Title: Neonatal hypoglycemia: continuous glucose monitoring

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Abstract

Purpose of review:

Continuous glucose monitoring (CGM) is increasingly used in the management of diabetes in children and adults but there are few data regarding its use in neonates. The purpose of this article is to discuss the potential benefits and limitations of CGM in neonates.

Recent findings:

Smaller electrodes in new sensors and real time monitoring have made CGM devices more approachable for neonatal care. CGM is well tolerated in infants including very low birth weight babies, and few if any local complications have been reported. Use of CGM in newborns may reduce the frequency of blood sampling and improve glycemic stability, with more time spent in the euglycemic range. However, CGM may also lead to more intervention, with potential adverse effects on outcomes. More information is also needed about reliability, calibration and interpretation of CGM in the neonate.

Summary:

Although the use of CGM in neonates appears to be safe, feasible and has been associated with better glycemic status, there is not yet any evidence of improved clinical outcomes. Clinical utility of CGM should be demonstrated in randomised trials prior to its introduction into regular neonatal care.

Keywords: neonatal hypoglycaemia, continuous glucose monitoring, infant preterm, hyperglycemia

Introduction

Hypoglycemia is common in neonates admitted to intensive care, and very preterm infants are also at risk of hyperglycemia, both of which have been associated with adverse neurodevelopment. Continuous glucose monitoring (CGM) has shown that abnormal glucose concentrations frequently go undetected in neonates, even with regular intermittent blood glucose testing. CGM has the potential to improve the detection and management of neonatal hypo- and hyperglycemia, and may reduce the need for frequent blood sampling. However, CGM devices have not been approved for use in neonates and there is as yet no evidence of clinical benefit from randomised trials. This review discusses the potential benefits and uses of CGM in neonates along with its limitations.

CGM technology for neonates

Although there are no CGM devices specifically designed or approved for use in neonates, as the size of these devices has decreased, it has become feasible to use CGM in even very preterm infants. Current CGM devices measure interstitial glucose concentration using a fine amperometric glucose oxidase needle sensor that is inserted into the subcutaneous tissue [1]. The sensor is powered by a recording or transmitting unit on the skin surface, which receives current from the electrode approximately every 10 seconds, and averages and processes this signal to give an output every 5 minutes. Blood glucose concentration is estimated from this signal using proprietary algorithms based on regular calibration to blood glucose measurements (minimum 12 hourly) [2*].

Two main CGM brands are in clinical use; Medtronic Minimed (Northridge, CA, United States) and DexCom (San Diego, CA, United States), both of which provide both real-time and retrospective modes. The latter are useful in research as data are continuously recorded

for later download but are not displayed at the bedside so do not influence clinical care. Neonatal studies have predominantly used Medtronic Minimed devices including Guardian RT and Paradigm VEO with ENLITE sensors [3-6], though a recent study used the Dexcom G4 Platinum device [7**].

Current practice in neonates is to insert the sensor in the subcutaneous tissue of lateral part of the thigh and to cover the device with an occlusive dressing [3, 5**-7**]. Needle insertion applicators are supplied with sensors, but it is unclear if these are useful in neonates as few studies have described insertion techniques in detail. However, in one study of very low birth weight infants, CGM was unsuccessful in 9% of subjects due to difficulty inserting the sensor. It is also common for topical anaesthetic to be applied prior to sensor insertion, although it is not known whether this affects glucose measurements [4*-6].

Two recent studies reported that needle sensors were well tolerated even in babies <1500 g, without interference with nursing cares [4*, 5**]. Some babies in these studies were as small as 579 g. Sensors have been used for up to 7 days without any apparent deterioration in performance [4*, 7**, 8], and there have been no reports of local complications such as infection, oedema, bleeding or bruising [4*, 6, 7**]. Galderisi et al reported that detachment of sensors was a problem in some very preterm babies, and that CGM had to be discontinued in two subjects due to multiple detachments [7**].

