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Continuous glucose monitoring in the neonatal intensive care unit: not quite ready for 'plug and play'

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In the very low birthweight (VLBW) infant population, high glucose concentrations have been associated with increased mortality, brain injury, retinopathy of prematurity and worse neurodevelopmental outcomes. However, trials to prevent or treat hyperglycaemia in this population with continuous insulin infusions or a combination of insulin and/or reductions in the glucose infusion rate have been complicated by more frequent episodes of low glucose concentrations. While the long-term significance of these episodes is unknown, most would agree that they should be avoided during treatment of hyperglycaemia with insulin. Emerging data further associate increased glycaemic variability with impaired long-term outcomes. Use of continuous (interstitial) glucose monitoring (CGM) in very preterm, VLBW infants has the potential to minimise the incidence and severity of hypoglycaemia and hyperglycaemia and increase glycaemic stability during critical developmental periods, providing new opportunities to improve long-term neurocognitive outcomes in these children by preventing these common but potentially harmful metabolic disorders.

Thomson *et al*[1] report the results of a single-centre study in which feasibility of CGM for very preterm infants was assessed. The study was divided into two phases. In the first phase, accuracy was assessed by comparison of real-time (RT) CGM (Paradigm Veo, Medtronic MiniMed) to point-of-care (POC) blood glucose concentrations (Statstrip, Nova Biomedical) in 20 infants. In the second phase, a pilot study was conducted in which 20 infants were randomised to unblinded RT-CGM in conjunction with a clinical guideline dictating care decisions based on the CGM values versus standard neonatal care. In the standard care arm, infant interstitial glucose concentrations were measured with a blinded retrospective

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recording CGM (iPro2, Medtronic MiniMed) while glucose was managed using the standard of care hospital protocol. The goal of these studies was to generate data to inform a randomised trial evaluating the impact of unblinded RT-CGM in the care of these infants. Using a single highly accurate POC glucose measurement method for all calibrations improved the agreement between RT-CGM and intermittently sampled glucose concentration compared with the authors' previous report.[2] Moreover, the results from this study are similar to other studies[34]: the CGM sensor was well tolerated, was acceptable to staff caring for the infants, and when combined with an algorithm informing clinical decisions based on RT-CGM data, allowed clinicians to keep glucose concentrations in these preterm infants within a more narrow range. This last feature, combined with the ability of CGM to uncover episodes of occult hypoglycaemia, is an important reason why the use of CGM in the care of the VLBW infant has been considered.

CGM was initially developed for use in adults and older children with diabetes mellitus as a way to personalise treatment. Typically, for this purpose, CGM devices did not provide glucose concentrations in real time to the patient. People with diabetes managed blood glucose concentrations using a combination of intermittent POC glucose fingersticks, dietary/lifestyle modifications and medications while glucose concentrations were recorded with a CGM. Retrospectively, the recorded CGM data were analysed according to algorithms that incorporated the POC glucose concentrations to determine patterns of glycaemia that were used to assess responses to treatments. Over the past 20 years, these biosensors and algorithms have undergone impressive technological revisions that have resulted in higher precision and accuracy, detection of directionality of blood glucose concentrations, improved comfort and quality of life for persons with diabetes, and a reduced or even eliminated need for POC fingersticks with calibration-free systems.[5] The most recent innovative and exciting applications of CGM to the management of diabetes can be found in models of the 'artificial pancreas' in type 1 diabetes, which links RT-CGM data to continuous subcutaneous insulin/glucagon infusion pumps, directing automated algorithm-driven insulin dosing that liberates the patient from self-managing insulin therapy. Although these systems continue to undergo development, they have already resulted in dramatic decreases in the incidence of hypoglycaemic episodes, particularly during the nocturnal period.[6] Because this instrumentation was developed in individuals with diabetes, the glucose concentration target was aimed at the 3.9–10 mmol/L (70–180 mg/dL) range. This contrasts with the more narrow glucose target ranges in trials testing the efficacy of insulin infusions to achieve ‘tight’ glycaemic control in intensive care unit (ICU) settings[7] that were aimed at reducing potential pathology from hyperglycaemia in critically ill patients receiving intravenous dextrose or total parenteral nutrition infusions. The studies clearly demonstrated that while current CGM accuracy is appropriate for outpatient care of patients with diabetes, they are not sufficiently accurate for management of glucose concentrations in critically ill patients and especially for preterm infants with very low glucose concentrations. Such patients require accuracy equivalent to laboratory glucose concentration measurements and in much lower glucose concentration ranges.

Thus, while CGM technology will continue to improve the management of patients with diabetes, several factors should be carefully considered for its use the neonatal population. The CGM algorithms used to derive interstitial glucose concentrations are based on

interstitial glucose–blood glucose kinetics in adults, which have not been tested specifically or rigorously in neonates. Very few reference data are available, even in children age 2–6 years.[8] Without a commercial incentive to expand the use of CGM to the newborn population, CGM development will remain focused on glucose concentration measurements in the 2.2–22 mmol/L (40–400 mg/dL) range, not the lower range of 0 to−2.6 mmol/L (0–47 mg/dL) that is necessary for management of term and late preterm newborns at risk for symptomatic and asymptomatic hypoglycaemia in the first days after birth. It also remains the case that there are no firm or widely accepted cut-off values for low or high glucose concentrations in neonates or the clinical meaning of any glucose concentration below or above such values, at one time or for different durations. It also is not clear whether finding low or high glucose concentrations in neonates who are asymptomatic more frequently (even continuously) using CGM will improve outcomes. Given the fact that no study has demonstrated improved outcomes following treatment of asymptomatic hypoglycaemia, it is even possible that CGM use could increase diagnostics and treatments that are not warranted and are potentially harmful (separating infants from mothers) as well as very costly (neonatal intensive care unit admissions, intravenous dextrose infusions).

Despite these caveats, if the goal for neonates is to guide the timing of when to check blood glucose concentrations with more accurate laboratory methods, then current CGM devices are ready to be tested off-label in randomised trials to determine their impact on patient care and outcomes, as asserted by the authors of this study and others.[9] Such tests will need to assess accuracy of CGM values versus laboratory glucose concentrations, the utility of continuous versus intermittent glucose concentration data, and the indication for as well as the responses to treatments.

At this point, given the current limited accuracy of CGM systems, we agree with the authors and others that this technology should be used first in research settings in preterm infants and other neonates in intensive care settings. Furthermore, because CGM systems intended for replacement of POC glucose testing continue to demonstrate differences of ≥15 mg/dL (15%) between interstitial and blood glucose concentrations,[10] we also agree that CGM data should not replace intermittent blood glucose measurements. Instead, the change over time and directionality of the CGM data should alert the clinician to measure the blood glucose concentration with laboratory accuracy and make changes in clinical management based on all of these factors. Assessment of clinical condition at the time of intermittent sampling should be compared with the CGM values before, at the time of and following the blood samples.

In the future, CGMs will improve in accuracy and correlation with blood glucose concentrations. Such improvements could be combined with computerised intravenous glucose dosing algorithms, perhaps including insulin in select cases of extreme hyperglycaemia, that will help clinicians adjust glucose and TPN treatments to produce and maintain more stable glucose concentrations over longer periods with less episodes of hypoglycaemia or hyperglycaemia.[11] The benefits of such approaches should be shown in larger randomised trials prior to widespread adoption of CGM into the clinical care of the critically ill newborn infant and those neonates with documented risk for hypoglycaemia and hyperglycaemia.

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