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Review

Continuous glucose monitoring in very low birth weight infants – a systematic review

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Abstract

Introduction: Dysglycemic events are common occurrences in preterm infants. This imbalance of blood glucose levels could lead to an increased risk of death, sepsis, neurosensorial impairment, retinopathy of prematurity, among other unfavorable consequences. Continuous glucose monitoring (CGM) allows for early detection of dysglycemic events. This systematic review aims to assess the impact of CGM in glycemic values of preterm infants.

Methods: We thoroughly searched several electronic databases from August 2020 to February 2021, we included randomized control trials regarding newborn infants with birth weight < 1,500 g, gestational age < 37 weeks, and postnatal life < 28 days, that compared intermittent methods vs continuous methods concerning glucose measurement. Primary outcomes were percentage of time spent in euglycemic range, number of dysglycemic episodes, and mortality.

Results: Three studies were included after screening, comprising a combined total of 278 preterm newborns. Two studies reported an increase in time spent in euglycemic range in the CGM group (83% vs 71% and 94% vs 84%). There were limitations in study design of included studies, interventions and outcomes evaluated differed between included studies; as such, comparisons between studies were difficult.

Conclusions: CGM allows for better glycemic control, reduces the number of painful readings, allows for early detection of dysglycemic events, and reduces time spent in dysglycemic states (both hyperglycemia and hypoglycemia) when combined with corrective measures. Further research needs to be conducted to evaluate the long-term impact of CGM in the neurosensorial and physical development of preterm infants.

Keywords

Continuous glucose monitoring, very low birth weight newborns, hyperglycemia, hypoglycemia, blood glucose measurements.

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Introduction

Preterm newborns often experience dysglycemic events, undergoing extensive periods of hyperglycemia or hypoglycemia. Included in this demographic are very low birth weight (VLBW) infants. These neonates were born with birth weight < 1,500 g and, due to glucose instability, can easily develop significant variations on blood glucose levels in a short amount of time [1-3].

There is a high level of uncertainty regarding the best approach when dealing with these events. It remains unclear what is the ideal target for blood glucose levels right after birth [4]. It is uncertain if a rapid or a slow rate of recovery is preferable when treating dysglycemic events, and the potential neurosensorial outcomes that could derive from this adjustment [5]. Additionally, it is unclear if tight glycemic control is beneficial in early life [6]. It is, so far, not well-established if hyperglycemia and/or hypoglycemia can cause long-term effects in neurological and physical devolvement [7-11].

Background

Hyperglycemia may occur due to a variety of reasons: insulin resistance [12] and deficit, clinical stress (hypoxia, sepsis) [13], drug treatment (i.e., steroid treatment) [14], high glucose infusion rates, among others. It is estimated that around 20% to 88% of all preterm infants may experience hyperglycemia, at some point in early life, with more recent studies pointing to a percentage of around 30% [1-2]. This condition is linked with increased mortality (more than double) [1], associated with neurosensorial impairment, retinopathy of prematurity [15, 16], and increased risk of intraventricular hemorrhage [17]. To treat this disorder, there are two options: reducing glucose infusion rates (lowering available energy) or increasing insulin infusion (that could lead to more hypoglycemic events, and a need for tighter glycemic control) [18].

On the other hand, hypoglycemia can affect up to 50% of all preterm infants [3]. It may occur due to a depletion of fat and glycogen reserves that build up during the 3rd trimester of pregnancy. In addition, preterm infants need a steady glucose supply of 6-8 mg/kg/min, compared with 2-3 mg/kg/day for term infants [19]. From the available energy to the preterm infants, about 90% of all available glucose will be used to fuel the high-level brain activity. This high demand and relatively low supply can easily cause hypoglycemic events and can potentially lead to neurological complications [20, 21].

We can ascertain that dysglycemic events are common and associated with poorer outcomes for VLBW infants. Early detection of these events is key to ensure better long-term outcomes and survivability. Despite this, there are few recommendations regarding glucose monitoring in VLBW infants [22].

In most Neonatal Intensive Care Units (NICUs), blood glucose is measured punctually (intermittent methods), using heel prick tests or, on occasion, venipuncture. These methods only provide with a singular measurement of an exact point in time. As such, dysglycemic events may linger unnoticed for long periods or even remain undetected. This could, in turn, lead to the increased time spent in hypoglycemic and/or hyperglycemic states [23, 24].

In addition, these tests are associated with increased levels of pain endured by the newborn and can represent additional stress for the infant [23, 25].

Continuous glucose monitoring (CGM) devices (CGMD) are already in widespread use for insulin delivery when treating diabetes, in both children and adults [26].

Despite similar accuracy when compared with heel prick tests, and relative safety [27], these devices are not regularly used in the NICU context [22].

Description of the intervention

Real-time CGM technology allows its users or caregivers to evaluate, in real-time, blood glucose concentrations [28].

This device utilizes sensor electrodes and small filaments inserted into subcutaneous tissue. The electrodes measure glucose concentration through a glucose oxidase reaction. The signal is then transformed into a glucose reading and conveyed wirelessly to a matching device [28]. Alerts can be customized for low or high glucose values.

These devices have only been deemed harmless for use in children age 2 or more, by USA authorities [29], due to lack of research in younger children.

CGM technology has been used in some studies to guide glucose infusion rates, or insulin administration, integrated into computer-guided algorithms for optimal glycemic control [24].

How the intervention might work

Studies demonstrate the feasibility, safety, and potential advantages (better glycemic control) of using these devices in preterm infants, compared with more standard methods such as capillary blood glucose measure [23, 24, 30, 31].

CGM reduces the number of heel prick tests necessary for better control glucose in neonatal settings [23], and the subcutaneous insertion of CGM system is associated with lower distress and pain when compared with heel prick tests [25].

In addition, CGMD could also provide these readings in real time, allowing caregivers to decide adjustments based on protocols, algorithms, or based on professional experience [24]. CGMD could also be associated with computer-guided algorithms for an independent, automated, and reliable way to ensure that blood glucose stays between preset interval ranges [24, 32].

CGMD provide a continuous influx of data on blood glucose concentration that could then be analyzed and processed by computer-based algorithms, who in turn could independently perform real-time adjustments. This process could become fully automated. This could reduce the number and time spent in dysglycemic states [24].

In increasingly automated health care services, CGMD could prove essential in the management of preterm infants.

Why is it important to conduct this review?

CGM is a growing field of research, several reports have been published, and many others are in development. Studies have shown that these devices are capable of accurate readings and can contribute to better and safer blood glucose control, both in children and adults [26, 27].

However, little evidence is available on the advantages or disadvantages of using CGMD in preterm infants in a NICU context [22].

Thus, some questions arise: are CGMD safe for use in the NICU context? Do CGMD detect significantly more dysglycemic events than traditional methods of blood glucose measurement (such as heel prick tests)? Is tight glycemic control beneficial for newborn infants? What are the long-term effects of CGM in neurodevelopment and physical outcomes?

Some recent systematic reviews and clinical trials have tackled these questions. Reilly et al. intended to evaluate the impact of CGM on glucose stability in preterm infants. The study was conducted in 2019 and included studies published until January 2019. They concluded that: "The potential of CGM is significant although more research is required as little is definitively known about short- and long-term benefits and risks regarding its use in the preterm population" [33].