A significant limitation of current technology is that glucose concentrations are only provided in the range of 40 mg/dl (2.2 mmol/L) to 400 mg/dl (22 mmol/L), thus limiting assessment of neonatal hypoglycemia. However, for retrospective analysis this can be overcome by point-to-point recalibration of the raw signal, which also improves the accuracy of CGM in the

lower glucose range [9]. Another limitation is that sensors require a “wetting” phase, which is typically around 2 hours, but the time required for stabilisation of the signal output has not been specifically studied in neonates. Both Harris et al [8] and Beardsall et al [10] found highest mean absolute error on day 1 after insertion, which may in part reflect increased error during the wetting phase.

Potential benefits and uses of neonatal CGM

CGM has several potential benefits in care of neonates at risk of dysglycemia. First, it may allow for decreased frequency of blood sampling and hence the number of heel pricks performed. For example, in a randomized trial of very low birth weight infants in the first 3 days after birth, Uettwiller et al compared real-time CGM to intermittent capillary glucose testing with retrospective CGM (N=48) [5**]. In the intermittent group, capillary blood glucose concentrations were measured 4-hourly, whereas in the CGM group capillary glucose was measured only when CGM reported glucose concentrations below 60 mg/dl (3.3 mmol/L). The use of real-time CGM resulted in a 25% reduction in the number of capillary blood tests ($P<0.001$), even though the number of hypoglycemic episodes, defined as consecutive CGM values <50 mg/dl (2.8 mmol/L), was similar in both groups. In infants born very preterm, neonatal pain-related stress has been associated with frontal and parietal cortical thinning at school age, independent of other neonatal risk factors [11]. Therefore, use of CGM to reduce the frequency of heel pricks in neonates may have beneficial effects on later development, but this requires confirmation in randomized trials.

Second, CGM may reduce exposure to hypoglycemia or hyperglycemia, due to either earlier detection or improved treatment of episodes. Studies in both preterm and at-risk term newborns have shown that episodes of hypoglycemia are common during neonatal transition,

but many are not detected by intermittent blood glucose screening. For example, in the CHYLD study, a large prospective cohort (N=614) of term and late preterm infants born at risk of hypoglycemia, 25% of infants with hypoglycemia had low interstitial glucose concentrations (<47 mg/dl [<2.6 mmol/L]) for >5 hours, despite regular blood testing and treatment by protocol. Further, nearly a quarter of infants with normal intermittent blood glucose testing had episodes of low glucose concentrations (>10 min) detected only by CGM [12*]. Similarly, in very low birth weight infants, Uettwiller et al found that 69% of subjects with normal intermittent blood glucose testing (N=16) had episodes of low interstitial glucose (<50 mg/dl [<2.8 mmol/L]), and that hypoglycemic episodes were detected nearly 1 hour earlier by CGM than by blood screening [5**].

CGM has shown that episodes of hyperglycemia are also common in preterm infants. For example, using masked CGM Beardsall et al identified hyperglycemia, defined as an interstitial glucose concentration >144 mg/dl (>8 mmol/L), for >10% of time (approximately 15 hours) in the first week, in almost half of very low birth weight infants (N=188), and moderate to severe hyperglycemia (>180 mg/dl [>10 mmol/L]) in one third [13]. Galderisi et al also found that mild hyperglycemia, defined as an interstitial glucose concentration >144 to 180 mg/dl (>8 to 10 mmol/L), occurred for >20 hours in 25% of very preterm or very low birth weight infants (N=25) in the first week, though severe hyperglycemia (>180 mg/dl [>10 mmol/L]) was uncommon [7**].

