Monitoreo continuo de glucosa en tiempo real en cuidados intensivos neonatales.

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Resúmen:

La hipoglucemia y la hiperglucemia son comunes en los lactantes que requieren cuidados intensivos y se asocian con peores resultados clínicos.

Sin embargo, los niveles de glucosa se toman con poca frecuencia, y sigue habiendo controversia con respecto al manejo óptimo.

En adultos y niños, la monitorización continua de glucosa (MCG) se ha establecido como un complemento importante para el cuidado de pacientes con riesgo de disglucemia.

Esta tecnología también proporciona cada vez más información sobre la regulación de la glucosa en el recién nacido, lo que demuestra períodos significativos de hipoglucemia e hiperglucemia clínicamente silenciosas.

Estos datos de referencia serán importantes para permitir evaluar la importancia de la desregulación de la glucosa en los resultados a largo plazo.

Pequeños estudios también han demostrado la posibilidad de que la MCG apoye de forma segura la focalización del control de la glucosa en los recién nacidos prematuros, y se está realizando un gran ensayo multicéntrico.

La tecnología actual no está diseñada específicamente para su uso en la UCIN, pero con rápidos desarrollos tecnológicos, CGM promete el cuidado futuro de los bebés en la UCIN.
Real time continuous glucose monitoring in neonatal intensive care

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ABSTRACT

Hypoglycaemia and hyperglycaemia are common in infants requiring intensive care and are associated with worse clinical outcomes. However, glucose levels are taken infrequently, and there remains controversy regarding optimal management. In adults and children continuous glucose monitoring (CGM) is now established as an important adjunct to caring for patients at risk from dysglycaemia. This technology is also increasingly providing insights into glucose regulation in the newborn, demonstrating significant periods of clinically silent hypoglycaemia and hyperglycaemia. This baseline data will be important to allow the significance of glucose dysregulation on long-term outcomes to be assessed. Small studies have also shown the potential for CGM to safely support targeting of glucose control in preterm infants, and a large multicentre trial is ongoing. Current technology is not specifically designed for use in NICU, but with rapid technological developments, CGM holds promise for the future care of babies in NICU.

1. Introduction

Hypoglycaemia and hyperglycaemia are common in babies requiring neonatal intensive care (NICU), but diagnosis and management of both remain controversial [1–4]. Both extremes have been associated with poor clinical outcomes [5], but data is conflicting and clinically significant thresholds of hypoglycaemia and hyperglycaemia remain to be determined [3,6]. Current follow up studies are dependent on infrequent glucose, taken for clinical reasons and there is inherent associated bias when assessing outcomes.

Standard intermittent blood glucose (BG) measurement results in long periods when glucose levels are unknown. In contrast other physiological parameters such as oxygen saturation, blood pressure and heart rate are all monitored continuously to allow interventions to prevent wide fluctuations. It is increasingly thought that fluctuations in glucose levels may also have a significant impact on long-term outcomes [7].

The factors that determine the methods used for measuring glucose in the newborn are predominantly those of utility and accuracy. Methodology needs to be practical for use by those caring for babies, provide a result within a short time frame to allow for efficient changes in clinical management, and also provide accurate data across the range of clinically relevant glucose levels.

2. Continuous glucose monitoring

Continuous glucose monitoring (CGM) is widely used in patients with type I diabetes. It has recently been agreed that it should be made available to all women with type 1 diabetes during pregnancy, and studies in adult intensive care have shown accuracy and safety with the ability to reduce the risk of hypoglycaemia. CGM has the potential to improve our understanding of the pathophysiology of glucose dysregulation in the newborn, to improve clinical management and to determine optimal targets of glucose control for different babies requiring intensive care. However, the use of CGM in neonatology has remained limited despite the challenges of glucose instability in the newborn. Despite great advances in the technology current devices are not designed for use in babies and there are technical challenges with using devices in the newborn which include: i) insertion methods, ii) accuracy, iii) clinical interpretation [8].