More recently, Galderisi et al. evaluated the impact of CGM in the neurodevelopment of preterm infants. The study was conducted in 2020, and included studies published until September 2020 and concluded: "There is insufficient evidence to determine if CGM improves preterm infant mortality or morbidity. Long-term outcomes were not reported" and "Further research is needed" [34].

Since then, new studies, involving a sizable number of newborns, were published. This could bring new insights and conclusions about these topics [30]. In addition, several ongoing clinical trials are being conducted [35-37], and are soon to be published.

In this review, we analyzed all the available information regarding the use of CGM in preterm infants.

Objectives

A systematic review that aims to assess the feasibility and safety of CGM when compared with other methods of intermittent glucose measure (i.e., capillary blood glucose or central line testing).

To assess the effect of CGM systems (CGMS) or CGMD in VLBW newborn infants, specific interventions were reviewed:

I. CGM using CGMS/CGMD compared with methods of intermittent glucose measure

(capillary blood glucose or central line testing), in detecting hyperglycemic events;
II. CGM using CGMS/CGMD compared with methods of intermittent glucose measure (capillary blood glucose or central line testing), in detecting hypoglycemic events;
III. safety of CGMS/CGMD compared with methods of intermittent glucose measure (capillary blood glucose or central line testing), regarding mortality, infection rate, among other short- and long-term outcomes listed hereafter in the "Types of outcomes" section.

Methods

Inclusion criteria

We reviewed studies that abided by the following criteria.

Types of studies

Randomized controlled trials or quasi-randomized controlled trials with randomized individual participants in parallel groups. We excluded feasibility and pilot studies. In this review, we included unpublished trials or trials reported solely in the abstract, only if the appraisal of study quality was feasible.

Types of participants

Newborn infants with birth weight < 1,500 g, gestational age < 37 weeks, and postnatal life < 28 days.

Types of interventions

CGM using CGMS/CGMD, compared with intermittent methods of glucose measure (capillary blood glucose or central line testing), both interventions utilizing the same methods to correct hyperglycemia and/or hypoglycemia. Corrective measures relevant for this review included:
I. computer-based algorithms (using a combination of glucose rate infusion and insulin rate infusion variations, delivered automatically);
II. pre-defined guidelines based on literature or clinical experience (using a combination of glucose rate infusion and insulin rate infusion variations);
III. glucose infusion rate adjustments (increases or decreases);
IV. insulin infusion rate adjustments (increases or decreases).

We included studies where corrective measures were identical in both groups. We planned on comparing between corrective measures to determine the most optimal for use, as we further explain in the subgroup analysis.

When intermittent glucose measure is associated with masked CGM (to preserve blinding), it was considered as intermittent glucose measure readings. This was done to, posteriorly, provide improved data analysis.

Types of outcomes

Primary outcomes

1. All cause mortality: mortality before discharge, mortality at 28 days, or as defined by the authors.
2. Median time to correct hypoglycemia, specified as hours to reach euglycemic concentration between 50 and 150 mg/dl, or as defined by the authors.
3. Median time to correct hyperglycemia, specified as hours to reach euglycemic concentration between 50 and 150 mg/dl, or as defined by the authors.
4. Number of hyperglycemic events per individual, defined as the mean number of episodes of hyperglycemia (> 150 mg/dl) per individual included in both groups, or as defined by the authors.
5. Number of hypoglycemic events per individual, defined as the mean number of episodes of hypoglycemia (< 50 mg/dl) per individual included in both groups, or as defined by the authors.
6. Median time spent in the euglycemic range, defined as blood glucose levels between 50 and 150 mg/dl, or as defined by the authors.

Secondary outcomes

1. Severe intraventricular hemorrhage, grade III or IV.
2. Skin lesions, skin infection, or other reported adverse effects attributed to the use of CGMS/CGMD.
3. Retinopathy of prematurity.
4. Late onset of sepsis, described as a positive culture for bacteria in the blood recorded after 72 hours of life up to 28 days of life.

5. Growth impairment, defined as weight, height, head circumference, and BMI, or as determined by the authors.
6. Neurodevelopmental outcome, defined as cerebral palsy, significant mental developmental delay, or as defined by the authors.
7. Percentage of weight loss during the study.
8. Bronchopulmonary dysplasia, defined as the necessity for respiratory support at 36 weeks corrected for gestational age.

Search methods

The following sources were searched.

Electronic searches

We searched electronic databases that included: MEDLINE (from 1966 to February 2021, via PubMed), the Cochrane Central Register of Controlled Trials – CENTRAL (until February 2021), and ClinicalTrials.gov. We applied no language restriction. The search started in September 2020 and concluded in February of 2021.

I. Query used in the online search (CENTRAL and PubMed) was the following: (blood glucose sensor OR blood glucose analyzer OR continuous glucose monitoring OR CGM OR self-monitoring OR glucose monitor measurements OR tight glucose control OR tight glucose monitoring) AND (low blood sugar OR hypoglycemia OR hypoglycemics OR hyperglycemia OR hyperglycemic OR high blood sugar OR glucose intolerance OR glucose metabolism OR euglycemia OR euglycemic OR normal blood glucose OR dysglycemia OR glycemia) AND (infant, very low birth weight OR very low birth weight OR VLBW OR extremely low birth weight OR ELBW OR preterm OR extremely low birth weight infants).
II. Query used in online search of ClinicalTrails.gov was the following: (hypoglycemia OR hyperglycemia OR dysglycemia) AND (newborn OR infants) AND (continuous glucose monitoring OR CGM OR self-monitoring).

Search and subsequent selection of reports were documented in a flowchart, following PRISMA recommendations.

Searching other resources

We reviewed the reference list of included studies, systematic reviews focused on this demographic group, and other relevant papers, in search of pertinent reports that were not identified in the initial electronic search. If relevant studies were found, they were included in the initial search results and reviewed following the method subsequently depicted.

Data collection and analysis

Standard methods of Cochrane were applied, as described below.

Study selection

The selection process was conducted independently by 2 authors.

After applying the search terms and retrieving the initial report yield, we proceeded to removed duplicate reports.

Subsequently, titles and abstracts of detected studies were assessed and reviewed, only retaining those relevant to this review.

Studies were then read in full and carefully chosen based on selection criteria previously listed under "Inclusion criteria". We removed all reports from the same studies, only retaining those with the most complete data.

If there was uncertainty regarding inclusion or exclusion of a particular study, the full report was assessed for eligibility.

Management of this process was performed using EndNote X9. Additionally, this program was used in citation managing.

All steps were documented in a flowchart according to PRISMA recommendations [38].

Data extraction

Included studies were reviewed in a comprehensive analysis. Data was collected regarding relevant information such as author, date of publication, study design, geographic location, clinical features of the population (birth weight, gestational age, maternal diabetes, male/female sex) sample size, interventions (type of CGMS, duration), outcomes, data analysis, among others.

This was done using data collecting forms designed for this review.

Ongoing studies were evaluated and if sufficient data were available, they were included in this review. If additional data was required, we planned to contact the authors of the reports for additional information.

Assessment of risk of bias

Every trial was evaluated for: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other forms of bias. Each category was classified as High, Low, or Unclear, with an explanation for each point. This was done using the Cochrane "Risk of Bias tool" [39].