Two trials have evaluated whether using real-time CGM to guide clinical care in the first week after birth improves glucose stability in very preterm or very low birth weight infants. Uettwiller et al found that using CGM to guide the need for blood glucose measurements not only reduced the frequency of blood tests but also reduced the median duration of

hypoglycemic episodes by 51 minutes ($p<0.05$) [5**]. This was attributed primarily to earlier detection of episodes by CGM than by regular intermittent capillary blood glucose testing. Galderisi et al compared use of a computer-adjusted glucose infusion rate based on either CGM alarm and trend data or intermittent capillary blood glucose concentrations (≤8 hourly), and found that neonates in the CGM group spent more time in the target glucose range of 72 to 144 mg/dl (4.0 to 8.0 mmol/L) (median percentage of time 84% vs 68%, $p<0.001$). This was due to less time in both the hypo- and hyperglycemic range [7**]. Both trials were limited by use of glucometers rather than more accurate measurement methods for CGM calibration and intermittent glucose monitoring.

Although these trials suggest that CGM may be useful in improving glucose stability in preterm infants during the early neonatal period, it is not yet known if use of CGM improves short- or long-term clinical outcomes. In both trials, the CGM groups received more carbohydrate, possibly indicating higher fluid intake, which has been associated with increased risk of bronchopulmonary dysplasia [14]. CGM was also associated with increased use of intravenous dextrose boluses, which is concerning as higher glucose concentrations after neonatal hypoglycaemia may increase the risk of neurosensory impairment [12*]. Nevertheless, in the CHYLD study, infants with undetected and thus untreated hypoglycemic episodes (by CGM only) had poorer executive function at 4.5 years of age, suggesting that improved detection of episodes may potentially improve neurodevelopmental outcomes [15*]. This may be even more important for infants with additional neurological insults, such as hypoxic ischaemic encephalopathy, although the accuracy of CGM in infants with severe illness, including those undergoing therapeutic hypothermia, is not known.

CGM may have a role in detecting late onset neonatal metabolic instability. CGM studies in stable, fully enterally fed preterm infants have shown that episodes of both hypo- and hyperglycemia are not uncommon. For example, Mola-Schenzle et al reported that in very low birth weight infants at approximately 5 weeks of age (N=51), episodes of low (<45 mg/dl [<2.6 mmol/L]) and high (>150 mg/dl [>8.3 mmol/L]) interstitial glucose concentrations were detected in 41% and 71% of infants, respectively [16]. By the time of primary hospital discharge, Pertierra-Cortada et al found that 10% of very preterm infants (N=60) continued to have episodes of low interstitial glucose (≤45 mg/dl [≤2.5 mmol/L]) for >30 min, 23% had isolated hyperglycemia (≥140 mg/dl [7.8 mmol/L]) for >30 min and 13% had both [17]. It is not known if this late glucose instability contributes to neurodevelopment impairment, nor if the glucose instability seen in these infants can or should be modified.

Is CGM a reliable measure of neonatal glucose concentrations?

CGM relies on a continuous shifting internal algorithm to convert the sensor current to blood glucose concentration, adjusted by regular calibration against blood glucose measurements [2*]. CGM has potential for relatively large errors and this has three main components: zero-mean error, drift and diffusion time lag. Zero-mean error is the random error of the sensor, which may be considerable due to the sensor technology and its interstitial location. Drift refers to shifts in sensor output between calibration points due to corrosion or biofilm build up on the needle surface, such that different currents are generated by the same blood glucose concentration. The potential for sensor drift is well recognised in adults but has not been assessed in neonates. The diffusion of glucose between the vascular and interstitial compartments also creates a time lag. In lambs this is approximately 20 minutes [18], which is consistent with indirect evidence in neonates [6]. A practical consequence of this time lag

is that CGM has increasing positive error when blood glucose concentration is falling and increasing negative error when blood glucose concentration is rising.

CGM point accuracy is usually expressed as mean absolute relative difference (MARD), defined as the mean of the absolute differences between CGM and simultaneous reference values as a percentage of the reference value. Errors of ≤13% are generally considered acceptable. Accuracy of CGM has been assessed in three neonatal studies. Beardsall et al reported MARD of 9% but Wackernagel et al found greater errors with MARD of 18%. Tiberi et al did not report MARD but found that more than a quarter of CGM values were >20% from the reference value. Errors may be even larger at extreme glucose concentrations or when glucose concentrations are changing rapidly. Thus, while Bearsdall et al reported acceptable overall error, the positive predictive value was poor for hypoglycemia (40%) and only modest for hyperglycemia (90%). Importantly, these studies included very few values in the low glucose range, and only glucometers rather than a reliable reference method were used for calibration or evaluation of the device.

