PEDIATRIC ORIGINAL

Uncertainties in the measurement of blood glucose in paediatric intensive care: implications for clinical trials of tight glycaemic control

Helen Hill
Paul Baines
Paul Barton
Paul Newland
Dianne Terlouw
Mark Turner

H. Hill (✉)
Alder Hey Children's NHS FT,
Liverpool, UK
e-mail: hhill@liv.ac.uk
Tel.: +44-0-1517024111
Fax: +44-0-1517024024

P. Baines
PICU Alder Hey Children's NHS FT,
Liverpool, UK

P. Barton · P. Newland
Biochemistry Alder Hey Children's
NHS FT, Liverpool, UK

D. Terlouw
Liverpool School of Tropical Medicine,
Liverpool, UK

M. Turner
University of Liverpool, Liverpool, UK

Abstract *Purpose:* In preparation for a tight glycaemic control (TGC) clinical trial we assessed the agreement between methods used to measure blood glucose in critically ill children. *Methods:* Service evaluation comparing blood gas and main laboratory analysers with point-of-care (POC) devices PCX, ACCU-Chek and Hemocue. *Results:* Two hundred forty-five samples from 157 children measured on 2–4 devices provided 790 values. Marked variation was evident in glucose values between devices, time between tests, sample (whole blood/plasma) and source; 39% of paired values had >20% difference. The decision to start insulin at 7 mmol/L differed depending on the device used for 33% of samples. At low glucose values (<4 mmol/L), differences up to 1.8 mmol/L were evident. The blood gas analyser read lower than all POC models and the laboratory analyser (less risk of undetected hypoglycaemia). An inverse relationship was evident between haematocrit (Hct) and glucose error using POC devices. PCX values for samples with Hct <30% were higher (85%), whereas those for Hct values >38% were lower (66%). Glycolysis occurred during transfer of samples to the laboratory. Using the PCX at the bedside resulted in 0.5 mmol/L mean difference higher than laboratory values; locating the PCX in the laboratory reduced this to 0.2 mmol/L. *Conclusions:* Discrepancies between measurements may mask hypoglycaemia, and the potential benefits of controlling hyperglycaemia may not be achieved. Variation introduced by different devices, sample or source may have led to misclassification of treatment decisions contributing to the conflicting results of TGC studies.

Keywords Blood glucose · Point of care · Tight glycaemic control · Insulin · Child · Paediatric · Intensive · Critical · Intensive insulin therapy

Introduction

Accurate glucose control is important in critical care and may have influenced the outcome in tight glycaemic control (TGC) studies. Neonates and young children may be more vulnerable to the adverse effects of hypoglycaemia [1, 2]; their safety depends on early, accurate detection and management. Control of hyperglycaemia within the normal range may improve outcomes, as demonstrated in randomised controlled trials in critically ill adults [3] and children [1].

In clinical practice, different devices and types of blood sample are used to measure glucose. Glucose values are known to be affected by interferences in the sample

including extreme biochemistry parameters that are common in the critically ill [4]. Glucose metabolises faster in samples with high haematocrit and infants due to their larger mean cell volume [5]. Conversely, low haematocrit can lead to higher glucose values depending on the device [6–8], leading to over-treatment with insulin and risk of masking hypoglycaemia. Blood gas analysers measure the molality of glucose, whereas POC devices measure glucose concentration in whole blood. There is an inherent difference of 18% in values between these methods, requiring adjustment to plasma equivalent laboratory values [6–8].

We speculate that inaccuracies in glucose measurements may have contributed to different TGC study outcomes. This view has gained increasing support [9–13]. A meta-analysis concluded that TGC was not associated with significantly reduced mortality but was associated with increased risk of hypoglycaemia [14]. The method for measuring glucose was only described in 10/27 studies, and protocols allowed different samples and devices to be used that may have led to insulin dosing errors [9]. Vlasselaer's paediatric study [1] and Van den Berghe's initial study [3] reduced mortality. Both specified arterial samples tested on blood gas analysers (Radiometer) and were single-centre studies.

In preparation for a clinical trial in paediatric intensive care (PICU) we conducted a series of evaluations of the agreement between glucose values to achieve targeted blood glucose and prevent undetected hypoglycaemia. The aim of the study is to define the magnitude of inaccuracies that occur in routine practice by comparing different devices, the effect of glycolysis and haematocrit.

Methods

The PICU at Royal Liverpool Children's NHS Foundation Trust UK is a 23-bed regional unit admitting around 1,100 children per annum including neonates (28%) and cardiac/general admissions. Additional tests were only performed when surplus blood (0.2 mL) remained from clinically indicated biochemistry or blood gas samples during 2007–2009. The study was registered with the Trust Research Directorate as a service evaluation consistent with National Research Ethics Service guidance [15].

Quality control was monitored by biochemists and adhered to manufacturer device standards including daily high and low control checks. The coefficient of variation for the blood gas analyser and clinical chemistry analyser was <2% at a range of glucose concentrations. The laboratory clinical chemistry analyser measures plasma, but all other devices measure whole blood (Table 1).