Measure of treatment effect

For every trial, we planned on using risk ratio (RR), odds ratio (OR), absolute risk difference (RD), number needed to treat (NNT), when dealing with categorical variables. For continuous variables, we planned on using mean differences (MD). If size measurement varied across trials, we used standardized mean difference (SMD), each with 95% CI.

If meta-analysis was possible, we planned on utilizing OR for categorical variables, with 95% CI. For continuous variables, we calculated weighted mean difference (WMD) with 95% CI.

Dealing with missing data

An effort was made to try and get the most complete data stets possible. If there was incomplete or unreported data on a study outcome or the dropout rate was too high (> 20%), we would try to contact the primary investigator.

If data outcome was still unavailable despite efforts to acquire full data sets, an available-case analysis based on available data would be carried out.

If an important portion of data were missing, despite efforts to obtain full information, the study would be excluded.

Assessment of heterogeneity

We planned to present the results of this review using meta-analysis. Before doing any meta-analysis, we decided that if there was enough similarity between studies, we would compare study design and clinical features such as population, type of intervention, and outcome evaluated. We assessed statistical heterogeneity by calculating statistic. Additional test will be used to determine if heterogeneity was statistically significant.

After this assessment, if enough similarities were found between studies, we would perform a meta-analysis. If not, each study's results would be described separately, analyzing it accordingly with criteria defined in "types of interventions" and "types of outcomes".

Assessment of reporting bias

We expected a relatively small number of included reports (< 10); as such, it would be difficult to perform funnel plots to assess any possible publication bias. If the number of clinical trials were superior to 10, we would present a funnel plot.

We searched for included trials on PubMed, ClinicalTrials.gov, and WHO ICTRP. We compared primary and secondary outcomes in the final report, with the outcomes submitted in trials registration, and evaluated if reporting outcomes were complete.

Data synthesis

Statistical analysis was performed using RevMan 5 [40], a statistic tool provided by Cochrane. For meta-analysis data would be presented utilizing RR, OR, RD, NNT, MD – all with a 95% CI.

If meta-analysis were deemed to be unsuitable, we would interpret the reports individually.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned with the subsequent order:

- blood glucose levels, time spent in hypoglycemia, euglycemia, hyperglycemia in the subsequent subgroups:
  - birth weight < 1,000 g, 1,000-1,200 g, 1,200-1,500 g,
  - gestational age: < 30 weeks, 30-32 weeks, 32-35 weeks;
- CGM with computer algorithms to control hyperglycemia and/or hypoglycemia;
- CGM with pre-defined guidelines to control hyperglycemia and/or hypoglycemia;
- CGM with glucose infusion rate increases (hypoglycemia)/decreases (hyperglycemias);
- CGM with insulin infusion rates increases (hyperglycemia)/decreases (hypoglycemias).

Results

Search results

Search and subsequent selection of reports were documented in a flowchart, following PRISMA

recommendations. The flowchart is presented in **Fig. 1**.

Seventeen studies were eligible for a full appraisal. Fourteen of those were excluded; the reasons for exclusion can be consulted in **Tab. 1**.

Three studies were eligible for this review: Galderisi et al., from 2017 [24] (**Tab. 2**), Beardsall et al., from 2021 [30] (**Tab. 3**), and Uetwiller et al., from 2015 [23] (**Tab. 4**). **Tables 2-4** contain the assessment of risk of bias.

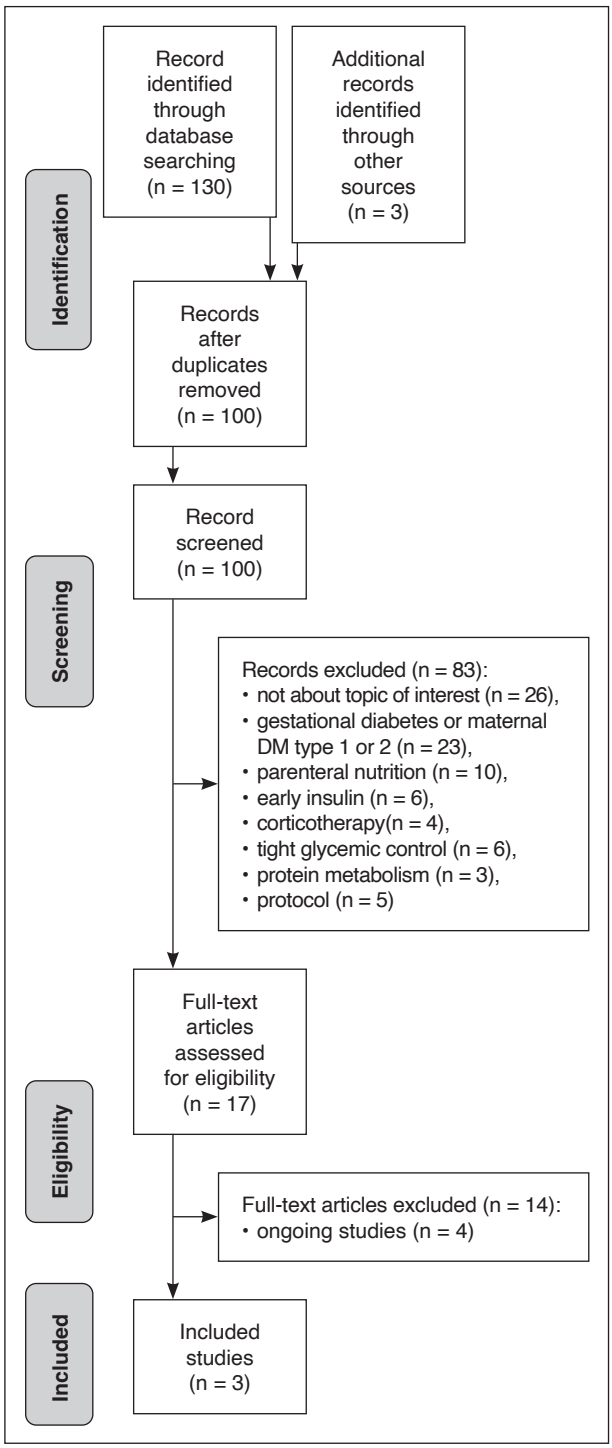

Figure 1. Flow diagram.

Table 1. Characteristics of excluded studies.

Study	Description
Perri et al., 2018 [27]	A non-randomized feasibility study, that aims to evaluate the feasibility and reliability of a CGM system in a population of VLBW infants.
Agus, 2014 [35]	Randomized controlled trail, that aims to evaluate the utility of CGM in improving the diagnosis and management of neonatal hypoglycemia in infants. Inclusion criteria: babies born more than 33 weeks and 6 days after the start of the pregnancy. Terminated (insufficient eligible participants to meet recruitment goal).
Beardsall et al., 2020 [32]	Single-center feasibility study with a randomized parallel design, both groups had subcutaneous CGM and the intervention group received closed-loop insulin delivery.
Galderisi et al., 2016 [41]	Randomized controlled trail, results published in another study [24].
Chemin, 2013 [42]	Randomized controlled trail, results published in another study [23].
Beardsall et al., 2013 [43]	Prospective study, comparing data obtained by CGMS from the NIRTURE Trial with data obtained simultaneously using point-of-care glucose monitors.
Saw et al., 2017 [44]	Non-randomized feasibility study.
Nally et al., 2019 [45]	Interventional, randomized, parallel assignment. It aims to study the utility of CGMS to monitor blood sugar in newborns. The investigators will evaluate the number of hypoglycemic events detected using CGM and compare it to standard methods. Inclusion criteria: newborns > 34 weeks born to mothers with gestational or pre-gestational diabetes. Exclusion criteria: infants < 2,000 g.
Thomson et al., 2019 [31]	Single center, pilot study. It compared CGM with standard methods of blood glucose measurement.
Beardsall, 2016 [36]	REACT trial, results published in included study [30].
Galderisi, 2020 [37]	Ongoing randomized clinical trial, that aims to assess the impacts of CGM on both short-term and long-term neurodevelopment. Not yet recruiting.
Kaiser, 2020 [46]	Ongoing clinical trial, not yet recruiting. Aims to evaluate the feasibility and precision of CGM in at-risk newborns.
Kim, 2020 [47]	Ongoing observational study, recruiting.
Perri, 2018 [48]	An ongoing randomized controlled trial, that aims to achieve a reduction on dysglycemic episodes varying glucose infusion rate.

