001).

None of the included trials within comparison 1 reported neonatal seizures; requirement for any medications for hypoglycemia; requirement for any medications for hyperglycemia; need for blood transfusions; any grade germinal matrix-intraventricular hemorrhage; cerebellar hemorrhage; cystic periventricular leukomalacia; brain MRI abnormalities at term equivalent age; retinopathy of prematurity; respiratory support or oxygen, or both, at 28 days of life; number of skin-breaking procedures.

Subgroup analysis

We were unable to conduct any of the planned subgroup analyses other than that in Analysis 1.4.

Comparison 2: CGM associated with prespecified interventions to correct hypoglycemia (e.g. algorithms; use of automated or strictly defined criteria to perform changes in glucose infusion) or hyperglycemia (e.g. changes in parenteral nutrition; insulin administration) versus CGM without prespecified interventions to correct hypoglycemia or hyperglycemia.

One trial (Beardsall 2020), with a total of 20 infants, met the eligibility criteria.

All outcomes, where rated, had very-low certainty evidence, downgraded for risk of bias and imprecision by one and two levels, respectively. The test for heterogeneity was not applicable as only one trial was included in Comparison 2.

Primary outcomes

Neurodevelopmental outcome

The included trial did not report this outcome.

Secondary outcomes

Hypoglycemia episodes per patient (Outcome 2.1)

One study (Beardsall 2020) reported on this outcome (RR 3.00, 95% CI 0.14 to 65.90; RD 0.10, 95% CI -0.14 to 0.34; 20 participants; 1 study; Analysis 2.1).

Requirement for any medications for hypoglycemia (Outcome 2.2)

One study (Beardsall 2020) reported on this outcome. A smaller proportion of infants in the intervention group required medication for hypoglycemia than in the control group (RR 0.13, 95% CI 0.02 to 0.82; RD -0.70, 95% CI -1.01 to -0.39; 20 participants; 1 study; Analysis 2.2).

None of the included trials within comparison 2 reported mortality; neonatal seizures; hyperglycemia episodes; requirement for any medications for hypoglycemia; need for blood transfusions; germinal matrix-intraventricular hemorrhage; cerebellar hemorrhage; cystic periventricular leukomalacia; brain MRI abnormalities at term equivalent age; retinopathy of prematurity; respiratory support or oxygen, or both; duration of initial hospital stay; pain during CGM insertion and blood sampling; number of skin-breaking procedures.

Subgroup analysis

We were unable to conduct any of the planned subgroup analyses as the analyses included only one trial in this comparison.

DISCUSSION

Summary of main results

We evaluated the benefits and harms of continuous glucose monitoring (CGM) in preterm newborn infants. Four trials (Beardsall 2020; Galderisi 2017; Thomson 2019; Uettwiller 2015), with a total of 138 preterm infants with gestational age less than 32 weeks or birth weight less than 1500 g, met the inclusion criteria of our review. Three studies (Galderisi 2017; Thomson 2019; Uettwiller 2015), compared the use of CGM to intermittent modalities (comparison 1), however, Uettwiller 2015 was analyzed separately because CGM was used as a standalone device, and not coupled to a control algorithm as in Galderisi 2017 and Thomson 2019. In one study (Beardsall 2020), the use of CGM coupled with an algorithm for insulin and glucose infusion (closed-loop) was compared to the use of CGM without the algorithm to achieve time in the target glycemic range (comparison 2).

None of the four included studies reported the neurodevelopmental outcome, i.e. the primary outcome of this review.

Within comparison 1 (118 infants), investigators compared the use of CGM to intermittent modalities. With great uncertainties due to very limited evidence, there appeared to be no clear differences in the outcomes of neonatal mortality, mortality during hospitalization and number of hypoglycemic episodes between infants who received CGM and infants who received intermittent monitoring. The number of hypoglycemic episodes was reported in two studies with conflicting data, possibly due to the different study design: CGM was coupled to a control algorithm in Galderisi 2017 whereas in Uettwiller 2015 CGM was used as a standalone device.

Within comparison 2 (20 infants), investigators compared the use of CGM associated with prespecified interventions to correct hypoglycemia or hyperglycemia to the use of CGM without such prespecified interventions.

Ongoing trials are currently assessing the effect of CGM coupled to paper or computer-based algorithms to achieve tight glycemic control in very low birth weight infants. Only one of the ongoing trials has planned to report longitudinal neurodevelopmental outcomes (up to five years of age) (NCT04347590).