Series 1: Routine practice—precision PCX (Abbott) point of care and main laboratory n = 95 (arterial n = 65, capillary n = 13 and central venous n = 17) The sample was measured on the PCX (POC) at the bedside then reached the main laboratory by vacuum pod system in lithium heparin bottles within 10–30 min (or by hand occasionally, delayed >4 h). Peripheral venous lines were not used.

Series 2 and 3 measured arterial samples on three POC devices and the laboratory, then separate samples on three POC devices with the blood gas analyser. To minimise glycolysis, tests were commenced on all four devices within 10 min by locating POC devices in the respective laboratories.

Series 2: time controlled between tests—PCX, Accu-Chek and Hemocue (whole blood) less laboratory (plasma) values and the effect of haematocrit (n = 100) Arterial samples had 0.2 mL whole blood removed in the laboratory followed by immediate testing on three POC devices. The remaining sample was centrifuged (3 min, 9,000 rpm) followed by full biochemistry analysis on the plasma. Hematocrit data was collected

Table 1 Device, enzymes and methods

Device	Enzymes	Device methods
Blood gas analyser (GAS), Rapid Lab Co-oximeter 1265 (Siemens NY, USA)	Glucose oxidase	Direct biosensor electrochemical amperometric technology; filters interferences
Clinical chemistry analyser laboratory (LAB), Architech 8000 (Abbott, Illinois, USA)	Glucose hexokinase	Spectrophotometer
Precision PCX plus point-of-care (POC) Medisense (PCX) (Abbott MA, USA)	Glucose dehydrogenase (GDH) Nicotinamide adenine dinucleotide (NAD)	Electrochemical
Accu-Chek[a] Performa (ACCU) (POC) (Roche, Mannheim, Germany)	Glucose dehydrogenase (GDH) Pyrroloquine quinine (PQQ) (test strips have been modified recently)	Electrochemical
Hemocue 201 (HEMO) (POC) (Hemocue, Angelholm, Sweden)	Modified glucose dehydrogenase (GDH) Nicotinamide adenine dinucleotide (NAD) Haemolysis (saponin)	Spectrophotometer

[a] Test strips have been modified recently

Table 2 Series of evaluations for blood glucose values

Series	Samples, n	Total values, n	Blood glucose devices				
			Laboratory	Blood gas	PCX	Accu-Chek	Hemocue
Series 1: Routine practice PCX point of care located in PICU less main laboratory (arterial/capillary/venous)	95	190	√		√		
Three point-of-care models: PCX, Accu-Chek and Hemocue, located in each laboratory to minimise glycolysis by controlling the time between tests (arterial samples)							
Series 2: three POC devices less laboratory + haematocrit effect	100	400	√		√	√	√
Series 3: three POC devices less blood gas located in PICU (GAS)	50	200		√	√	√	√

when a routine full blood count (Sysmex XE-2100) was available within 1 h of biochemistry analysis.

Series 3: time controlled between tests—PCX, Accu-Chek and Hemocue (whole blood) with the blood gas analyser (whole blood) ($n = 50$) Arterial samples in heparin-balanced syringes 0.3–0.5 mL (Siemens) were processed on the blood gas analyser then tested immediately on three POC devices (Table 2).

Data analysis

Pairs of values were compared to demonstrate the variation produced by different methods; agreement therefore does not equal accuracy. Laboratory values were used for comparison but were not referred to as a gold standard, as plasma is measured, whereas all other devices measure whole blood and are affected by glycolysis.

Clarke error grid [16] zones A–E represent varying degrees of clinical accuracy to identify when glucose error could lead to a different clinical decision in diabetes (Fig. 1).

Bland and Altman's [17] method for clinical measurement determines the mean difference (bias) and crude 95% limits of agreement (LOA) to provide a comparison between pairs of devices; individual graphs (MS Excel 2007) are provided in the Electronic Supplementary Material (ESM). Kendall's tau-b rank correlation coefficient was used to determine the significance of variability and the magnitude of the glucose value. Measurements were log-transformed using natural logarithm to base e; the antilog was then used to determine the 95% LOA relative to the glucose values using Stata 10 (Stata Corp., College Station, Texas). Glycolysis was investigated by comparing the systematic mean difference when samples were tested with then without time delays between tests. The effect of haematocrit on glucose error was analysed by linear regression.

To determine when different values would alter the decision to start insulin at 7 mmol/L (1 mmol/L = 18 mg/dL), each pair of values from the same sample were grouped as: (A) both <7 mmol/L, (B) mixed values ±7 mmol/L, or (C) both above 7 mmol/L (2 pairs with differences <1 mmol/L variation were excluded). Groups B and C contained at least one value >7 mmol/L, providing the percentage of values leading to a different decision to start insulin.

Results

Two hundred forty-five samples collected from 157 patients were tested on 2–4 devices, providing 790 values.