CGM: continuous glucose monitoring; CGMS: continuous glucose monitoring systems.

Table 2. Characteristics of the study by Galderisi et al., 2017 [24].

<table>
<tr><td>Methods</td><td>Randomize controlled trial, parallel, single-center.</td></tr>
<tr><td>Participants</td><td>Fifty newborns were arbitrarily allocated (1:1) (after 48 hours from birth) to receive computer-guided glucose infusion rate with or without CGM.
Inclusion criteria were:
I. infants born ≤ 32 weeks of gestation;
II. birth weight ≤ 1,500 g.
From this study were excluded:
I. newborns with congenital malformations;
II. newborns with chromosomal abnormalities;
III. birth weight < 500 g.
All newborns wore a G4 Platinum CGM system, this device was worn for a maximum of 7 days, calibrations were performed twice daily.</td></tr>
<tr><td>Interventions</td><td>I. In the CGM group, the glucose infusion rate adjustments were driven by CGM and rate of glucose change.
II. In the control group, the glucose infusion rate adjustments were driven using standard-of-care glucometer based on blood glucose determinations, associated with a blind CGMS.</td></tr>
<tr><td>Outcomes</td><td>Primary:
percentage of time spent in euglycemic range (72-144 mg/dl).
Secondary:
I. percentage of time in mild hypoglycemia (47-71 mg/dl);
II. percentage of time in severe hypoglycemia (< 47 mg/dl);
III. percentage of time in mild hyperglycemia (145-180 mg/dl);
IV. percentage of time in severe hyperglycemia (> 180 mg/dl);
V. glucose variability.</td></tr>
<tr><td>Risk of bias</td><td>
<table>
<tr><th>Bias</th><th>Risk</th><th>Support</th></tr>
<tr><td>Random sequence generation</td><td>Low</td><td>Quote: “Patients were randomly assigned by using electronically generated block randomization of 5 blocks of 10 subjects per block (www. sealedenvelope.com) with an allocation ratio 1:1 to the randomization groups”.</td></tr>
<tr><td>Allocation concealment</td><td>Low</td><td>Quote: “Opaque envelopes containing the allocation group were sealed and sequentially numbered according to an electronically generated randomization list”.</td></tr>
<tr><td>Blinding of participants and personnel</td><td>High</td><td>Assigned intervention could not be blinded. Masking of the study intervention is very difficult.</td></tr>
<tr><td>Blinding of outcome assessment</td><td>Low</td><td>Quote: “Data were electronically anonymized by using an individual alphanumeric code and analyzed by investigators not involved in patient enrollment or data collection”.</td></tr>
<tr><td>Incomplete outcome data</td><td>Low</td><td>From the 50 participants that were initially randomised not all were included, 6 were excluded (4 were transferred to a closer hospital, 2 required sensor replacement more than once and were discontinued as per protocol). This is a reasonable attrition and not expected to affect results. 88% of newborns completed the study.</td></tr>
<tr><td>Selective reporting</td><td>Low</td><td>Protocol is available, reported on pre-defined outcomes.</td></tr>
<tr><td>Other bias</td><td>Low</td><td>The study seems to have no other sources of bias.</td></tr>
</table>
</td></tr>
</table>

CGM: continuous glucose monitoring.

Table 3. Characteristics of the study by Beardsall et al., 2021 [30].

<table>
<tr><td>Methods</td><td>Randomize controlled trial, parallel-group, multi-center.</td></tr>
<tr><td>Participants</td><td>One hundred and eighty newborns were randomly assigned (1:1) (within 24 hours from birth) to receive glucose/insulin infusion guided by CGM or by standard care (intermittent methods of glucose measure).
Inclusion criteria were:
I. newborns ≤ 33 weeks of gestation;
II. birth weight ≤ 1,200 g;
III. < 24 hours after birth;
IV. written consent from parent or guardian.
From this study were excluded:
I. newborns with congenital malformations;
II. newborns with congenital metabolic disorders.
All infants had an Enlite glucose sensor (Medtronic, Northridge, CA, USA) inserted subcutaneously into the thigh. Calibration was done every 12 hours using blood sample utilizing Nova StatStrip meters (Nova Biomedical, Waltham, MA, USA) for measurements.</td></tr>
<tr><td>Interventions</td><td>I. For the newborns assigned to the CGM group, real-time data was available to view by the clinical team, they were provided with a specifically designed guideline to better control blood glucose levels based on CGM readings. This guideline consisted of adjusting glucose infusion rates or insulin infusion rates. The guidelines were based on CGM data, but it was advised to check blood glucose values whenever there were rapid changes in CGM values, or if CGM values dropped to less than 4 mmol/L.
II. Infants assigned to the control group had blood glucose managed accordingly with standard methods. In this group, CGMS were used but data collected was masked to the clinical team.</td></tr>
<tr><td>Outcomes</td><td>Primary:
percentage of time spent in euglycemic (target) range (2.6-10 mmol/L).
Secondary, as stated:
• “the proportion of time sensor glucose concentrations were in the target range of 4-8 mmol/L;
• overall mean sensor glucose concentration;
• sensor glucose concentration variability (assessed by within-patient standard deviation);
• proportion of time that sensor glucose concentrations were in the severe hyperglycaemic range (> 15 mmol/L);
• incidence of hypoglycaemia (any recorded blood glucose concentration of 2.2-2.6 mmol/L or any continuous episode of sensor glucose concentration of < 2.6 mmol/L for > 1 h);
• severe hypoglycaemia (any recorded blood glucose ≤ 2.2 mmol/L);
• clinical outcomes: mortality before 36 weeks’ corrected gestational age, retinopathy of prematurity (maximum grade across all examinations), bronchopulmonary dysplasia (need for supplemental oxygen or respiratory support at 36 weeks’ corrected gestational age), infection (microbiologically confirmed or clinically suspected late-onset invasive infection from trial entry until hospital discharge), necrotising enterocolitis (requiring surgical intervention including peritoneal drainage or causing death), patent ductus arteriosus (requiring medical or surgical treatment), intracerebral pathology before discharge, growth at the end of week 1 and at 36 weeks’ corrected gestational age, nutritional intake in week 1 and use of insulin in weeks 1 and 2”.</td></tr>
<tr><td>Risk of bias</td><td>
<table>
<tr><th>Bias</th><th>Risk</th><th>Support</th></tr>
<tr><td>Random sequence generation</td><td>Low</td><td>Quote: “Babies were randomly assigned (1:1) within 24 h of birth to receive either the intervention with real-time CGM or standard care until 7 days of age. Randomisation was done using a central web randomisation system, Trans European Network ALEA, using blocks of random size (four, six, eight), stratifying by recruiting centre and gestational age (< 26 or ≥ 26 weeks)”.</td></tr>
<tr><td>Allocation concealment</td><td>Low</td><td>Quote: “The programme will notify the local research team of treatment allocation who will then inform their clinical team regarding the practicalities of management”.</td></tr>
<tr><td>Blinding of participants and personnel</td><td>High</td><td>Quote: “Masking of the study intervention was not feasible”.</td></tr>
<tr><td>Blinding of outcome assessment</td><td>Low</td><td>Quote: “The real-time CGM device collected glucose data continuously but the values were masked to the clinical team (in an opaque bag with a tamper proof seal)”.</td></tr>
<tr><td>Incomplete outcome data</td><td>Low</td><td>From the 180 participants that were initially randomised not all were included, 25 newborns were excluded. This is a reasonable attrition, and it is not likely to change results. 86% of newborns completed the study.</td></tr>
<tr><td>Selective reporting</td><td>Low</td><td>Protocol is available, reported on pre-defined outcomes.</td></tr>
<tr><td>Other bias</td><td>Low</td><td>The study seems to have no other sources of bias.</td></tr>
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</td></tr>
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CGM: continuous glucose monitoring; CGMS: continuous glucose monitoring systems.