3. The technology

Early CGM models used microdialysis with a hollow fibre that acts as a semipermeable membrane, but devices were large, and have limited practical clinical use for neonates [9,10]. CGM technology has subsequently been transformed since first receiving FDA approval, for the management of type I diabetes, in 1999. Current technology in clinical practice, uses a fine disposable filament sensor (oxidase-based
The use of masked CGM and understanding physiology in prematurity led to their use in intervention trials [14]. Newer models provide data in real-time read out, or transmits it to a monitor or blue tooth device, for real-time read out. Currently there are two device companies whose technology has been used in the newborn: Medtronic (Northridge, CA, United States) and Dexcom (San Diego, CA, United States). However, none of the current devices are licensed for use in the newborn.

Early CGM models collected data in real-time but the data could only be downloaded retrospectively in 5-minute epochs. This is useful for research and for stable patients, but not well suited to acute management in intensive care. However, the use of such devices has demonstrated significant periods of clinically silent hyperglycaemia and hypoglycaemia in the newborn [11,13]. Newer models provide data in real-time, and key advances in technology including: extended life, smaller sensors and better accuracy at lower glucose thresholds have led to their use in intervention trials [14].

4. Use of masked CGM and understanding physiology in neonates

There remains controversy regarding what is a ‘normal’ glucose profile during healthy transition and for babies considered at risk from neonatal hypoglycaemia, as evidence is currently based on cross-sectional data and intermittent sampling. The use of masked CGM provides the opportunity to gain further insights into understanding the physiology and pathophysiology of neonatal transition.

4.1. Healthy newborn

It is traditionally taught that healthy babies have a physiological nadir in glucose levels after birth, however recent studies have failed to demonstrate this. The use of CGM to better understand neonatal transition is challenging as sensors require a minimum of 2 h ‘warm up’ and tend to be the least accurate in the first 24 h, which is the critical time of interest. The soon to report GLOW (Glucose in well babies study) has succeeded in collecting CGM data in 67 well term babies alongside measurement of alternative fuels, and this will provide much insight into what we might consider normal neonatal glucose transition.

4.2. Newborn infants at risk of hypoglycaemia

The CHYLD study was a large prospective study of term and late preterm infants at risk from neonatal hypoglycaemia, and in whom masked CGM was undertaken for the first 48 h of life [13]. This study showed that despite regular BG testing and a clinical aim to maintain BG >2.6 mmol/l, many babies were exposed to prolonged periods when the sensor glucose (SG) was <2.6 mmol/l. Furthermore of the babies who did develop hypoglycaemia (BG <2.6 mmol/l) 25% spent at least 5 h with SG <2.6 mmol/l, and nearly a quarter of babies who were considered clinically to have normal BG levels had episodes of clinically silent hypoglycaemia detected using CGM [13]. At 2 year follow up of the CHYLD study 404 children underwent neurodevelopmental assessment, but there was no association with hypoglycaemia. However, those with neurodevelopmental impairment had higher SG concentrations during the first 48 h of life, and a steeper rise post treatment for hypoglycaemia. These studies suggested that glucose variability with hyperglycaemia post hypoglycaemia may be harmful to the developing brain, and are in keeping with animal studies where such neuronal injury is associated with the generation of reactive oxygen species.

In contrast by 4.5 year follow up these episodes of clinically silent hypoglycaemia were associated with a four-fold increased risk of impaired executive function. In comparison those with clinically detected hypoglycaemia (i.e. with a BG <2.6 mmol/l), who had therefore been treated, the increased risk was only two fold [15]. This highlights the importance of clinically silent hypoglycaemia as well as the importance of developmental follow up beyond 4 years of age to assess executive function and the potential impact of glucose dysregulation.

Further studies have been undertaken using CGM to describe the glucose profiles of the offspring of mothers with type I diabetes, in the early neonatal period, and its association with maternal intrapartum glucose control. Sixteen women had a CGM sensor inserted 2–3 days before delivery, and infants had a masked CGM immediately after delivery. Fifteen infants had at least one BG concentration <47 mg/dl (2.6 mmol/l), and in the first 24 h after delivery 4 infants spent >50% time with SG <47 mg/dl (2.6 mmol/l). However, the relationship between maternal intrapartum and neonatal glucose control was poor [16].

CGM will be important in exploring the physiology of hypoglycaemia in these at risk babies, and the effect of different treatment or feeding strategies on glycaemic stability. Moreover, it is only with robust data on actual exposure that we can interpret later outcome studies.