CGM trending, i.e., the rate and direction of change, may be important clinically but assessment of trend accuracy requires a different approach [7**, 19], and this has not been measured in neonates. In addition little attention has been given to optimisation of CGM calibration. Use of an accurate blood glucose measurement, such as by gas or laboratory analyser, is likely to improve accuracy, as is recalibration during periods of low trending. Tiberi et al compared thrice and twice daily calibration and found no difference in CGM accuracy. This probably reflects the fact that most CGM devices employ multiple point, weighted calibration, which means that each calibration value influences GCM measurements for up to 24 hours, depending on the device algorithm. Point-to-point calibration using

accurate glucose concentrations from a blood gas analyser may be more appropriate for neonatal intensive care, but this option is currently not available in real-time.

Should CGM be used in neonatal intensive care?

CGM has promise as a tool for reducing the frequency of blood sampling and improving glucose stability by adjusting glucose intake in real-time according to individual metabolic requirements. However, caution is required before this technology is adopted into neonatal practice as there are very few data from randomised trials on the short-term clinical effects of CGM, and no data on longer term outcomes. Without this information, CGM could lead to increased intervention that may be of little benefit or even harmful.

Further research is needed in several areas before CGM can be considered for routine use in neonatal intensive care. First, CGM point accuracy needs to be evaluated against a reliable measure of blood glucose concentration, such as a blood gas analyser, with sufficient samples in the low glucose range and during fluctuating glucose concentrations. Assessment of trend accuracy is also required. A better understanding of CGM reliability is important as this has implications for whether CGM is used primarily to guide timing of blood glucose measurements or whether CGM data are used directly in clinical decision making. It is also important for determining the alarm limits that should be used with CGM to indicate need for a clinical response.

Second, further data are needed on the impact of different calibration methods on the accuracy of neonatal CGM. It is currently not known whether all blood glucose measurements should be used in CGM calibration or only certain measurements, for example, those within the target blood glucose range or during periods of low trending. Information is

also needed on the frequency and extent of sensor drift, and the situations in which it is most likely to occur, as this may help to determine the optimal frequency of calibration.

Third, more information is needed about which CGM parameters are most useful for guiding clinical care. With real-time CGM, alarms can be set at fixed thresholds and for trending (rate of change), and some devices provide prediction alarms based on proprietary algorithms. Graphical display of interstitial glucose concentrations is also provided. The utility of different parameters and alarms will depend somewhat on whether CGM is used for predictive or corrective action, and whether management is aimed at minimising extreme excursions or maximising time within a central range. The benefit of CGM may also be influenced by whether it is combined with clinician or computer guided adjustment of glucose and nutritional intake.

Conclusion

The use of subcutaneous CGM sensors in neonates appears to be safe and feasible, even in very preterm infants. CGM has the potential to reduce the frequency of blood sampling and improve detection and prevention of hypo- and hyperglycemic episodes. However, CGM devices have neither been designed nor approved for use in neonates, and there is potential for harm with increased intervention. Before this technology is introduced into routine neonatal care, further information is needed about reliability, calibration and interpretation of CGM. At present CGM should remain a research tool until clinical benefit is demonstrated in randomised trials that include long term outcome data.

Key points

- Continuous glucose monitoring (CGM) may detect episodes of neonatal hypo- and hyperglycemia that would otherwise go undetected with intermittent blood sampling.
- It is not yet clear whether CGM should be used primarily to guide the need for blood glucose measurement or whether CGM data can be used directly for clinical decision making.
- Further research is needed about CGM reliability, calibration and interpretation of parameters.
- CGM should not be introduced into routine neonatal care until clinical benefit is demonstrated in randomized trials.

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Conflicts of interest

None

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