Table 4. Characteristics of the study by Uetwiller et al., 2015 [23].

<table>
<tr><td>Methods</td><td>Randomized clinical trial, parallel, single-center.</td></tr>
<tr><td>Participants</td><td>Forty-eight newborns, were randomly assigned, within 24 hours from birth and during their first 3 days of life to:
I. real-time CGM – total participants allocated to this group: n = 25;
II. intermittent capillary glucose testing – total participants allocated to this group: n = 23.
Inclusion criteria were:
I. pre-term infants ≤ 32 weeks;
II. birth weight ≤ 1,500 g.
From this study were excluded, as stated:
• “Serious congenital abnormalities,
• a skin condition that contraindicated CGM,
• a transfer to another hospital during the first days of life
• or an absence of parental agreement”.</td></tr>
<tr><td>Interventions</td><td>I. In the CGM group, blood glucose levels were measured using real-time CGMS, glucose values ≤ 60 mg/dl were notified by an alarm, they were then controlled by capillary blood testing.
II. In the intermittent capillary glucose testing group, standard methods (intermittent capillary blood glucose testing), performed every 4 hours, were used to measure blood glucose levels, associated with a blind CGMS.
In the two groups, whenever glycemic values were in the range of 50 to 60 mg/dl, the influx of glucose supply was raised by 1 g/kg/day and the glycemic value was verified after 2 hours. Hypoglycemia events, defined as < 50 mg/dl, were handled by an intravenous bolus of 10% dextrose (3 ml/kg) and an increase of glucose influx (+2 g/kg/day), and then tested 30 to 60 min later.</td></tr>
<tr><td>Outcomes</td><td>Number and duration of hypoglycemic (≤ 50 mg/dl) episodes per patient detected by CGMS.</td></tr>
<tr><td>Risk of bias</td><td>
<table>
<tr><th>Bias</th><th>Risk</th><th>Support</th></tr>
<tr><td>Random sequence generation</td><td>Low</td><td>Quote: “The random allocation sequence was automatically generated by the statistical software of the University of Tours, with 8 patients per block. Two series (one per birth weight category) of numbered and sealed envelopes were created, containing a note with the device to be used for each patient”.</td></tr>
<tr><td>Allocation concealment</td><td>Unclear</td><td>Quote “Two series (one per birth weight category) of numbered and sealed envelopes were created, containing a note with the device to be used for each patient”. Unclear whether envelops were opaque.</td></tr>
<tr><td>Blinding of participants and personnel</td><td>High</td><td>Assigned intervention could not be blinded. Masking of the study intervention is very difficult.</td></tr>
<tr><td>Blinding of outcome assessment</td><td>Low</td><td>Quote: “All the stored data (real-time- and blind-CGMS) were then secondarily transferred to an online securized database and analyzed retrospectively with an access restricted to the principal investigator”.</td></tr>
<tr><td>Incomplete outcome data</td><td>Low</td><td>From the 47 participants that were initially randomised not all were included, 4 were excluded (2 in each group were discontinued). This is a reasonable attrition and it is not likely to alter results. 91% of newborns completed the study.</td></tr>
<tr><td>Selective reporting</td><td>Low</td><td>Outcomes pre-defined in protocol were reported on the final study.</td></tr>
<tr><td>Other bias</td><td>Low</td><td>The study seems to have no other sources of bias.</td></tr>
</table>
</td></tr>
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CGM: continuous glucose monitoring; CGMS: continuous glucose monitoring systems.

Included studies

All 3 studies included in this review compared CGM vs intermittent methods of glucose measurement.

While Uetwiller et al. evaluated the effects of CGM on time spent in hypoglycemic states, Galderisi et al. documented the impact of CGM on time spent in both hyperglycemic and hypoglycemic states. More recently, Beardsall et al. compared CGM with intermittent methods of blood glucose measurement in a large multinational study. Interventions slightly differed between included studies. We further analyzed each trial in more detail and accordingly with types of interventions that were previously defined.

Interventions

Comparison 1: Comparing continuous glucose monitoring with intermittent methods using computer-based algorithms to correct hyperglycemia/hypoglycemia

Galderisi et al. compared CGMS with intermittent methods of glucose measurement, both paired with computer-based algorithms for titration of glucose infusion to adjust blood glucose levels. Fifty newborn infants were enrolled in this study, inclusion criteria were: gestational age ≤ 32 weeks or birth weight ≤ 1,500 g.

The goal of this study was to maintain blood glucose levels in a euglycemic range (between 72-144 mg/dl).

Participants were divided into two groups. In the CGM group, proportional-integral-derivative (PID) control algorithm adjustments were driven by CGMS. In the control group, PID control algorithm adjustments were driven using a standard-of-care glucometer based on blood glucose determinations; in this group, blind CGM was used.

Further information about this trial can be consulted in **Tab. 2**.

Comparison 2: Comparing continuous glucose monitoring with intermittent methods using pre-defined guidelines to correct hyperglycemia/hypoglycemia

Beardsall et al. performed a randomized controlled trial, parallel-group, multi-center, and multinational (UK, Spain, Netherlands). One hundred and eighty newborns were arbitrarily allocated (1:1) (within 24 hours after birth) to receive glucose and/or insulin infusion guided by CGM, or standard care (intermittent methods of glucose measure). Inclusion criteria were newborns ≤ 33 weeks gestation, birth weight ≤ 1,200 g, < 24 h after birth, and written consent from parent or guardian. From this study, newborns with congenital malformations and newborns with congenital metabolic disorders were excluded.

In the intervention group (CGM), real-time blood glucose values were accessible to the clinical team and guided glucose or insulin administration accordingly with previously defined guidelines. In the control group (intermittent blood glucose measurement), blood glucose was managed according to standard methods; in this group, CGMS was used but data collected was masked to the clinical team.