4.3. Prematurity

Preterm babies are at risk of wide fluctuations of glucose levels and masked CGM has been used to characterize this and demonstrate the high prevalence of undetected hypoglycaemia and hyperglycaemia. The first large trial to use CGM in these babies was the NIRTURE study, which used blinded CGM in 389 preterm babies [12,17]. CGM was well tolerated even in babies of 23 and 24 weeks gestation and with birth weights of 500 g. There were no concerns about infection or skin integrity and the CGM did not interfere with nursing care. More than half the babies had SG >10 mmol/l at some time and this was found to be associated with gestational-age, birth weight and the use do inotropes [17].

Studies with CGM have also highlighted babies to be at risk from clinically silent hypoglycaemia as intravenous support is weaned and during surgery Fig. 2 [18]. Preterm babies who are presumed to be stable tolerating intermittent feeds when monitored with CGM also demonstrate significant dysglycaemia [19,20]. Infants born at <1000 g, studied at corrected gestation age of 32 ± 2 and 33 ± 2 weeks when clinically stable showed clinically silent SG <2.5 mmol/l (40%) and >8.3 mmol/l (83%) with rapid fluctuations in
levels [21].

5. Clinical applications

The wealth of data available from CGM makes it attractive for use in NICU where many physiological variables are measured continuously. Adult intensive care studies have demonstrated that the time within a physiological target range is linked to less organ injury and better survival but this remains to be determined for neonates. The benefits in NICU may be greater as BG sampling is much less frequent, in keeping with the aims of minimal handling and limiting blood loss as well as the importance of the potential impact of reducing dysglycaemia on the vulnerable developing brain.

5.1. Preterm infant

Up to 50% of preterm babies are exposed to glucose levels >10 mmol/l [17,22]. Both hyperglycaemia and hypoglycaemia have been associated with increased mortality and multiple morbidities in these babies including retinopathy of prematurity, necrotizing enterocolitis, sepsis and long-term neurodevelopmental impairment [23]. Animal studies suggest this association to be causal [24,25]. The management of babies with hyperglycaemia however remains challenging; balancing the desire to optimize nutrition against the risks of insulin [12,26].

A trial in very low birth weight babies (VLBW n = 43) aiming to use CGM to detect silent hypoglycaemia, demonstrated that the CGM detected three times the number of hypoglycaemic episodes (SG <2.8 mmol/l) compared to intermittent BG measurement. CGM also reduced the median duration of these episodes from 95 to 44 min (50%) [27]. However, those with CGM had more dextrose infused as boluses and this may cause glucose instability which has been linked to increased morbidity [7,28].

Alternative strategies using CGM to support the use of insulin have shown that CGM can increase the time in target without increasing the risk of hypoglycaemia [29]. These feasibility studies have led to an international randomized controlled trial of the use of CGM in preterm infants. This will randomize babies to standard care with masked CGM (for comparative data collection), or the use of CGM to support the targeting of glucose control with the support of insulin.

The concept of the ‘artificial pancreas’ and closed loop technology is gaining momentum in adult medicine. Computerized control can reduce the frequency and duration of hypoglycaemia in diabetic patients at home and adults in ITU [30]. Pilot studies of computer algorithm guided glucose control in NICU have shown promise. A trial in VLBW newborns (n = 50) used a computer-guided program to determine glucose infusion rate (GIR) with or without CGM. Neonates using CGM had a greater percentage of time spent in a euglycaemic range (72–144 mg/dl, 4–8 mmol/l) compared with the blinded CGM group (median, 84% vs 68%, P < .001). Use of CGM also decreased glycaemic variability [31]. The alternate strategy of computer guided insulin delivery has been explored in a cohort of extremely preterm infants (n = 20) and also showed an increase in time in target (4–8 mmol/l) from 26% in the control group to 97% in those with ‘closed loop’ CGM. (Fig. 3) Further studies are needed and many regulatory hurdles will need to be crossed before this can be introduced as a fully automated system in clinical care.

5.2. Term hypoxic ischaemic encephalopathy (HIE)

Hyperglycaemia and hypoglycaemia are common in babies following HIE, and both have been associated with poorer neurological outcomes, although findings are not consistent [5,32,33,34]. The pragmatic clinical and physiological approach to care is to aim to maintain euglycaemia. CGM could be helpful in providing trend information to guide clinical management but the accuracy and functioning of sensors during cooling remains to be determined. Pilot studies are ongoing to validate their use in these high risk babies.

