Glucose monitoring and management in the NICU – how are we doing?

Differentiating physiological verses pathological glucose levels during the period of transition following birth makes managing glucose control in the newborn challenging. Historically methods for measuring glucose have been dependent on technology designed for patients with diabetes, with different thresholds for intervention and fewer confounding variables. When managing extremely preterm infants requiring intensive care, the problem of immaturity is combined with critical care pathologies. Recent developments in monitoring may improve understanding of the physiological verses the pathological implications, and help to guide future management.

Tanya Li[1]
Medical Student

Lynn Thomson[1,2]
RSCN
Research Sister

Amanda Ogilvy Stuart[2]
MD, FRCP
Consultant Neonatologist

Kathryn Beardsall[1,2]
MD, FRCPCH
University Lecturer and Consultant Neonatologist
kb274@cam.ac.uk

[1]Department of Paediatrics, University of Cambridge
[2]Neonatal Unit, Cambridge University Hospitals NHS Foundation Trust

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Key points

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1. Glucose dysregulation is common in preterm infants.
2. Assessment of glucose control is currently limited by infrequent sampling of variable accuracy.
3. Optimal targets for glucose control and how to achieve them are debatable.
4. The role of real time continuous glucose monitoring remains to be determined.

Hyperglycaemia and hypoglycaemia remain difficult to define, as the clinical significance will critically be dependent on the context and length of exposure.[1] Both hyperglycaemia and hypoglycaemia are associated with increased mortality and morbidity in preterm infants[2-7] but causality is not clear and optimal treatment strategies have yet to be determined. The methods used for glucose measurement vary widely across clinical services, which try to balance a desire for limited blood sampling and an 'immediate' result with the need for clinically acceptable accuracy.[8]

Thresholds for intervention also remain controversial particularly in the preterm infant in the neonatal intensive care unit (NICU), some clinicians tolerate relative hypoglycaemia or hyperglycaemia and others treat more aggressively. Equally controversial remains the clinical approach to management of hyperglycaemia, with limitation of nutritional intake (and a reluctance to use insulin) being advocated by some, while others strive to optimise growth by combining nutritional intake with insulin.[9]

Controversy tends to occur where robust evidence is lacking. Current developments in continuous glucose monitoring (CGM) could in some way address these issues by providing a more detailed picture of glucose levels in preterm babies over time without the bias associated with intermittent glucose sampling.[10] It could help to guide acute management as well as provide future insights into clinical significance and optimal treatment strategies.

What is normoglycaemia for a preterm infant?

Glucose levels are normally maintained between 4-6mmol/L[11,12] *in utero* but infants born preterm frequently have glucose levels outside of these limits for periods that are often poorly defined.[8,13-16] The clinical importance of such levels is not fully understood and widely debated in terms of either physiological or pathological significance.[9,16] Most neonatal units aim to maintain glucose levels in these babies between 2.6-10mmol/L but this can be difficult to achieve.

A fall in blood glucose levels is a normal part of physiological transition for healthy term infants which is characterised by a short period of catabolism.[17] There is evidence that at this time the newborn can utilise alternative fuels such as ketones and lactate while the enzymes involved in gluconeogenesis are upregulated.[17] However, in preterm infants with limited fat and glycogen stores and the presence of other potential factors such as sepsis or hypoxic ischaemia, there is impaired counter regulation which places them at risk from exposure to hypoglycaemia.[18]

For preterm infants requiring intensive care hyperglycaemia is also common and can result from a combination of excess glucose delivery, counter regulatory response to stress and infection, or the impact of prematurity and growth restriction on insulin secretion and sensitivity.[14,19] Acutely hyperglycaemia can lead to an osmotic diuresis, hypernatraemia and increased fluid replacement

with increased risks of patent ductus arterisous and intraventricular haemorhage.[20] An association has been demonstrated between early hyperglycaemia in preterm infants and reduced white matter at term,[6] increased risk of retinopathy of prematurity[3] and chronic lung disease,[21] but these studies cannot assume causality. Animal and adult studies do, however, indicate a direct effect of hyperglycaemia on inflammatory and coagulation pathways.