The primary outcome was the percentage of time spent in the euglycemic (target) range (2.6-10 mmol/L). Secondary outcomes involved the proportion of time spent in dysglycemic states and several relevant clinical outcomes to this review. Additional data can be consulted in **Tab. 3**.

Comparison 3: Comparing continuous glucose monitoring with intermittent methods using glucose infusion adjustments to correct hyperglycemia/hypoglycemia

No study was found that compared this intervention to correct both hyperglycemia and hypoglycemia.

Uetwiller et al. compared CGMS with intermittent methods of glucose measurement, both combined with glucose infusion rate increases to solely correct hypoglycemia. Forty-eight newborns participated in this study. Inclusion criteria were gestational age ≤ 32 weeks and birth weight ≤ 1,500 g.

The aim of this study was to maintain blood glucose above 50 mg/dl.

Participants were distributed into two groups. In the CGM group, blood glucose levels were measured using CGM, glycemic values ≤ 60 mg/dl were signaled by an alarm. Capillary blood testing was carried out to verify these indications. In the control group, standard methods (intermittent capillary blood glucose testing) were carried out every 4 hours; in this group, blind CGM was used.

Hypoglycemia events, defined as ≤ 50 mg/dl, were handled by an intravenous bolus of 10% dextrose and tested 30 to 60 min later.

Outcomes reported in this trial include the number and duration of hypoglycemic events per patient detected by CGMS.

Further information about this trial can be consulted in **Tab. 4**.

Comparison 4: Comparing continuous glucose monitoring with intermittent methods using insulin infusion adjustments to correct hyperglycemia/hypoglycemia

No trial tested this intervention isolated. Both Beardsall et al. and Galderisi et al. used insulin and blood glucose infusion rates to correct dysglycemic events.

Excluded studies

Some studies were reviewed in full, but later excluded. We documented the reasons for exclusion, which can be consulted in **Tab. 1**.

Ongoing studies

Four ongoing studies were found. The summary of each clinical trial can be found in the last rows of **Tab. 1**.

Risk of bias in included studies

The risk of bias was evaluated, as previously discussed under "Assessment of risk of bias".

After the appraisal, Galderisi et al. and Beardsall et al. presented with a low risk of bias in most parameters evaluated, but it was discovered that there was a high risk of bias regarding the blinding of personnel.

Uetwiller et al. presented a high risk of bias regarding blinding of personnel, unclear risk regarding allocation concealment, and low risk in the remaining parameters.

Each study and each parameter can be view in detail, in the "Risk of bias" sections of **Tables 2-4**. The risk of bias is summarized in **Fig. 2**.

Effects of interventions

In the following section, for each comparison we discussed the impact of each intervention on the outcomes previously defined in the "Types of outcomes" section.

Due to the low number of included studies, subgroup analysis was not performed.

We decided to compare CGM vs intermittent methods, summarizing relevant results and comparing reported outcomes.

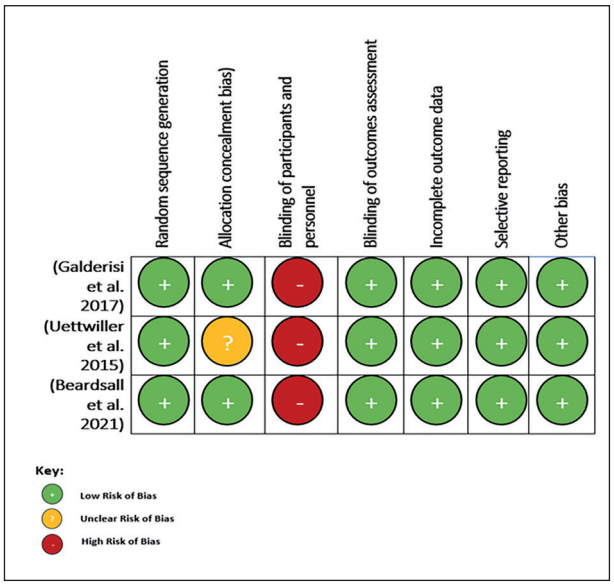

Figure 2. Risk of bias.

Primary outcomes

Mortality before discharge. Galderisi et al. reported 1 death in the control group and 0 deaths in the CGM group, with a p-value of 0.99. No significant difference was found in mortality before discharge. Beardsall et al. reported no significant difference in mortality rate, with 6% (6/95) in the control group, and 2% (2/84) in the CGM group, with an adjusted (for gestation and center) OR of 0.263 (95% CI: 0.0353, 1.3) and p-value < 0.13. Uetwiller et al. did not report this outcome. Mortality before discharge is presented in **Fig. 3**.

Mortality at 28 days. Galderisi et al. reported no deaths in both groups. Beardsall et al. did not report this outcome. Uetwiller et al. did not report this outcome. Mortality at 28 days is presented in **Fig. 4**.

Mean time spent in euglycemic level. Galderisi et al. reported significantly more time spent in glycemic target range in the CGM group when compared with the control group, with the CGM group reporting 83% (95% CI: 79, 87), compared with 71% (95% CI: 67%, 76%) in the control group, with a p-value of < 0.001. Beardsall et al. reported a significant difference in mean time spent in the euglycemic range, with 84% in the control group, and 94% in the CGM group, with adjusted (for gestation and center) MD of 8.9 (95% CI: 3.4, 14.4) and p-value of 0.005. Uetwiller et al. did not report this outcome.

Time to resolve hypoglycemia. Galderisi et al. did not report this outcome. Beardsall et al. did not

report this outcome. Uetwiller et al. did not report this outcome.

Time to resolve hyperglycemia. Galderisi et al. did not report this outcome. Beardsall et al. did not report this outcome. Uetwiller et al. did not report this outcome.

Number of recurring hyperglycemic events per individual or proportion. Galderisi et al. stated a substantial reduction in the number of episodes of hyperglycemia in the CGM group when compared with the control group, with the CGM group reporting 0.8 ± 1.6 episodes per individual, compared with 2.2 ± 3.3 in the control group, with a p-value of 0.04. Beardsall et al. did not report this outcome. Uetwiller et al. did not report this outcome. The number of recurring hyperglycemic events per individual or proportion is presented in **Fig. 5**.

Number of episodes of recurrent hypoglycemia per individual or proportion. Galderisi et al. stated a substantial reduction in the number of episodes of hypoglycemia in the CGM group when compared with the control group, with the CGM group reporting 1.4 ± 2 episodes per individual, compared with 4.7 ± 6.2 in the control group, with a p-value of 0.01. Beardsall et al. did not report this outcome. Uetwiller et al. reported a significant difference between the CGM group and control group, with the CGM group reporting 1.2 ± 0.4 episodes per individual, compared with 0.4 ± 0.2 (while blinded episodes per patient were 1.2 ± 0.4) in the control group, with a p-value < 0.01. The number of recurring hypoglycemic events per individual or proportion is presented in **Fig. 6**.