Overall completeness and applicability of evidence

To date, four trials on CGM use in preterm infants have enrolled 138 newborns. Study authors reported extremely limited data on critical outcomes such as mortality. None of the four included trials reported long-term neurodevelopmental assessment. We could not perform an appropriate a priori subgroup analysis to detect differential effects because of the paucity of the included trials. We identified two ongoing studies. Other larger trials are required to draw any conclusions. Of note, the accuracy of CGM in preterm infants has been addressed in a systematic review including 13 diagnostic studies, which reported high sensitivity and specificity for hyperglycemia and high specificity for hypoglycemia (Nava 2021). However, sensitivity to diagnose hypoglycemia was low, thus limiting CGM applicability in preterm infants.

Quality of the evidence

According to the GRADE approach, we rated the overall certainty of evidence for critical outcomes as very low because of limitations in study design (i.e. unclear and high risk of bias in three domains, one level) and imprecision of results (low information size and wide confidence intervals, two levels; see Summary of findings 1; Summary of findings 2). Studies where CGM was coupled to a control algorithm (e.g. Galderisi 2017) were not pooled with studies where CGM was used as a standalone device (Uettwiller 2015). Of note, these studies showed conflicting results, e.g. on the number of hypoglycemic episodes (Figure 5). Additional possible explanations for this discrepancy include the different strategies for hypoglycemia treatment (preventive interventions based on CGM vs treatment interventions), different algorithms for glycemic control, use of insulin, differences in neonatal age during the intervention and length of the examined interventions.

We did not explore possible bias through generation of funnel plots because fewer than 10 trials met the inclusion criteria of this Cochrane review.

Potential biases in the review process

We used the standard methods of Cochrane Neonatal in conducting this systematic review. It is unlikely that the literature search applied to this review may have missed relevant trials, thus we are confident that this systematic review summarizes all the presently available randomized trial evidence on CGM use in preterm infants. We applied no language restrictions. We excluded four trials because of the different methodology to monitor glucose

concentrations (Beardsall 2007; Beardsall 2008; Galderisi 2018; Tottman 2018), and a fifth study because it was an editorial (Hay 2010). As two review authors (AG and DT) are also the authors of one of the trials that was included (Galderisi 2017), the other review authors (CR, RH and MB) conducted quality assessments of these trials. We succeeded in obtaining additional information from study authors.

Agreements and disagreements with other studies or reviews

We are not aware of any other review that address the same clinical question. We described the characteristics of the only clinical trials that have been published. This is the first systematic review on CGM in newborns. A Cochrane review has been conducted on CGM for patients of any age with type 1 diabetes mellitus (Langendam 2012). Though some of the included studies enrolled children, no infants were identified (as diabetes mellitus is extremely rare in infants). We agree with the conclusion of the narrative review by McKinlay and colleagues, i.e. CGM should be introduced into routine clinical care once benefits and harms are reported in randomized trials (McKinlay 2017b).

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to determine if CGM improves preterm infant mortality or morbidity. Long-term outcomes were not reported. Clinical trials are required to determine the most effective CGM and glycemic management regimens in preterm infants before larger studies can be performed to assess the efficacy of CGM for reducing mortality, morbidity and long-term neurodevelopmental impairments. The absence of CGM labeled for neonatal use is still a major limit in its use as well as the absence of dedicated neonatal devices.

Implications for research

Large trials targeting at-risk neonatal populations (i.e. very preterm infants, small/large for gestational age infants, maternal diabetes) should investigate the effect of CGM, and different CGM-associated interventions, on long-term outcomes such as neurodevelopment as well as short-term morbidity and mortality. Only one of the ongoing trials has planned to report longitudinal neurodevelopmental outcomes (up to five years of age). None of the ongoing trials is powered to detect the effect of CGM alone or coupled with an algorithm on mortality. Trials examining different interventions associated with CGM use are expected to examine the effect of clinical-advisor algorithms, nutritional interventions, as well as to evaluate the use of glucose adjustment alone or combined with the use of insulin in very preterm neonates. The results of the included studies represent the framework for designing future clinical trials targeting clinically significant outcomes.

ACKNOWLEDGEMENTS

We have based the Methods section of this review on a standard template used by Cochrane Neonatal.

We thank Matthias Bank (Library and ICT services, Lund University) for defining and running the search strategy.

We thank Cochrane Neonatal: Colleen Ovelman, Managing Editor, Jane Cracknell, Assistant Managing Editor, Roger Soll, Co-coordinating editor, and Bill McGuire, Co-coordinating Editor, who provided editorial and administrative support.

