Early Human Development 86 (2010) 263–267

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Best Practice Guideline article

Measurement of glucose levels in the newborn

Kathryn Beardsall *

University of Cambridge, Department of Paediatrics, Box 116, Addenbrookes University Hospital NHS Trust, Hills Road, Cambridge, CB2 2QQ, United Kingdom

ARTICLE INFO

Keywords:
Glucose
Measurement
Newborn

ABSTRACT

Accurate measurement of blood glucose levels in the newborn is important as hypoglycaemia and hyperglycaemia are common treatable conditions and there is evidence linking both with detrimental clinical outcomes. Point of care (POC) glucose testing provides rapid results with small sample volumes and therefore clinical care can be modified quickly if needed. However the common thresholds for the diagnosis of hypoglycaemia in the newborn (blood glucose <2.0 mmol/l or <2.6 mmol/l) and hyperglycaemia (blood glucose >10 mmol/l) are at the limits of accuracy for many POC glucose analysers. Therefore although useful for screening, such devices cannot be relied upon for accurate diagnosis of hypoglycaemia. Stand alone local laboratory devices or glucose biosensors incorporated into blood gas analysers help to balance the benefits of POC testing with the accuracy of laboratory analyses. However these clinical methods all rely on intermittent blood sampling and there may be many hours between measurements, when both hypoglycaemia and hyperglycaemia may be undetected clinically. Less invasive and continuous methods of glucose monitoring are under development. Continuous glucose monitoring provides detailed information regarding glucose levels and has led to improvements in the care of patients with diabetes mellitus. These devices also have the potential to help provide improved glucose monitoring and management in the high risk neonate.

Contents

1. Introduction

The accurate measurement of blood glucose in the newborn is clinically important as hypoglycaemia and hyperglycaemia are not always associated with overt clinical signs [1], although both extremes have been associated with poor clinical outcomes [2,3]. As interventions are available to maintain glucose levels within a 'normal range' it is important that glucose levels can be measured efficiently and accurately so that any necessary clinical interventions can be made. Accuracy of measurement is dependent on many factors related to the sample itself and device used for analyses. There is a wide range of devices and different methodologies available for measurement of glucose and it is important that devices are validated for use in the newborn before being used for clinical care. One of the particular difficulties in the newborn is that the blood glucose (BG) levels at the thresholds for changes in clinical management are at levels that are at the limits of the accuracy for many glucose analysers. New methods such as continuous subcutaneous glucose monitoring are increasingly being used to help improve glucose control in patients with diabetes mellitus and may in the future provide the opportunity to improve glucose management in the newborn.

* Tel.: +44 01223 763404.
E-mail address: Kb274@cam.ac.uk.

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doi:10.1016/j.earlhumdev.2010.05.005

2. Why measure glucose levels?

Hypoglycaemia can be detected after birth in a healthy population of term neonates, as part of physiological adaptation [4], and therefore routine testing of all babies is not indicated. The fasting newborn produces lactate and ketones which can be used as alternative fuels in the neonatal period having a glucose sparing effect. However infants who are unable to produce alternative fuels due to limited fat and glycogen reserves or impaired counter regulation are at risk from hypoglycaemia. In such infants (with for example sepsis, evidence of previous hypoxia–ischaemia, prematurity, growth restriction, or infants of diabetic mothers) it is therefore important to monitor glucose levels. It is widely accepted that prolonged or recurrent periods of hypoglycaemia can lead to long term neurocognitive impairment, although how low and for how long have not been clearly determined [1,2] [2] but is likely to be dependent on an infant's ability to produce alternative fuels.

Hyperglycaemia has historically been viewed as part of the normal physiological stress response however there is increasing evidence that it may be detrimental [5]. High glucose levels are common in the preterm neonate resulting from a combination of insulin resistance and relative insulin deficiency. Intensive care interventions such as increases in intravenous fluid may lead to excess glucose load and drugs such as corticosteroids and catecholamines reduce insulin sensitivity and can therefore lead to hyperglycaemia. Importantly studies have shown associations between neonatal hyperglycaemia and both mortality and morbidity including retinopathy of prematurity and intraventricular haemorrhage [3] [6]. However these studies have been retrospective observational studies and although attempts have been made to allow for potential confounders, causality cannot be determined. Interventional studies in adults have demonstrated that improved glucose control can lead to improvements in clinical outcomes [5], however similar attempts to maintain tight glucose control in the very low birth weight infant are challenging [7]. It has also been suggested that interventions to reduce glucose variability may be as important as absolute glucose levels in improving clinical outcomes [8].