There is also increasing evidence that it is not simply the mean glucose level that is important but that rapid fluctuations in glucose levels may be an added risk factor for poor outcomes.[22-24] Whether this is simply that glucose fluctuations are a marker of metabolic instability or direct effect remains to be determined. The impact of increased fluctuations appears to be significant even within what might be considered a normal physiological range, which is of relevance to preterm infants who demonstrate increased glucose variability with feeds even when they reach term corrected.[23]

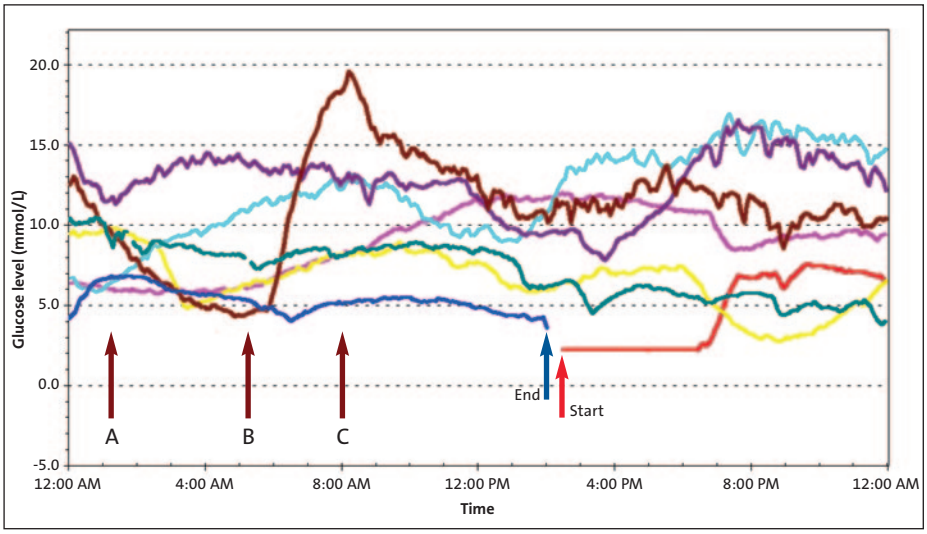

FIGURE 1 Blinded continuous glucose monitoring data from a preterm infant in the first week of life. Each different coloured line represents a different day from the same baby. The 'start' arrow represents sensor insertion and the beginning of the monitoring period. 'End' represents sensor removal. The brown arrows highlight a clinically undetected fall in glucose (A to B) on the brown line that occurred in association with longline extravasation (delivering maintenance fluids) followed by a rapid rise in glucose levels (B to C) following line replacement and restarting of parenteral nutrition.

What do long-term outcome studies tell us?

Historically the lower limit for blood glucose for the preterm population was based on two papers from 1988. The Lucas group reported that children whose blood glucose levels fell below 2.6mmol/L for three or more days had worse neurocognitive outcomes at 18 months.[25] The studies by Koh demonstrated abnormal sensory evoked potentials in children (only five babies) when glucose levels fell to <2.6mmol/L (although the threshold varied between individuals).[26] These studies were supported by studies by Duvanel which showed that recurrent episodes of hypoglycaemia were strongly correlated with persistent neurodevelopmental and physical growth deficits at five years of age.[27] However, more recent prospective studies have failed to demonstrate a similar relationship with neurocognitive outcomes.[28-30]

On the other hand, retrospective studies are often dependent on single daily measurements and subject to sampling bias in babies whose glucose levels fluctuate widely over a short period of time, with no data regarding length of exposure. The clinical significance of glucose levels will be dependent on other aspects of the clinical condition such as availability of alternative fuels in the setting of hypoglycaemia or the presence of sepsis or ischaemia with hyperglycaemia.[31] These variables are often difficult to define or measure in clinical practice.

How should we monitor glucose levels in the preterm infant?

In contrast to later in life, hyperglycaemia and hypoglycaemia do not usually present with obvious clinical symptoms or signs in preterm infants. We are therefore reliant on regular monitoring to detect high or low glucose levels. In addition, the thresholds that are considered of clinical significance are more extreme than are tolerated in older populations.[32] Biological variables that are common in preterm infants, such as high haematocrit and hyperbilirubinaemia, all add to the complexities of ensuring an accurate measurement of glucose levels in these babies.[8] Pre-analytical errors in measurement also need to be avoided by ensuring good quality blood sampling and it needs to be remembered that differences will be found between devices reporting whole blood compared to plasma glucose levels.[8]

Many units rely on cotside point-of-care meters but there remains debate regarding their use for guiding clinical management. Methodologies for point-of-care measurement have progressed greatly from reflectance strips which were subject to significant interference and not accurate at the glucose thresholds advocated within neonates. Some devices correct for haematocrit and are not subject to interference but the requirements for accuracy for these devices is not to the same level that is required by laboratory analyses. However laboratory analysis, often considered the gold standard, is limited by the larger volumes of blood required and long turnaround time for results making it unhelpful in acute management. Furthermore, even when using fluoride samples, which inhibit the breakdown of glucose by glycolysis, there can be a significant fall in blood glucose levels in the time taken between sampling and laboratory measurement. The balance of speed of results and small samples, as well as ease of use by staff, can be addressed in intensive care where blood gas analysers can measure glucose with accuracy comparable to laboratory methods.

