

Point of care analysis of blood glucose in infants

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Low blood glucose concentrations are often found in neonates, and have potential to cause adverse neurodevelopmental effects, particularly if persistent or profound. In order to assess the adequacy of the neonatal glycaemic status, accurate, precise and rapid measurements of blood glucose concentrations are needed.

Clinical correlates of low blood glucose concentrations such as jitteriness, lethargy, pallor, apnoea and altered alertness or tone are non-specific and can occur with a variety of other pathologies. Moreover, low blood glucose levels are often found in babies without any clinical symptoms, the so called 'asymptomatic' hypoglycaemia. Neuronal fuel adequacy depends not only on blood glucose concentrations but also upon the availability of alternative fuels such as ketones and lactate, cerebral microcirculatory adaptation, and concurrent neonatal conditions such as hypoxia. No single blood glucose value can therefore define the risk of brain injury or predict sequelae. This has led to adoption of pragmatic 'operational thresholds' – blood glucose concentrations, interpreted in the context of the clinical status and known risk factors, that serve as thresholds for altering the nutritional management of the baby¹.

Measurement in a quality-controlled laboratory environment by appropriately trained personnel provides the ideal means of estimation of blood glucose. This is however often impractical in routine neonatal practice mainly due to the unacceptable time delay involved in specimen transport and laboratory processing in the face of a need for rapid intervention, and generally higher sample volume requirements of laboratory methods. Moreover, glucose concentration in a whole blood sample continues to decline after collection due to ongoing glycolysis, and commonly used glycolytic inhibitors such sodium fluoride are

not completely effective in preventing this fall. These considerations have led to widespread adoption of point of care testing (POCT) for blood glucose levels in neonatal units.

CHOICE OF METHOD

Methods for determination of glucose most commonly employ enzymatic assays based on glucose oxidase, glucose dehydrogenase, or hexokinase/glucose-6-phosphate dehydrogenase reactions. All three are highly specific for glucose, and any differences in imprecision between methods are due to the measurement of reactants and auxiliary reactions rather than glucose itself.

Reagent strips

Reagent strips continue to be used in neonatal units despite a warning by the Medical Devices Agency. These methods are neither accurate nor precise. They were primarily developed for measuring blood glucose in the normal to high range in diabetic patients, and their application to screen for low blood glucose values in neonates is questionable. Compared to laboratory glucose estimation, reagent-strip based methods show wide confidence intervals at all glucose levels, producing large and unpredictable errors². Much of this imprecision results from variations in operator technique (timing, wiping etc), effects of haematocrit, skin cleansing agents, altitude, atmospheric conditions, and lack of any quality assurance. The weight of published evidence suggests that such methods should be abandoned

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FIGURE 1 The blood sample is drawn from the medial and lateral limits of a warm well perfused heel. Repeated sampling at previous puncture sites should be avoided. The site may be cleaned and dried with cotton wool, particularly if visibly soiled. If alcohol impregnated swabs are used, careful drying of the skin is necessary.



FIGURE 2 The aim is to obtain blood from the capillaries located at the junction of the lower dermis and upper subcutaneous tissue, estimated at a depth of 0.35-1.5 mm from the skin, so a heel incision device with a suitable controlled blade/lancet length should be used.



FIGURE 3 Application of gentle pressure and holding the foot downwards will encourage a good blood flow. The first drop of blood should be wiped away to avoid contamination from the skin.



FIGURE 4 It is important to ensure that the drop of blood is big enough to fill the B-Glucose microcuvette completely (5uL). The tip of the microcuvette should be introduced into the middle of the drop of blood.



FIGURE 5 The microcuvette should be filled in a continuous process - it should never be "topped up". When sampling is complete, application of gentle pressure on the heel with a cotton wool ball should stop the bleeding. Any monitors removed for sampling should be reconnected and their working ensured.



FIGURE 6 Any surplus blood should be wiped off from the tip of the microcuvette taking care not to draw any blood out of the microcuvette. The sample should be analysed immediately to avoid continuing glycolysis.



FIGURE 7 The microcuvette is then placed in the holder and inserted into the photometer.



FIGURE 8 The blood glucose level is normally displayed within one minute.



FIGURE 9 Analysers with data management and connectivity store and display comprehensive data, including patient and operator identification.

in favour of a laboratory-standard quality assured method for near-patient testing.