Definitions of both clinically significant hypoglycaemia and hyperglycaemia in the newborn are still controversial [1] [9]. However monitoring glucose levels may also guide other aspects of clinical management as impaired glucose homeostasis may be an early sign of sepsis, or falling glucose levels the first indication that a central line has extravasated.

3. How should glucose levels be measured?

Balancing efficiency and accuracy are the factors that influence decisions regarding the choice of method for measuring glucose levels. In infants requiring intensive care BG levels may change quickly and they therefore require frequent glucose measurements. Therefore minimal sample volumes must be used to avoid the need for frequent blood transfusions, and rapid results are required so that changes in clinical care can be made in a timely fashion. However this has to be balanced by the importance of obtaining accurate results on which changes in clinical care can be based. Devices must be accurate at all levels but particularly at levels that will lead to changes in clinical care (normally glucose levels <2.6 mmol/l and >10 mmol/l).

Accuracy of measurements is critical and is affected by two kinds of error; preanalytical (sample collection, physiological factors) [10] and analytical (precision of the device being used). Samples taken after squeezing from a poorly perfused heel, or from an inadequately flushed arterial or central line will lead to misleading results. When comparing results between samples one needs to consider that arterial samples will have slightly higher glucose level than venous samples (10–15%), with capillary samples having intermediate levels. In the newborn, especially preterm infants, high haematocrits can lead to abnormally low glucose levels [11–13].

Performance of any device for measurement of glucose levels should be evaluated against glucose levels obtained simultaneously using the current gold standard methodology. As well as general performance one needs to consider accuracy at extremes and at levels of particular clinical significance. Simple correlation of results should not be relied upon as it measures the relationship between measurements not the agreement between them and does not give any indication of bias or clinically significant differences in glucose levels. Bland Altman analyses should be undertaken as it provides information about systematic bias between methods, whether one method over or under reads compared to another. It involves comparing the mean of all data pairs against the absolute difference of each pair of readings [14]. Use of the Clarke Error Grid attempts to address the issue of clinical significance of any error in readings. Results of measurements taken using two different methods are displayed on a scatter plot separated into 5 zones of clinical significance [15]. However the zones have been defined based on the clinical significance of glucose levels in adults using POC meters for control of diabetes mellitus. The clinical significance of such difference in the newborn infant, who may be requiring intensive care, are likely to be quite different. In addition it is important to assess the specificity and sensitivity of any new device to correctly detect clinically significant levels of hyperglycaemia and hypoglycaemia [16]. For any test there is a trade off between the two and the importance of accurately detecting an abnormality such as a true episode of hypoglycaemia needs to be balanced against the implications of a false positive result.

4. Current clinical methods for measuring glucose levels

The first line in glucose measurement in most clinical settings is a point of care glucose meter. Point of care testing can provide rapid results (in as little as 3 s) using small sample volumes (as small as 0.3 μl). This is potentially helpful in providing efficient clinical care and has been shown to reduce the need for blood transfusions [17]. There have been dramatic developments in point of care devices for measurement of glucose over the last 40 years. The first dry reagent blood glucose test, the Dextrostix was developed in 1964 but was dependent on the subjective interpretation of colour changes in the test strips. This methodology was improved by the introduction of reflectance meters (photometric devices), which brought more objectivity to the reading of the strips. However these devices required blood to be placed on the strips for specific time periods, wiped and then inserted into a meter, and lead to inaccurate readings. The wide confidence limits of these devices mean they should not be used to detect hypoglycaemia in the newborn. More recent glucose meters use an enzyme reaction (glucose oxidase or glucose dehydrogenase), to generate a current which is measured by a meter. The size of the current is proportional to the amount of glucose in the blood sample and these give a much more accurate reading.