Monitoring in intensive care, however, is not just about how you measure something but how often – the less frequently you check a variable the less likely you are to find something abnormal. Glucose monitoring is often undertaken as part of blood gas analysis and is therefore undertaken frequently when babies require respiratory support. Preterm infants, particularly those who are growth restricted, are susceptive to hypoglycaemia as the volume of feeds are increased and

intravenous support is reduced and this hypoglycaemia may be clinically silent. Monitoring glucose levels needs to be considered in relation to nutritional needs and support, not simply alongside blood gas measurement.

There are good reasons to limit the frequency of blood glucose monitoring in extremely preterm infants both to limit breaking of central lines, use of heel lances, reduced blood sampling and to minimise handling. In contrast many biological variables are continuously measured and monitored. Heart rate, blood pressure, oxygen saturation and carbon dioxide levels are monitored constantly, without the need for blood sampling. This informs about fluctuations that would otherwise be clinically undetected. This is undertaken in many cases even where we are not entirely sure of the optimal target range. The use of CGM has revealed that glucose levels in the preterm infant fluctuate widely and current standard blood glucose measurement fails to identify potentially clinically significant (but silent) episodes of glucose dysregulation (**FIGURE 1**).[33] Recent developments in CGM, with reduced sensor size and better accuracy at low glucose levels, may provide an opportunity for improved glucose monitoring in neonatal intensive care.

What is CGM?

CGM devices comprise a subcutaneous sensor to measure interstitial glucose using glucose oxidase methodology to generate an electric current, a transmitter is then linked to the sensor that communicates this signal to a monitor. The monitor records the glucose levels and may display the glucose levels in real time (**FIGURE 2**).

There are a number of different CGM devices on the market, but none is specifically designed for use in neonates. Most models have devices to aid insertion of sensors in children and adults but with limited subcutaneous tissue in preterm infants the inserter devices cannot be safely used and the devices need to be inserted by hand. Manufacturers variably recommend different sites for insertion in children, but in preterm infants the limited fat stores on the arms and abdomen and the risk of infection make insertion in the thigh the preferred site.

Early devices simply recorded glucose levels, being calibrated retrospectively with clinically obtained blood glucose levels. These have been used in patients with diabetes mellitus to review and advise on management. Newer devices can now provide glucose levels in real time but do require calibration with blood glucose levels every 12 hours. They are designed to support blood glucose management not as a replacement to it. The data, however, allow observation of trends in glucose levels and enable more rapid identification and potential treatment of rising or falling glucose levels. The devices can be left *in situ* for up to six days when data can then be downloaded for review.

Accuracy of CGM has been assessed in preterm babies[34-36] and the devices have been used to highlight the high prevalence of glucose dysregulation and risk of hypoglycaemia but not in active management.[37-39] The devices have also been used in newborn term infants at risk of hypoglycaemia.[40] The sensors are well tolerated and give glucose levels comparable to the point-of-care meters.

It remains to be determined how the use of CGM readings impact on clinical management of babies in terms of efficacy, safety and utility and this is currently under investigation as part of the REACT trial (doi: 10.1186/ISRCTN12793535). The REACT trial is an international multicentre randomised controlled trial which aims to recruit 200 babies over two years to determine the safety, efficacy and utility of CGM in the preterm infant. It is recruiting babies born less than 1,200g who will be followed up until 36 weeks' gestation. Babies in the trial will have sensors inserted within 24 hours of birth and be randomised to either real time CGM to target glucose control or standard care with blinded CGM to collect comparative continuous glucose data.

What other new methodologies are available?

There are other developments in the area of CGM in adults such as the OptiScanner (OptiScan Biomedical Corporation). This monitor is designed to link to an existing cannula or port and uses mid-infrared spectroscopy on automatically drawn venous samples.[41] This would reduce the frequency of heel pricks for glucose monitoring, but still poses a problem due to regular blood draws and size of preterm infants. Other attempts for non-invasive glucose monitors have included light reflection and absorption[42] and transdermal iontophoresis in which fluids can be drawn across the skin to be sampled.[43] However, it has proven difficult to obtain accurate readings with these methods even in the adult population and they will need to be validated for use in the preterm infant.

How should we manage glucose levels in the preterm infant?