5.3. Prolonged hypoglycaemia and hyperinsulinism

A small group of babies have prolonged hypoglycaemia that can last several weeks. Glucose dysregulation can be associated with intrauterine growth restriction and with congenital hyperinsulinism. These infants can be challenging to care for with the need for central access to avoid the risk of profound hypoglycaemia and long-term neurodevelopmental consequences. These infants require frequent BG sampling but we have found CGM can be an adjunct to BG monitoring to support their management and progress them on to enteral feeds and therefore home. CGM also has a role in neonatal diabetes where the combination of CGM and insulin pump therapy can allow better control and reduced the risk of hypoglycaemia [35].

6. Limitations of use in the newborn

Although the CGM has great potential to be of clinical benefit, it is
important to understand the current limitations.

6.1. Practicalities of insertion

Sensors have a length of around 8.5–11 mm, are designed for insertion into the subcutaneous tissue, and have varying insertion techniques and angles of insertion. Although insertion kits are available, they are not always appropriate for the preterm infant with limited subcutaneous tissue and therefore hand insertion may be required. This needs appropriate training as the devices are not as yet designed for ease of use in these babies.

6.2. Accuracy

The CGM does not measure BG it measures interstitial glucose and there is a physiological lag in the diffusion of glucose between the two compartments. As BG levels fall the time delay increases, so there can be a delay in the detection of hypoglycaemia relative to BG levels. Accuracy assessed using the MARD will be higher where the difference between interstitial and BG is larger. This value often varies with glucose levels, being higher at low levels but similar levels have been shown in the preterm population as in adults. The lack of point accuracy the CGM means it is not a tool for diagnostic thresholds. However, the wealth of data can warn of incipient falls or increases in BG and if guidelines are in place and trends in CGM are used it is the falling SG that can prompt BG to be checked and earlier intervention.

6.3. Calibration

If calibrations are undertaken at a time of glucose instability then the effect of the lag between blood and interstitial glucose levels will make calibrations more inaccurate. If there is a wide difference between the sensor and a BG this may result in a request for a sensor to be changed or for it to stop working. The rapid glucose fluctuations in the newborn after birth may increase the risk of calibration failure, and waiting for blood glucose levels to be stable before calibration is important. The first calibration normally occurs at about 2 h but in some babies sensors will not calibrate unless allowed a longer ‘wetting time’.

The CGM accuracy can be subject to drift, i.e. a change in sensor accuracy over time, due to changes in the probe surface, related to biofilm build up with different currents are generated by the same BG concentration. If multiple calibration points are used by algorithms when there is significant drift then calibrations can be affected by BG levels taken up to 24 h earlier and may lead to more inaccuracy. In NICU, where a blood gas analyser or an accurate point of care device is used for calibration, a single point calibration may be better. Now systems are moving towards factory calibration of sensors to avoid the need for BG calibration, but how robust this calibration will be for the NICU population remains to be determined.

6.4. Clinical interpretation

Although the CGM provides a wealth of data that helps to guide management, the point accuracy of single readings is currently not as good as BG sampling. CGM can be an adjunct to support care providing early warning of fluctuations in glucose levels. However, the clinical significance of the dysglycaemia revealed by this technology still needs to be better understood. Responding inappropriately to these findings may unintentionally cause more harm than good.

7. Future technology

There is currently a technological race to develop novel sensors for non-invasive CGM for patients with diabetes mellitus. Development in sensor technology includes a contact lens with embedded microchips, optical sensors using near infrared spectroscopy and microneedles that use reverse iontophoresis. These hold promise for NICU as further developments are required before CGM will be able to demonstrate its full potential in the newborn.

8. Conclusion

CGM is well established for the management of adults and children who are at risk from glucose dysregulation. CGM in neonatology is increasing our understanding of the unique physiology at this time. There remain technical issues with the use of the current devices in the
newborn but also clinical challenges in interpretation of the data and implications for clinical practice. However, the rapid technological developments in sensor technology, and closed loop systems, hold the potential for us to optimize the management of glucose levels in this vulnerable population.

Declaration of competing interests

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