However there are continuing concerns about the accuracy of these devices in neonatal intensive care. POC devices were originally developed for use at home in adult diabetic patients to detect hyperglycaemia. Their use in patients requiring intensive care can lead to a number of potential inaccuracies due to the effect of metabolic acidosis [18], hypoxia, [19] hypoperfusion [20] or oedema [21]. High blood oxygen tension levels may lead to abnormally low glucose readings on some devices using glucose oxidase methodology [19]. There are also concerns due to the specific problems that may be encountered in the newborn, especially the preterm infant. These include high haematocrit leading to abnormally low glucose levels and this effect is most marked at low blood glucose levels [11–13]. High bilirubin levels can also interfere with some analysers [22]. Some meters have been designed specifically for use in the newborn such

as the Elite XL, EML 105, and appear to be minimally influenced by the high haematocrit seen in the neonatal period, and are more accurate than other devices at low glucose levels [23], but they cannot be relied upon for accurate diagnosis of hypoglycaemia. The latest development in POC meters includes the StatStrip (Nova biomedical) meters which simultaneously measure glucose and haematocrit in a sample adjusting the BG result for the measured haematocrit. These meters are also not affected by oxygen or bilirubin, but there is limited data currently available about their use in the newborn.

For glucose levels at the threshold of hypoglycaemia, it is important to appreciate the limitations in sensitivity and specificity of individual POC devices [24]. For example in the critical range of glucose levels <2.6 mmol/l even devices such as the glucometer Elite XL which has reported a sensitivity of 0.63, and a specificity of 0.98 would still miss some infants who may have benefited from treatment. It has been suggested that it might be advisable to increase the screening threshold for hypoglycaemia to a limit of 3.2 mmol/l, with further confirmation of 'true hypoglycaemia' using more accurate methodology. This would provide a sensitivity of 1.0 with a specificity of 0.98 [25] [11], but this would also result in a large number of samples requiring laboratory confirmation, repeated heel pricks or venepuncture, and a potential delay in management.

Laboratory analysers use a number of different enzymes to measure glucose eg glucose oxidase, hexokinase or glucose dehydrogenase. These methods measure plasma glucose and are less affected by interference by metabolites, are not affected by haematocrit and are considered the gold standard for clinical measurement of glucose levels. However although laboratory analyses is often considered the gold standard for glucose measurement, the addition of fluoride to the sample tube does not completely prevent red cell glycolysis reducing glucose levels in samples sent to a distant laboratory [26]. Chan et al. observed a fall in glucose levels of 0.3–0.34 mmol//l over the first hour in samples collected into either heparin or sodium fluoride containing tubes [27]. This resulted in the reporting of falsely low glucose levels. Therefore although the analysers may provide accurate results these results are still dependent on the quality of the sample being analysed.

The balance of speed of results, small samples and ease of use by clinical staff versus accuracy of results may be addressed by the use of blood gas analyzers with glucose modules to measure glucose in whole blood. These can have an accuracy comparable to laboratory methods [28] [29] [30]. These modules typically use a multilayer membrane with glucose oxidase immobilized between the inner and outer membranes, and pores limit the red cells from crossing into the glucose oxidaze layer. The enzymatic reaction generates a current which the analyzer converts to a plasma glucose concentration. Alternatively some units have Yellow Springs glucose analysers on their units and routinely measure all glucose levels in this way to provide rapid accurate results.

5. Continuous glucose monitoring

Current clinical methods for measuring glucose in the newborn rely on blood sampling to provide single one off measures. Developments in continuous subcutaneous glucose monitoring can now provide detailed information on glucose levels throughout the 24-hour period. Continuous glucose monitoring has demonstrated that glucose levels can fluctuate widely particularly in infants requiring intensive care and may result in undetected periods of both hypoglycaemia and hyperglycaemia [31] (Fig. 1). This allows clinical management to be guided by trends over time, like continuous saturation monitors. These monitors are increasingly being used in the management of adults and children with diabetes and have led to improved glucose control, with reduction in hyperglycaemia and prevention of hypoglycaemia.