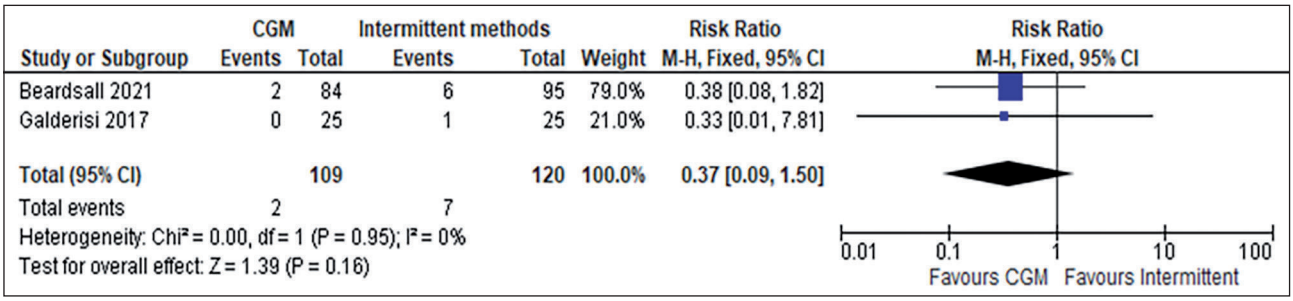

Figure 3. Mortality before discharge.

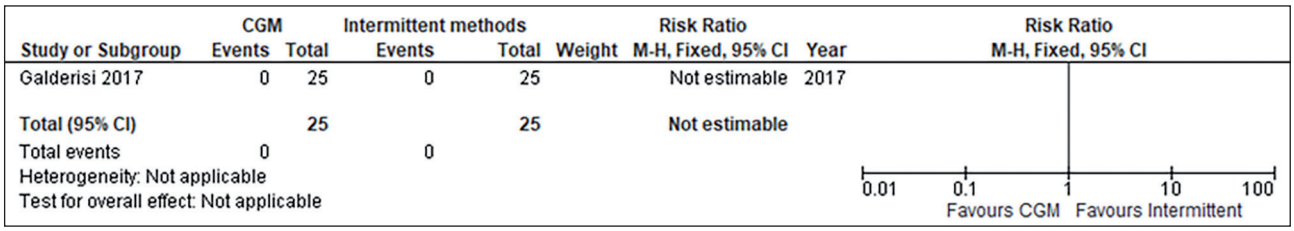

Figure 4. Mortality at 28 days.

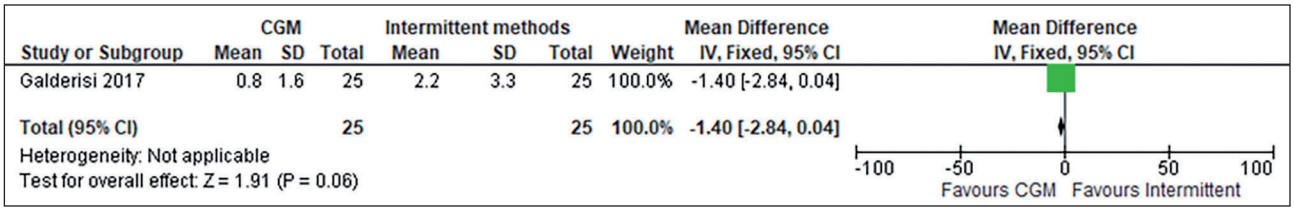

Figure 5. Number of recurring hyperglycemic events per individual or proportion.

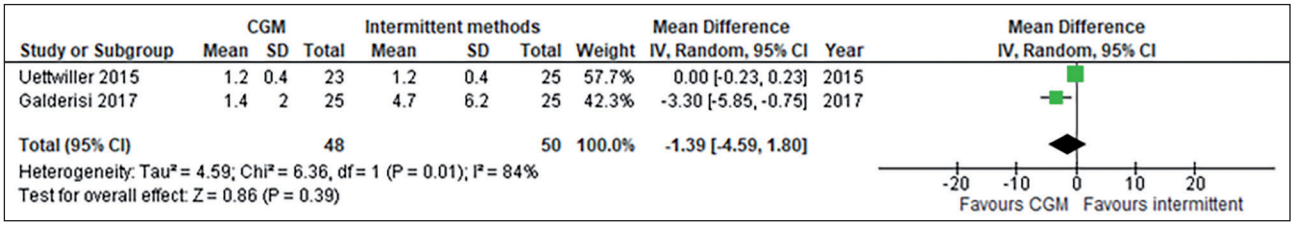

Figure 6. Number of recurring hypoglycemic events per individual or proportion.

Secondary outcomes

Percentage of weight loss. Galderisi et al. reported 7.6% (95% CI: 1.9, 10.3%) in the control group and 9.9% (95% CI: 5.0, 12.9) in the CGM, with a p-value of 0.22. Weight loss between groups was not statistically significant. Beardsall et al. reported no significant difference between weight at 7 days, with mean (SD) -1.26 (0.79) in the CGM group and -1.3 (0.75) in the control group, with adjusted (for gestational and center) MD of 0.05 (95% CI: -0.19, 0.28), p = 0.69. Uetwiller et al. did not report this outcome.

Neurodevelopmental outcome. Galderisi et al. did not report this outcome. Beardsall et al. did not report this outcome. Uetwiller et al. did not report this outcome.

Severe intraventricular hemorrhage. Galderisi et al. reported no significant difference between the CGM group compared with control group, with the CGM group reporting 0 cases, compared with 2 cases in the control group, with a p-value of 0.49. Beardsall et al. reported no significant difference between both groups, with CGM group reporting 33% (25/75) and control group 32% (27/4), with an adjusted (for gestation and center) OR of 1.02 (95% CI: 0.51, 2.1), p = 0.95. Uetwiller et al. did not report this outcome. Intraventricular hemorrhage is presented in **Fig. 7**.

Growth impairment. Galderisi et al. did not report this outcome. Beardsall et al. reported no significant difference in body length at day 7 between both groups, with CGM group reporting mean (SD) -1.81 (1.07) and control group -1.78 (0.87), with an adjusted (for gestation and center) MD of -0.02 (95% CI: -0.36, 0.31), p = 0.89. Uetwiller et al. did not report this outcome.

Skin lesions or skin infection. Galderisi et al. did not report this outcome. Beardsall et al. did not report this outcome. Uetwiller et al. did not report this outcome.

Number of episodes of retinopathy of prematurity. Galderisi et al. did not report this outcome. Beardsall et al. reported only the maximum grade across all examinations (2). Uetwiller et al. did not report this outcome.

Late onset of sepsis. Galderisi et al. reported no significant difference between the CGM group compared with control group, with the CGM group reporting 0 cases, compared with 2 cases in the control group, with a p-value of 0.49. Beardsall et al. did not report this outcome. Uetwiller et al. did not report this outcome. Late onset of sepsis is presented in **Fig. 8**.

Bronchopulmonary dysplasia. Galderisi et al. stated no substantial difference between the 2 groups. In the CGM group, 0 cases were reported, and the control group reported 1 case out of 25 newborns. Beardsall et al. stated no major difference in bronchopulmonary dysplasia between the 2 groups, with CGM group reporting 45 episodes out of 75 and control group 56 of 85 newborns, with an adjusted (for gestation and center) OR of 1.2 (95% CI: 0.52, 2.8), p = 0.66. Uetwiller et al. did not report this outcome. Bronchopulmonary dysplasia is presented in **Fig. 9**.