Cochrane Neonatal Senior Editor Dr David Osborn, and Dr Nai Ming Lai, peer reviewed and offered feedback for this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Beardsall 2020

Study characteristics	
Methods	Randomized parallel design, single-center feasibility study
Participants	Newborn with birth weight < 1200 g, age < 48 hours
Interventions	Infants randomized to: • either CGM alone supported by a paper algorithm • or to CGM with an additional intervention period of closed-loop CGM Closed-loop system used for 24 hours, between 48 and 72 hours post-birth. The closed-loop system comprised a sensor, a laptop computer running a predictive control algorithm, using CMG to to calculate insulin delivery, and two syringe pumps. After that period, CGM data were used in combination with the paper algorithm by the clinical team, to guide glucose control in all babies (as in the control group), for a total time of 7 days CGM.
Outcomes	Primary outcome: time in target glucose range (SG 4 to 8 mmol/L) Secondary outcomes: • time in target (% time sensor glucose 2.6 to 10 mml/L), • prevalence of hyperglycemia (% time sensor glucose > 10.0 mmol/L), • prevalence of severe hyperglycemia (% time sensor glucose > 15 mmol/L) • prevalence of hypoglycemia (% time sensor glucose glucose < 2.6 mmol/L • frequency of hypoglycemia (any single blood glucose < 2.6 mmol/L and/or more than 6 sensor glucose readings < 2.6 mmol/L) • other adverse events
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerized randomization (with stratification according to gestational age and birth weight).

Beardsall 2020 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Assigned intervention could not be blinded.
Blinding of outcome assessment (detection bias) Objective	Low risk	The 2 outcomes reported in this review could not be affected by the lack of blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants remained in the study throughout the intervention period from 48 to 72 hours.
Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	Low risk	None.

Galderisi 2017

Study characteristics	
Methods	Randomized controlled trial
Participants	Newborn ≤ 32 weeks, birth weight ≤ 1500 g, < 48 hours after birth
Interventions	Within 48 hours of birth, infants were randomly assigned to: • glycemic control by using an unblinded CGM with active alarms coupled with a proportional-integrative derivative (PID) control algorithm (unblinded-CGM (UB-CGM)) • or a control group in which a blinded CGM was used and glucose infusion rate (GIR) was calculated on the basis of standard-of-care blood glucose levels measured by a glucometer (blinded-CGM (B-CGM)) Calibrations performed at least twice per day by using capillary blood glucose values. Glucose infusion rate adjusted every 3 hours driven by CGM with active alarms for hypoglycemia and hyperglycemia, coupled with a PID control algorithm. CGM for at least 48 hours, maximum 7 days.
Outcomes	Primary outcome: Percentage of time spent in euglycemic range (72 to 144 mg/dL) Secondary outcomes: • time in mild (47 to 71 mg/dL) and severe (< 47 mg/dL) hypoglycemia; • time in mild (145 to 180 mg/dL) and severe (> 180 mg/dL) hyperglycemia; • glucose variability (coefficient of variations and SD) • number of episodes of mild/severe hypoglycemia • number of mild/severe hyperglycemia • BPD • severe IVH • length of hospital stay • neonatal mortality

Galderisi 2017 *(Continued)*

- mortality during first admission

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomization 5 blocks of 10 subjects per block with an allocation ratio 1:1 to the randomization groups.
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes. An officer not involved in the study performed the procedure.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Assigned intervention could not be blinded.
Blinding of outcome assessment (detection bias) Objective	Low risk	Outcomes could not be affected by the lack of blinding of outcome assessment. Data were electronically anonymized by using an individual alphanumeric code and analyzed by investigators not involved in patient enrollment or data collection.
Blinding of outcome assessment (detection bias) Subjective	High risk	Pain scales could be affected by the lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	88% of the infants (44/50) completed the study; missing data and drop-outs (< 20%) are described.
Selective reporting (reporting bias)	Low risk	Protocol available. Changes to reported outcomes were shared.
Other bias	Low risk	None.

Thomson 2019

Study characteristics

Methods	Single-center study - randomized pilot study
Participants	Birth weight < 1200 g, age < 48 hours, written informed parental consent
Interventions	Infants randomized to either: • control (standard care with masked CGM data collection) • or real-time CGM monitoring along with a specifically designed paper guideline Real time-CGM was calibrated at least twice daily using blood glucose levels . Infants remained in the study until 7 days of age.