There are a number of devices on the market such as CGMS Gold or Guardian (Medtronic Watford UK) (Fig. 2), or Free Style Navigator

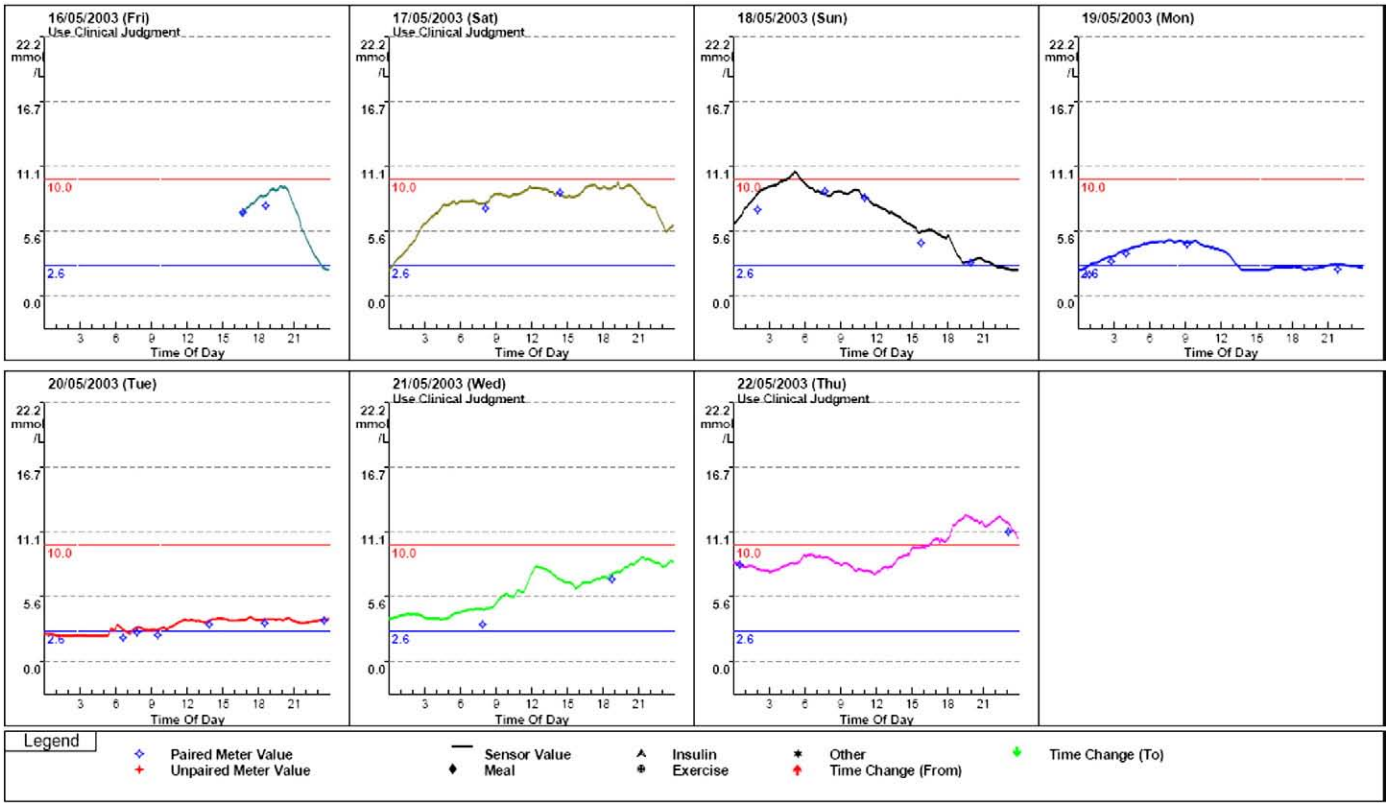

Fig. 1. Continuous glucose monitoring data. Data from continuous glucose monitoring over 7 days in an infant born at 28 weeks gestation and weighing 638 g. Each panel has time on the horizontal axis (representing a 24-hour period), and glucose level (mmol/l) recorded on the vertical axis.

Fig. 2. Real time continuous glucose monitoring device. Sensor attached to transmitter next to real time monitor displaying 3-hour glucose profile (mg/dl) and demonstrated in situ in an adult. Images provided by Medtronic Ltd.

(Abbott Maidenhead, Berks,UK), some which record glucose levels with data needing to be retrospectively downloaded for analyses and others with real time readouts. These devices typically comprise a disposable glucose oxidase-based platinum electrode sensor that catalyzes interstitial glucose generating an electrical current every 10 seconds, which is recorded by a pager sized monitor. The sensors are soft and flexible, simple to insert subcutaneously and well tolerated. The monitor records an averaged value every 5 min and the data provides a 24-hour profile of glucose control.