Laboratory-standard POCT methods

Many laboratory-standard POCT methods are often employed in the neonatal units but very few such devices have been adequately evaluated in this setting^{3,4}, and their applicability is not universally accepted. Confirmation of an abnormally low blood glucose result on POCT by a laboratory method is therefore recommended. One reason for this discrepancy may be the acceptance of a laboratory-based enzymatic method as gold standard. The laboratory methods themselves can vary significantly from each other due to different enzymatic reactions, sample matrices, varying

influence of haematocrit and preanalytical factors and there is no consensus on the reference methodology for this measurement. The hexokinase methodology is generally suggested as the reference method, but is only applicable in serum or plasma matrix, and thus unsuitable for POCT analysis. The recent development of an isotope dilution gas chromatography-mass spectroscopy (ID GC-MS) method offers an accurate and precise method for determination of glucose in a whole blood sample⁵.

In recent years, electrochemical glucose biosensors that measure glucose directly in undiluted whole blood have been incorporated into the blood gas and multi-analyte analysers. Such biosensors

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measure the molality of glucose (mg glucose per kg water) in the water phase of undiluted plasma or whole blood, and the values are often mathematically adjusted to report plasma equivalent concentrations (mg glucose per litre of plasma). These biosensors have not been extensively evaluated in the neonatal population but appear promising.

Given such discrepancies between various analytical techniques, an evaluation of clinical applicability is necessary. For a clinician, the primary concern is whether the measured blood glucose value is above or below the operational threshold. Using a model-based approach, we found the probability of classifying a blood glucose value differently in relation to a chosen threshold to vary between 5.9% and 7.1% (about 1 in 15 samples) between four laboratory-standard methods of glucose measurement (hexokinase on Cobas Bio, glucose oxidase on YSI 23 AM, glucose oxidase on Kodak Ektachem, and glucose dehydrogenase on HemoCue)*.

Given these limitations, how should a clinician proceed? Use of a quality-assured robust device with published evidence of its accuracy and precision in the measurement of neonatal blood glucose concentrations should be the first step. The exact selection of the device would depend upon the ease of use by non-laboratory personnel, maintenance, cost, and should ideally be done in conjunction with the laboratory services.

PREANALYTICAL FACTORS

Perhaps of greater importance in the meaningful interpretation of a neonatal blood glucose value are the preanalytical factors (the preparation of the baby, collection of the sample, and adherence to analytical instructions) rather than the analytical performance of various glucose measuring instruments. Blood glucose concentrations show a cyclic response to an enteral feed, peaking about an hour after the feed and reaching a nadir just before the next feed is due. Therefore measurements should be made before a feed is due rather than at arbitrary pre-fixed time intervals.

Whilst plasma or serum samples are preferred for measurement of glucose in the laboratory setting, they are less suitable for POCT due to the need for centrifugation, additional time and difficulties in obtaining an adequate sample volume. Whole blood based methods are thus preferred for POCT. Although the molality of glucose is the same in plasma and whole blood, its concentration is higher in plasma than in whole blood by about 10-18% due to the lower water content of the latter. Whole blood based methods are also subject to the effects of varying haematocrit.

In many ill babies, blood samples for glucose estimation are often drawn from indwelling vascular catheters. It is important to avoid catheters with previous glucose infusion in lines, and to discard a volume six times that of the catheter before obtaining the measurement sample. Arterial blood samples have slightly higher glucose concentrations than simultaneous venous samples, with capillary blood samples being in the intermediate zone. While these differences are of little clinical significance in well babies, capillary blood sample measurements of blood glucose in poorly perfused infants may be misleading.

Taking a capillary blood sample for measurement of glucose

Wherever possible, this procedure should be synchronised with other blood tests or interventions to minimise disturbances. The procedure (Figs 1-9) should be explained to the parents. Comforting the baby during and after the procedure are important aspects of care. These measures may include swaddling, maintaining skin-to-skin contact, and multisensorial stimulation, consisting of delicate tactile, vestibular, gustative, olfactory, auditory and visual stimulation which promotes interaction between the nurse and baby.

TRAINING AND DOCUMENTATION

Whichever POCT method is chosen, it is essential that the users receive coordinated training and are assessed in their competency to use the device. Such training should include, besides the use of the system, instruction on collection and disposal of sample (including health and safety aspects), performance of calibration and quality control procedures, and documentation of results. The trainer should be satisfied with the user's competence in using the equipment and formal reassessment of this competence should be carried out at least annually.

All the patient test results should be recorded in the patient charts or case notes. There should be a separate logbook to record all the blood glucose analyses including the date, time and identity of the operator as well as details of the QC tests and maintenance of the equipment. Ideally, such data should be captured electronically, and should be part of an external quality assurance scheme.

CONCLUSION

POCT offers a rapid, accurate and easy method for measurement of blood glucose concentrations that can be integrated into routine neonatal care. Attention to both preanalytical preparation and adherence to training are necessary to obtain accurate, precise and meaningful estimations.

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