Thomson 2019 *(Continued)*

	Real time viewing of sensor glucose data were used in conjunction with the paper guideline to support clinical management. The paper guideline provided simple guidance and was not a rigid algorithm and had not undergone formal in silico testing.
Outcomes	Primary outcomes: • % time in target (47 to 180 mg/dL) • % time in target (72 to 144 mg/dL) • prevalence of hyperglycemia (> 180 mg/dL) • prevalence of severe hyperglycemia (> 270 mg/dL) Secondary outcomes: • % time in hyperglycemia (> 180 mg/dL) and severe (> 270 mg/dL)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomisation (accounting for gestational age and birth weight) .
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Assigned intervention could not be blinded.
Blinding of outcome assessment (detection bias) Objective	Low risk	All the stored data (RT- and blind-CGMS) were analyzed retrospectively with an access restricted to the principal investigator. However outcomes could not be affected by the lack of blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	23 infants recruited, no data were found at the time of data download in two control infants (one infant in the intervention group died of a massive pulmonary hemorrhage, within 24 hours of birth). These three infants were excluded from the analyses and 20 infants were analyzed.
Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	Low risk	None.

Uettwiller 2015

Study characteristics

Methods	Randomized controlled trial
Participants	VLBW preterm infants (birth weight ≤ 1500 g) admitted before 24 hours of life to the Neonatal Intensive Care Unit of the University Hospital of Tours
Interventions	Infants randomized to:

Uettwiller 2015 *(Continued)*

	• Real time-CGM • Intermittent capillary glucose testing associated with a blind-CGM to detect retrospectively missed hypoglycemia CGM started between 6 and 27 hours of life. Calibration twice per day by using blood samples. Median duration of recording of 71.8 (3.5 to 87.7) hours.
Outcomes	Primary outcome: number of hypoglycemic episodes (< 50 mg/dL) Secondary outcomes: • number of hypoglycemia episodes per patient • duration of these episodes • number of blood samples per patient for glucose determination • daily carbohydrate intake and caloric supplies
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomization (8 patients per block).
Allocation concealment (selection bias)	Unclear risk	Sequentially numbered sealed envelopes; not specified whether opaque.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Assigned intervention could not be blinded. No blinding
Blinding of outcome assessment (detection bias) Objective	Low risk	Outcomes could not be affected by the lack of blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	43/47 patients analyzed, 0 lost to follow up (2 in each group discontinued the intervention)
Selective reporting (reporting bias)	Low risk	All outcomes specified in the protocol were reported in the manuscript.
Other bias	Low risk	None.

B-CGM = blind-CGM
BPD = bronchopulmonary dysplasia
CGM = continuous glucose monitoring
GIR = glucose infusion rate
IVH = intraventricular hemorrhage
PID = proportional-integrative derivative
SD = standard deviation
SG = glucose range
UB-CGM = unblinded continuous glucose monitoring
VLBW = very low birth weight

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

Study	Reason for exclusion
Beardsall 2007	Wrong intervention
Beardsall 2008	Wrong comparator
Galderisi 2018	Wrong comparator
Hay 2010	Editorial
Tottman 2018	Wrong intervention

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

Beardsall 2018

Study name	Protocol of a randomized controlled trial of real-time continuous glucose monitoring in neonatal intensive care 'REACT'
Methods	International multicenter randomized controlled trial
Participants	Infants who have a birth weight ≤ 1200 g, are ≤ 24 hours of age, ≤ 33+6 weeks' gestation and in whom written informed parental consent has been received
Interventions	Real-time CGM or standard care (with blinded CGM data collection)
Outcomes	The primary outcome is time in target 2.6 to 10 mmol/L during the study intervention assessed using CGM. Secondary outcomes include efficacy relating to glucose control, utility including staff acceptability, safety outcomes relating to incidence and prevalence of hypoglycemia and health economic analyses.
Starting date	July 2016
Contact information	Dr Kathryn Beardsall: kb274@cam.ac.uk
Notes	

NCT04347590

Study name	Continuous glucose monitoring and cerebral oxygenation in preterm infants (Babyglucolight)
Methods	Randomized controlled trial
Participants	Inclusion Criteria: preterm infants less or equal to 32 weeks gestation, birth weight less than 1500 g
Interventions	Exclusion Criteria: birth weight less than 500g; congenital pathologies; lack of parental consent; perinatal maternal infections; albinism
Outcomes	Primary Outcome :