The first models did not have real time read outs and therefore although useful for research had a limited role in neonatal clinical practice. However more recent developments have lead to glucose levels being available in real time. Such real time monitors have been used to monitor paediatric patients after cardiac surgery and were reported to perform well without interference from body temperature, inotropes or oedema. They have also been used in the management of infants with neonatal diabetes and can be linked to subcutaneous insulin pumps. Although the sensors can be left in situ for 7 days without loss of accuracy, they do need to be calibrated with a blood glucose level at least 4 times a day, so do not completely avoid the need for blood glucose sampling. These devices like point of care meters were originally designed for use to detect hyperglycaemia and their accuracy particularly at low glucose levels is limited [28]. They do however provide alerts to falling glucose levels and the risk of hypoglycaemia that could then instigate the need for more accurate measurement of true blood glucose levels. They may therefore prove to be useful in the management of preterm infants at risk of both hypoglycaemia and hyperglycaemia, but their use in clinical practice needs to be fully evaluated before they become part of standard clinical care.

Alternative methods of continuous glucose monitoring include microdialysis. This comprises a semi-permeable dialysis fibre or double lumen catheter with micro-holes, which is inserted into the subcutaneous tissue and perfused with isotonic glucose free fluid. A dialysate of interstitial fluid is then collected which contains glucose equivalent to that in the interstitial fluid. A number of different devices are available such as the CMA Microdialyses catheter (Solna Sweden) which has been designed to be small enough to use on the newborn (shaft 60 mm in length diameter 0.9 mm and tip 10 mm by 0.6 mm). However these devices are invasive, need calibration, and there is a significant lag time in collection and measurement, and the equipment is expensive. Therefore these devices are limited to use in research within neonatal intensive care [32].

6. Non invasive devices

Attempts have also been made to develop non invasive techniques to measure glucose levels to prevent the need for frequent blood sampling. Such methodologies include optical sensors or transdermal devices but attempts have generally been unsuccessful. Optical sensors measure the characteristics of reflected light that are changed as a result of an interaction with glucose. Spectrophotometry is based on specific absorption in different spectral ranges with glucose concentration derived indirectly from the glucose induced changes in refractive indices. This means that other physiological changes such as water balance between compartments may influence the scattering co-efficients. Currently despite much research these sensors do not provide sufficient precision within the clinically relevant glucose range to make them clinically useful. Transdermal devices using reverse iontophoresis, drawing intradermal fluid across the skin by the application of a low current have been developed for use in adults with diabetes (Glucowatch, Redwood City CA, USA). However the amounts of glucose are about 1/1000 of those in blood and therefore analyses techniques are at the limits for obtaining precise results. These devices also require calibration with blood glucose levels, and have been reported to cause irritation to the skin in adults and have a lag time for glucose measurement. There are no devices available for use in the newborn.

7. Summary

The ability to measure glucose levels in the newborn is a critical part of good clinical care. Glucose monitoring devices need to give accurate results particularly at levels that would affect clinical care. However devices also need to be practical to use and maintain by neonatal staff and cost efficient. There is a wide range of methodologies and devices available for measurement of glucose but it is important that devices are validated for use in the newborn before being used for clinical care. Recent developments have lead to the possibility for continuous glucose monitoring. This has proved useful in research and in the future may reduce the risk of hyperglycaemia and hypoglycaemia in the high risk neonate.

8. Key guidelines

- Accurate measurement of glucose levels in the newborn at risk of hyperglycaemia or hypoglycaemia is important.
- Accuracy of any measurement is affected by both preanalytical and analytical errors.
- POC devices although useful for screening cannot be relied upon for the diagnosis of hypoglycaemia.
- Laboratory analyses although considered the gold standard will give inaccurately low levels if there is a delay in samples being analysed.
- Optimal glucose levels in the newborn are not known.

- Any new methodology for measurement of glucose levels in the newborn should be evaluated specifically in this population before being adopted into clinical practice.

9. Research directions

- What are optimal glucose levels for the newborn both term and preterm?
- What are the optimal interventions to achieve these targets?
- Validation of the use of continuous glucose monitoring as part of clinical care
- Development of improved methods for non invasive continuous glucose monitoring in the newborn

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