Identifying an 'abnormal' level then leads to the question of what should we do? Interventions remain consistent in the setting of intensive care where babies are often predominantly receiving parenteral nutrition (PN). Increasing calorie intake with increased volume or strength of dextrose solution is advocated plus or minus a dextrose bolus based on the clinical scenario. It is important that a

FIGURE 2 (A) A preterm baby with an *in situ* real time continuous glucose sensor with transmitter attached to the leg. (B) The sensor attached to the transmitter demonstrating size compared to an adult hand. (C) The real time monitor that can be used for both data display and data collection. *Credit: www.media-studio.co.uk.*

bolus of dextrose is not given without a concomitant increase in nutritional intake as this is likely to result in rebound hypoglycaemia. Oral dextrose gel has been trialled for the treatment of hypoglycaemia in term infants at risk but the impact on preterm infants has not been explored[44] and, given the potential to increase glucose fluctuations, needs to be balanced with risk.[45]

The management of hyperglycaemia in the preterm infant remains controversial as has been highlighted by surveys[46] and reviews.[9] Some clinicians favour a reduction in PN on the premise that this is the driver for hyperglycaemia, and due to concerns about the risk of hypoglycaemia associated with insulin use. There remains controversy as to whether optimising amino acid delivery may ameliorate the problems of hyperglycaemia and therefore a reduction in PN may be counter-productive.[47] Those that advocate 'optimising' nutritional delivery will prescribe insulin in the hope of driving anabolism and growth. This needs to be balanced with the aims of achieving healthy postnatal growth. Simply increasing calorie intake may be detrimental[16] but optimising amino acid and insulin has the theoretical potential to improve lean body mass and pancreatic function and therefore reduce the risk of long term metabolic risk.[48]

The only interventional study to target glucose levels in the preterm infant is that from New Zealand which tried to target glucose levels between 4-8mmol/L (compared to 8-10mmol/L for those in the control arm of the study) with the aim of promoting growth. There was a reduction in mean glucose levels in those in the intervention arm but at the cost of significant increased rates of hypoglycaemia.[49] The study also demonstrated an increased weight gain and head growth but with a somewhat paradoxical reduction in linear growth. This study highlights the risk of trying to 'optimise' glucose levels without robust monitoring.

Summary

It is important in a clinical setting to monitor preterm infants' glucose levels as accurately and efficiently as possible. With a lack of robust evidence for optimal targets the neonatal principal of aiming to mimic physiological levels would seem reasonable. Developments in glucose monitoring including accuracy at critical thresholds and CGM are promising. These will not only provide us with more information to highlight glucose dysregulation to guide acute management but by providing more comprehensive data regarding glucose control over time they will help to provide better insight as to the long-term impact on health outcomes. To determine the real impact of hyperglycaemia and hypoglycaemia, large, prospective long-term studies must be carried out to follow up infants into childhood and adult life. This could then provide a robust evidence base to support development of optimal treatment strategies.

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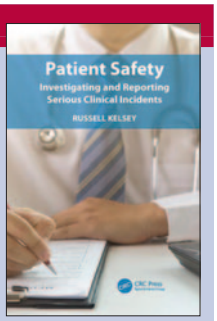
Book review

Patient Safety: Investigating and Reporting Serious Clinical Incidents



Russell Kelsey
CRC Press
ISBN: 9781498781169
£29.99, paperback
214 pages

The NHS has significant experience of recognising and investigating patient safety incidents in acute care but this is somewhat less established in primary care settings. Considered the first book to provide detailed guidance on conducting incident investigations in primary care, *Patient Safety: Investigating and Reporting Serious Clinical Incidents* comes at a time of increasing emphasis on training staff in root cause analysis investigation.

Russell Kelsey, an experienced GP, brings his expertise in serious incident investigation from many years in senior medical director roles to this publication, which strikes a nice balance between a technical manual and a best-practice handbook.

Root cause analysis forms the basis of the book and Dr Kelsey explores the difficulty in applying this technique to healthcare situations, which are often complex and non-linear. A useful distinction is provided: 'We are not looking to find out what went wrong; we are looking to see *whether* something went wrong.' The focus on root cause analysis as a process is maintained throughout.

The role of human factors is covered in depth and, as ever, fascinates. For example, the challenge within primary care to keep up-to-date with clinical guidelines is considered a system issue, illustrated by an example of 'unconscious incompetence' during insulin prescribing by a GP.

Real-life case studies from a primary care setting are drawn upon throughout. In particular, the case of Baby Anna – who died six hours after being prescribed home management by an out-of-hours GP – weaves itself through the book and provides a detailed illustration of a serious clinical incident investigation worked through from start to finish.

The book is full of practical advice and tips, such as avoiding common pitfalls in writing reports, and contains many useful resources, including template letters, sample reports and the author-developed 'serious incident recognition tool'.

Dr Kelsey is a confident voice who adopts a reassuring and supportive tone to prepare any reader embarking on a serious incident investigation. The book complements Dr Kelsey's website (www.patientsafetyinvestigations.com), which shares experience and tips on incident investigation techniques. Together, they are a welcome resource for clinicians or service managers in any clinical field – not at all restricted to those in primary care.

Catriona Vernal
Senior Project Officer
Maternity and Children Quality Improvement Collaborative
Scottish Patient Safety Programme
Healthcare Improvement Scotland