NCT04347590 *(Continued)*

	• Number of hemodynamically significant hypoglycemic events according to posterior areas. Hypoglycemic events are defined as any value < 72 mg/dL (mild hypoglycemia) or < 47 mg/dL (severe hypoglycemia). They are classified as "significant" in the presence of a reduction from baseline HbT >= 15% (posterior areas) Secondary Outcomes: • Number of hemodynamically significant hypoglycemic events according to the overall tested average of areas. Hypoglycemic events are defined as any value < 72 mg/dL (mild hypoglycemia) or < 47 mg/dL (severe hypoglycemia). They are classified as "significant" in the presence of a reduction from baseline HbT >= 15% (average of tested areas) • Effect of CGM-based interventions on Bayley III performance at 12, 24, 18, 36, 50 months
Starting date	30 April 2020; estimated primary completion: 30 April 2022
Contact information	Alfonso Galderisi, Neonatal Intensive Care Unit - University Hospital of Padua, Padua, Italy, +390498213545 alfonsogalderisi@gmail.com
Notes	

UMIN000032812

Study name	Strict glycemic control in VLBW infants at high risk of glycemic disorders using a continuous glucose monitoring system: randomized controlled clinical trial
Methods	Randomized controlled clinical trial
Participants	VLBW infants fed with parenteral nutrition during the first week of life. VLBW and SGA infants with a documented prenatal history of severe placental insufficiency (umbilical doppler sonography assessing AED or ARED or brain sparing)
Interventions	Continuous glucose monitoring duration: at least 96 hours.
Outcomes	Primary outcome: to achieve the reduction of 33% of dysglycemic episodes in the intervention arm.
Starting date	2018
Contact information	Giovanni Vento: giovanni.vento@unicatt.it
Notes	

AED = absent end-diastolic
ARED = absent or reversed end-diastolic
CGM = continuous glucose monitoring
HbT = tissue hemoglobin concentration
SGA = small for gestational age
REACT = Real Time Continuous Glucose Monitoring in Neonatal Intensive Care
VLBW = very low birth weight

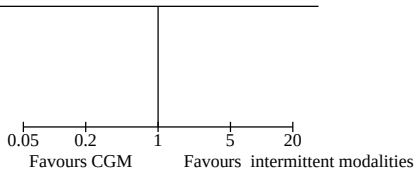
DATA AND ANALYSES

Comparison 1. CGM with or without prespecified interventions versus intermittent modalities to measure glycemia with or without prespecified interventions

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Neonatal mortality	1	50	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Death during initial hospitalization (all-cause mortality)	1	50	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 70.30]
1.3 Hypoglycemia episodes (yes/no)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 4.67]
1.4 Hypoglycemia episodes per patient	2	98	Mean Difference (IV, Fixed, 95% CI)	0.78 [0.60, 0.96]
1.4.1 CGM coupled to a control algorithm	1	50	Mean Difference (IV, Fixed, 95% CI)	-3.30 [-5.85, -0.75]
1.4.2 CGM as a standalone device	1	48	Mean Difference (IV, Fixed, 95% CI)	0.80 [0.62, 0.98]
1.5 Hyperglycemia episodes per patient	1	50	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.84, 0.04]
1.6 Severe intraventricular hemorrhage	1	50	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [0.25, 99.16]
1.7 Bronchopulmonary dysplasia, defined as respiratory support or oxygen, or both, at 36 weeks of postmenstrual age	1	50	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 70.30]

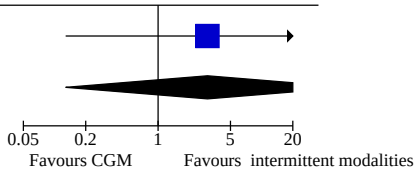
Analysis 1.1. Comparison 1: CGM with or without prespecified interventions versus intermittent modalities to measure glycemia with or without prespecified interventions, Outcome 1: Neonatal mortality

	CGM		intermittent modalities			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Galderisi 2017	0	25	0	25		Not estimable	
Total (95% CI)		**25**		**25**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



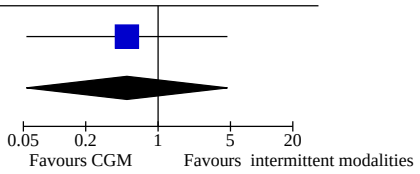
Analysis 1.2. Comparison 1: CGM with or without prespecified interventions versus intermittent modalities to measure glycemia with or without prespecified interventions, Outcome 2: Death during initial hospitalization (all-cause mortality)

	CGM		intermittent modalities			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Galderisi 2017	1	25	0	25	100.0%	3.00 [0.13 , 70.30]	
Total (95% CI)		**25**		**25**	**100.0%**	**3.00 [0.13 , 70.30]**	
Total events:	1		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.68 (P = 0.49)							
Test for subgroup differences: Not applicable							