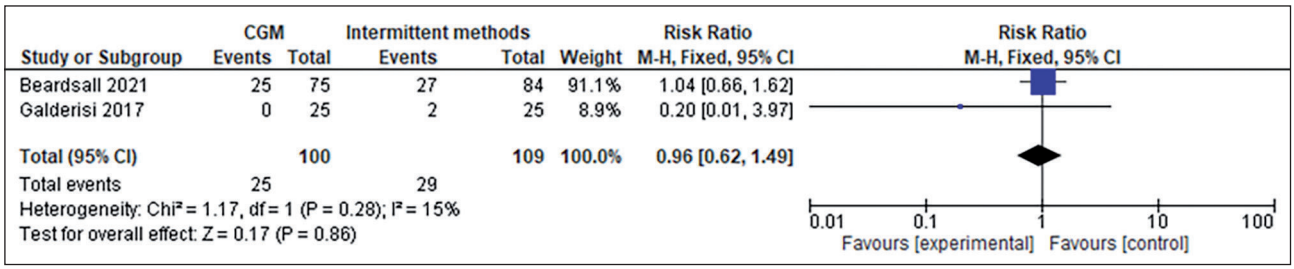

Figure 7. Intraventricular hemorrhage.

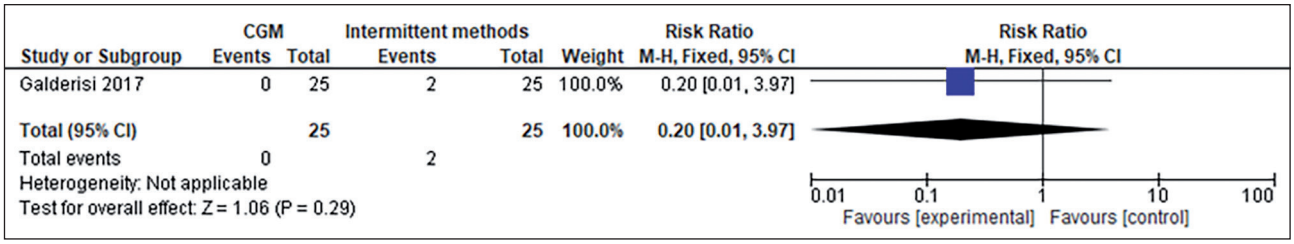

Figure 8. Late onset of sepsis.

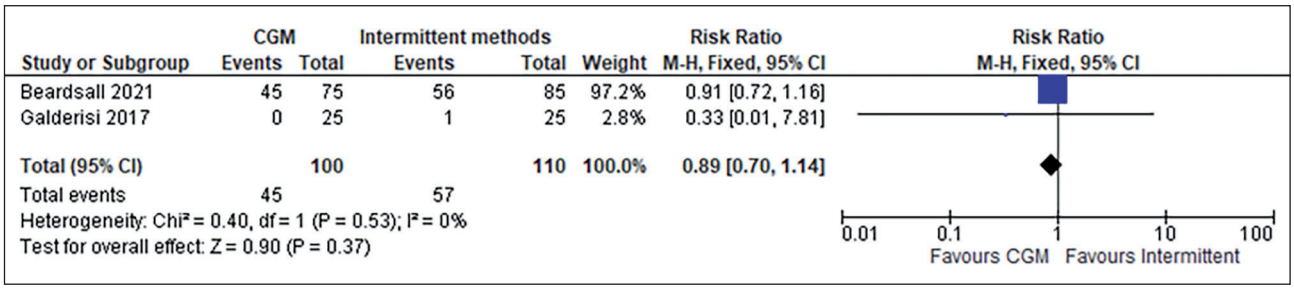

Figure 9. Bronchopulmonary dysplasia.

Discussion

Summary of evidence

Review results

Three trials were eligible for this review: Galderisi et al., Uetwiller et al. and Beardsall et al.

Galderisi et al. compared CGM vs intermittent methods of glucose measurement while utilizing, in both groups, computer-based algorithms to correct hyperglycemia and/or hypoglycemia. On the other hand, Uetwiller et al. compared CGM vs intermittent methods of glucose measurement utilizing increases in glucose infusion rates to correct hypoglycemia. Lastly, Beardsall et al. compared CGM vs intermittent methods utilizing predefined guidelines (variation in insulin and glucose infusion rates) to treat dysglycemic events.

No trials were found that compared CGM vs intermittent methods of blood glucose measurement, employing only insulin increases or decreases to correct hyperglycemia/hypoglycemia, or utilizing glucose infusion rate decreases to correct hyperglycemia.

The main objective of this review was to determine the impact of CGMS on dysglycemic events (hypoglycemia/hyperglycemia), assess short- and long-term mortality in both groups, as well as evaluate the feasibility and safety of utilizing CGMS in the context of NICU.

Primary outcomes

From the primary outcomes analyzed in this review, time spent in the euglycemic range was significantly increased in newborns assigned to CGM groups in the Galderisi et al. and Beardsall et al. studies.

No significant difference was found in terms of short-term mortality in the Galderisi et al. and Beardsall et al. studies.

Regarding dysglycemic events per individual, we can compare Galderisi et al. and Uetwiller et al. regarding the number of hypoglycemic episodes per individual. Uetwiller et al. detected significantly more hypoglycemic events per individual in the CGM group, 1.2 ± 0.4, than in the control group, 0.4 ± 0.2 (with a real value of 1.2 ± 0.4), while Galderisi et al. reported significantly fewer episodes (1.4 ± 2) in the CGM group than in the control group (4.7 ± 6.2). This could be attributed to the different interventions evaluated. Excluding intervention, we can infer that CGM detects more episodes than intermittent methods of glucose measurement.

Secondary outcomes

Regarding secondary outcomes, Uetwiller et al. did not report outcomes relevant to this review. Galderisi et al. and Beardsall et al. only reported on the percentage of weight loss, severe intraventricular hemorrhage, and late onset of sepsis, with no substantial difference between groups.

While not considered in this review, Uetwiller et al. also concluded that, by reducing the number of heel prick testes by 25% in the CGM group, the pain experienced by newborns was reduced.

Review limitations

We performed an extensive research method, and we believe that we identified all relevant studies for this review. We applied no language barrier. We excluded pilot studies and feasibility studies, only including randomized clinical trials.

However, the number of included trials was relatively small, and this impacted the quantitative analyses of this review. In addition, included studies had differences regarding the tested interventions, using different methods to resolve dysglycemic events.

Only 3 studies, with a combined total of 278 enrolled newborns, were found. These trials

reported on limited outcomes relevant to this review, and none evaluated the long-term effects of CGM in physical and neurological development.

Future considerations

CGM is a promising field, and it can be successfully used to improve glycemic control in preterm newborns. Despite this, some questions remain unanswered, such as what the best glycemic targets are to ensure proper physical and neurosensorial development, what is the cost-benefit of CGM, or what are the potential long-term outcomes of such interventions.

Therefore, and due to limitations present in this systematic review, we believe that further investigation needs to be conducted to properly answer relevant matters in this important medical field.

Larger studies need to be performed, and long-term outcomes (neurological and physical) need to be evaluated. It is important to understand the real impact of tight glycemic control, and the ideal range for blood glucose values that allows for optimal development of preterm infants.

The use of automated glucose and insulin delivery needs to be further explored, as it is being done in some studies, to improve glycemic control [24, 32].

Conclusion

CGM offers advantages in terms of time spent in the euglycemic range (when combined with methods of glucose correction).

Although the potential of CGM is high, new studies need to be conducted to ensure the safety and cost-benefit of such intervention, as well as long-term outcomes and the best glycemic target range for ideal neonatal development.

Declaration of interest

The Authors declare that there is no conflict of interest.

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