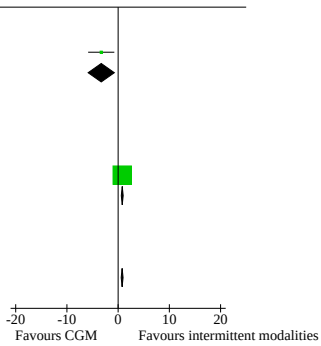
Analysis 1.3. Comparison 1: CGM with or without prespecified interventions versus intermittent modalities to measure glycemia with or without prespecified interventions, Outcome 3: Hypoglycemia episodes (yes/no)

Study or Subgroup	CGM Events	CGM Total	intermittent modalities Events	intermittent modalities Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Thomson 2019	1	10	2	10	100.0%	0.50 [0.05 , 4.67]
Total (95% CI)		**10**		**10**	**100.0%**	**0.50 [0.05 , 4.67]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
Test for subgroup differences: Not applicable						



Analysis 1.4. Comparison 1: CGM with or without prespecified interventions versus intermittent modalities to measure glycemia with or without prespecified interventions, Outcome 4: Hypoglycemia episodes per patient

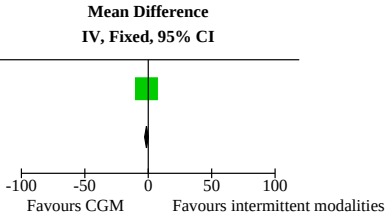
Study or Subgroup	CGM Mean [mg/dL]	CGM SD [mg/dL]	CGM Total	intermittent modalities Mean [mg/dL]	intermittent modalities SD [mg/dL]	intermittent modalities Total	Weight	Mean Difference IV, Fixed, 95% CI [mg/dL]
1.4.1 CGM coupled to a control algorithm								
Galderisi 2017 (1)	1.4	2	25	4.7	6.2	25	0.5%	-3.30 [-5.85 , -0.75]
Subtotal (95% CI)			**25**			**25**	**0.5%**	**-3.30 [-5.85 , -0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.53 (P = 0.01)								
1.4.2 CGM as a standalone device								
Uettwiller 2015 (2)	1.2	0.4	23	0.4	0.2	25	99.5%	0.80 [0.62 , 0.98]
Subtotal (95% CI)			**23**			**25**	**99.5%**	**0.80 [0.62 , 0.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 8.65 (P < 0.00001)								
Total (95% CI)			**48**			**50**	**100.0%**	**0.78 [0.60 , 0.96]**
Heterogeneity: Chi² = 9.85, df = 1 (P = 0.002); I² = 90%								
Test for overall effect: Z = 8.45 (P < 0.00001)								
Test for subgroup differences: Chi² = 9.85, df = 1 (P = 0.002), I² = 89.9%								



Footnotes
(1) events defined as <47mg/dL
(2) episode per patient. SD not available for the CGM group; hypoglycemia defined as <=50mg/dL

Analysis 1.5. Comparison 1: CGM with or without prespecified interventions versus intermittent modalities to measure glycemia with or without prespecified interventions, Outcome 5: Hyperglycemia episodes per patient

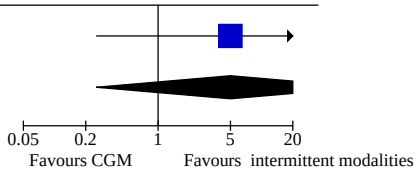
Study or Subgroup	CGM Mean	CGM SD	CGM Total	intermittent modalities Mean	intermittent modalities SD	intermittent modalities Total	Weight	Mean Difference IV, Fixed, 95% CI
Galderisi 2017	0.8	1.6	25	2.2	3.3	25	100.0%	-1.40 [-2.84 , 0.04]
Total (95% CI)			**25**			**25**	**100.0%**	**-1.40 [-2.84 , 0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.91 (P = 0.06)								
Test for subgroup differences: Not applicable								



Analysis 1.6. Comparison 1: CGM with or without prespecified interventions versus intermittent modalities to measure glycemia with or without prespecified interventions, Outcome 6: Severe intraventricular hemorrhage

Study or Subgroup	CGM Events	CGM Total	intermittent modalities Events	intermittent modalities Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galderisi 2017	2	25	0	25	100.0%	5.00 [0.25 , 99.16]
Total (95% CI)		**25**		**25**	**100.0%**	**5.00 [0.25 , 99.16]**
Total events:	2		0			

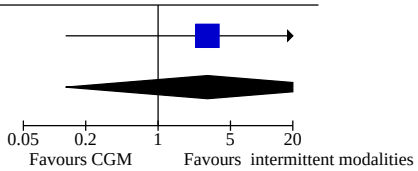
Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: CGM with or without prespecified interventions versus intermittent modalities to measure glycemia with or without prespecified interventions, Outcome 7: Bronchopulmonary dysplasia, defined as respiratory support or oxygen, or both, at 36 weeks of postmenstrual age

Study or Subgroup	CGM Events	CGM Total	intermittent modalities Events	intermittent modalities Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Galderisi 2017	1	25	0	25	100.0%	3.00 [0.13 , 70.30]
Total (95% CI)		**25**		**25**	**100.0%**	**3.00 [0.13 , 70.30]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.49)
Test for subgroup differences: Not applicable



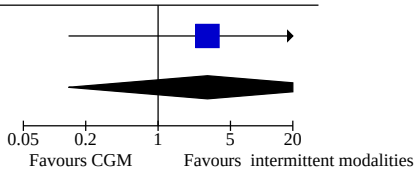
Comparison 2. CGM associated with prespecified interventions to correct hypoglycemia or hyperglycemia versus CGM without prespecified interventions to correct hypoglycemia or hyperglycemia

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 Hypoglycemia episodes (yes/no)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.14, 65.90]
2.2 Requirement for any medications for hyperglycemia	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.02, 0.82]

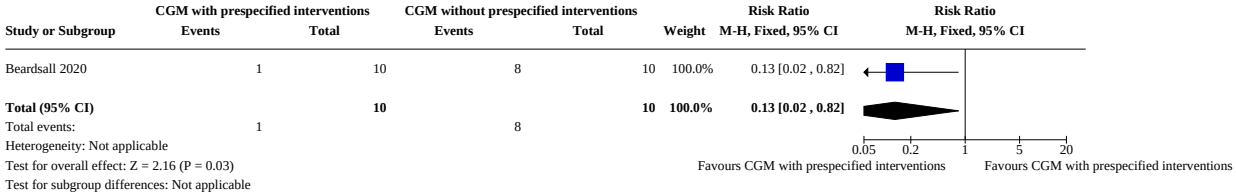
Analysis 2.1. Comparison 2: CGM associated with prespecified interventions to correct hypoglycemia or hyperglycemia versus CGM without prespecified interventions to correct hypoglycemia or hyperglycemia, Outcome 1: Hypoglycemia episodes (yes/no)

Study or Subgroup	CGM Events	CGM Total	intermittent modalities Events	intermittent modalities Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Beardsall 2020	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Total (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: CGM associated with prespecified interventions to correct hypoglycemia or hyperglycemia versus CGM without prespecified interventions to correct hypoglycemia or hyperglycemia, Outcome 2: Requirement for any medications for hyperglycemia



APPENDICES

Appendix 1. Search strategy

PubMed, 25 September 2020

#1 (("Blood Glucose"[Mesh] AND "Monitoring, Physiologic"[Mesh]) OR continuous glucose monitor* OR CGM[Title/Abstract] OR "glucose control")

#2 (infant, newborn[MeSH] OR newborn*[TIAB] OR "new born"[TIAB] OR "new borns"[TIAB] OR "newly born"[TIAB] OR baby*[TIAB] OR babies*[TIAB] OR premature[TIAB] OR prematurity[TIAB] OR preterm[TIAB] OR "pre term"[TIAB] OR "low birth weight"[TIAB] OR "low birthweight"[TIAB] OR VLBW[TIAB] OR LBW[TIAB] OR infan*[TIAB] OR pediatric[Title] OR neonat*[TIAB])

#3 (((((("controlled clinical trial"[Publication Type] OR "randomized controlled trial"[Publication Type])))) OR (randomized[Title/Abstract] OR randomised[Title/Abstract] OR placebo[Title/Abstract] OR randomly[Title/Abstract] OR trial*[Title/Abstract] OR group*[Title/Abstract])) OR clinical trial as topic[MeSH Terms]) OR "drug therapy"[MeSH Subheading]

#4 #1 AND #2 AND #3

Embase, 25 September 2020

#1. 'blood glucose monitoring'/exp

#2. 'monitoring'/exp AND 'glucose blood level'/exp

#3. 'continuous glucose monitor*' OR cgm:ti,ab OR (glucose NEAR/3 control*) OR (glucose NEAR/3 monitor*)

#4. #1 OR #2 OR #3

#5. 'prematurity'/exp OR 'infant'/exp

#6. newborn*:ti,ab OR 'new born':ti,ab OR 'new borns':ti,ab OR 'newly born':ti,ab OR baby*:ti,ab OR babies:ti,ab OR premature:ti,ab OR prematurity:ti,ab OR preterm:ti,ab OR 'pre term':ti,ab OR 'low birth weight':ti,ab OR 'low birthweight':ti,ab OR vlbw:ti,ab OR lbw:ti,ab OR infant:ti,ab OR infants:ti,ab OR infantile:ti,ab OR infancy:ti,ab OR neonat*:ti,ab

#7. #5 OR #6

#8. 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'controlled clinical trial'/exp OR 'controlled clinical trial' OR 'randomized':ab,ti OR randomised:ab,ti OR 'placebo':ab,ti OR 'randomly':ab,ti OR 'trial':ab,ti OR 'clinical trial'/exp OR 'clinical trial'

#9. #4 AND #7 AND #8

Cochrane Library, 25 September 2020

#1 (infant or infants 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):ti,ab,kw (Word variations have been searched)

#2 MeSH descriptor: [Blood Glucose] explode all trees

#3 MeSH descriptor: [Monitoring, Physiologic] explode all trees

#4 #2 AND #3

#5 (continuous glucose monitor* OR cgm OR "glucose control"):ti,ab,kw (Word variations have been searched)

#6 #4 OR #5

#7 #1 AND #6

Cinahl, 25 September 2020

#	Query
S8	S5 AND S6 AND S7
S7	(randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
S6	(infant or infants 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 pre-maturity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW)
S5	S1 OR S2 OR S3 OR S4
S4	glucose N3 monitor* OR glucose N3 control*
S3	continuous glucose monitor* OR TI CGM OR AB CGM
S2	(MH "Blood Glucose") AND (MH "Monitoring, Physiologic+")
S1	(MH "Blood Glucose Monitoring+")

Searches in clinical trial registries, 25 September 2020

Clinicaltrials.gov

Advanced search

Intervention/treatment: Continuous glucose monitoring
Other terms: premature OR prematurity OR preterms OR preterm OR “very low birth” OR “low birth weight” OR newborn OR newborns OR neonate OR neonates OR infant OR infants
No further limits applied

ICTRP / WHO

No additional results

ISRCTN registry
Text search “continuous glucose monitoring” AND infants

https://www.isrctn.com/ISRCTN12793535?q=%22continuous%20glucose%20monitoring%22%20AND%20infants&filters=&sort=&offset=3&totalResults=5&page=1&pageSize=10&searchType=advanced-search

Appendix 2. Risk of bias tool

We used the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the included trials. For each trial, we sought information regarding the method of randomization, blinding, and reporting of all outcomes of all the infants enrolled in the trial. We assessed each criterion as being at either low, high, or unclear risk of bias. Two review authors separately assessed each study. We resolved any disagreement by discussion. We added this information to the 'Characteristics of included studies' table. We evaluated the following issues and entered the findings into the 'Risk of bias' table.

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

For each included study, we categorized 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.

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

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

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

3. 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 categorized 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 categorized the methods as:

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

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

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

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

5. 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 randomized 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 categorized the methods as:

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

6. 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. We searched study protocols of the included trials in ClinicalTrials.gov (clinicaltrials.gov); the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; http://apps.who.int/trialsearch/default.aspx), and the ISRCTN Registry (www.isrctn.com/). 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.

7. 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;
- unclear risk.

If needed, we planned to explore the impact of the level of bias through sensitivity analyses.

HISTORY

Protocol first published: Issue 4, 2019
Review first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

AG and MB reviewed the background literature and wrote the review.

CR, RH, and DT commented on and reviewed the review.

All authors read and approved the final review version.

DECLARATIONS OF INTEREST

MB has no interest to declare.

AG: my institution received research support from Dexcom, Inc - USA for an investigator initiated study (equipment). Dexcom, Inc had no role in the study design and data analysis. I am an author of an included trial (Galderisi 2017).

RH employed by the Cochrane Collaboration as part of the Central Executive Team, acting as Product Owner for RevMan, the review authoring tool.

CR has no interest to declare.

DT is an author of an included trial (Galderisi 2017).

As two of the review authors (AG and DT) are also the authors of one of the trials that was included, the other three review authors (CR, RH and MB) conducted quality assessments of these trials.

SOURCES OF SUPPORT

Internal sources

- Institute for Clinical Sciences, Lund University, Lund, Sweden

  MB is employed by this organization

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

We updated the search methods in September 2019, following the publication of the protocol (Galderisi 2019).

We reported the outcome hypoglycemia episodes as both continuous and dichotomous measures, though the latter was not specified in the protocol (Galderisi 2019).

Following editorial feedback, we better clarified the objective of the review (outcomes were not changed).