Wide variation in glucose estimates was evident between the PCX and laboratory, particularly when samples were taken from venous or capillary sources (series 1). A high proportion of paired values had >20% difference, as 39% of values fell outside zone A on the Clarke error grid [16] (Fig. 1); 12% fell in zone D, classed as 'a dangerous failure to detect and treat blood glucose clinically'.

Agreement improved in series 2. Having controlled the time between tests and limiting the sample source to arterial lines, 97% of values fell within zone A and 3% within zone B. Similarly, the mean difference between PCX and laboratory values reduced from a positive bias of 0.5 mmol/L in series 1 to 0.2 mmol/L in series 2 (Fig. 2). A subset of samples in series 1 ($n = 65$) taken from arterial lines showed closer agreement (95% LOA −1.0 to 2.0 mmol/L) than when venous and capillary samples were included (95% LOA −1.7 to 3.0 mmol/L).

Even at low blood glucose values (<4 mmol/L), differences up to 1.8 mmol/L (series 1, Fig. 2) were evident. The natural scale was compared with the log-transformed data and antilog LOA for series 1–3 (ESM Table 1). The PCX and Accu-Chek demonstrated a relationship between difference and magnitude, but this was corrected by log transformation. The Hemocue appeared to produce little relationship between error and magnitude but had the widest potential difference when compared with the GAS.
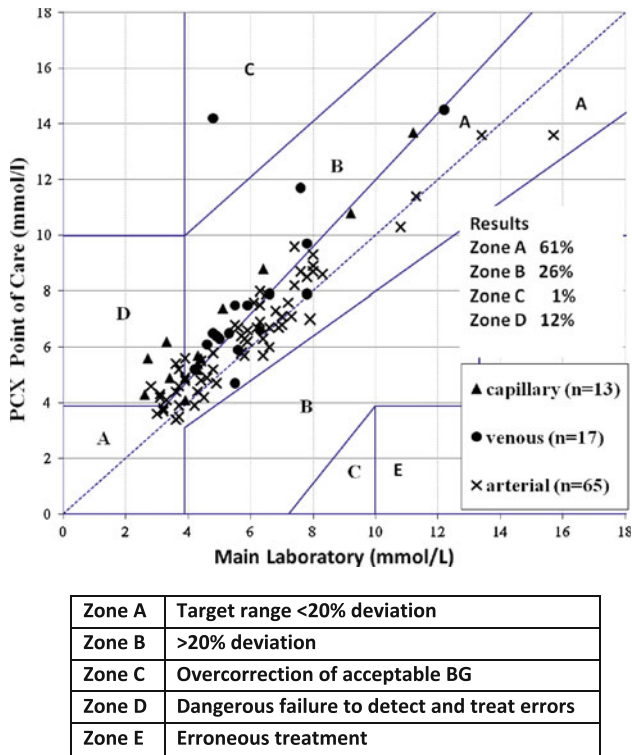
Zone A	Target range <20% deviation
Zone B	>20% deviation
Zone C	Overcorrection of acceptable BG
Zone D	Dangerous failure to detect and treat errors
Zone E	Erroneous treatment

Fig. 1 Clarke error grid illustrating the difference in glucose values that can arise during routine practice and effect on clinical decisions by comparing the PCX point of care to laboratory blood glucose values (mmol/L) for arterial, venous and capillary samples ($n = 95$, series 1)

Fig. 2 Bland–Altman plots comparing the agreement between blood glucose values (mmol/L) from arterial samples measured in the main laboratory with point-of-care PCX based in PICU (series 1, $n = 65$), then with PCX located in the laboratory to control the time between tests (series 2, $n = 100$)

Variation between values when the same sample was measured on all four devices is summarised in Fig. 3; the mean and crude 95% LOA are plotted to illustrate trends (individual Bland–Altman plots are provided in ESM Figs. 1-5). The mean difference between all three POC devices was consistently higher when compared with the GAS (mean PCX 0.8 mmol/L, Accu-Chek 0.04 mmol/L and Hemocue 0.6 mmol/L) than with the laboratory (PCX 0.2 mmol/L, Accu-Chek −0.4 mmol/L and Hemocue 0 mmol/L). Similarly, the Accu-Chek read lower than other POC devices and had closest agreement with the GAS (series 3). In contrast, the PCX produced higher values than other POC devices, laboratory and GAS. Although the Hemocue had close agreement with laboratory values, it produced wide variation from the GAS.

Low haematocrit produced higher glucose values on POC devices (whole blood) compared with the laboratory (plasma). The inverse relationship between glucose error and haematocrit is illustrated by the subset of the lowest ($n = 21$) haematocrit values: 85% read higher on the PCX, in contrast to the highest haematocrit values ($n = 21$), of which 66% read lower (series 2, Fig. 4). Regression analysis confirmed the inverse relationship between glucose error and haematocrit for the PCX ($P = 0.004$, $R^2 = 0.082$) and the Accu-Chek ($P = 0.003$,
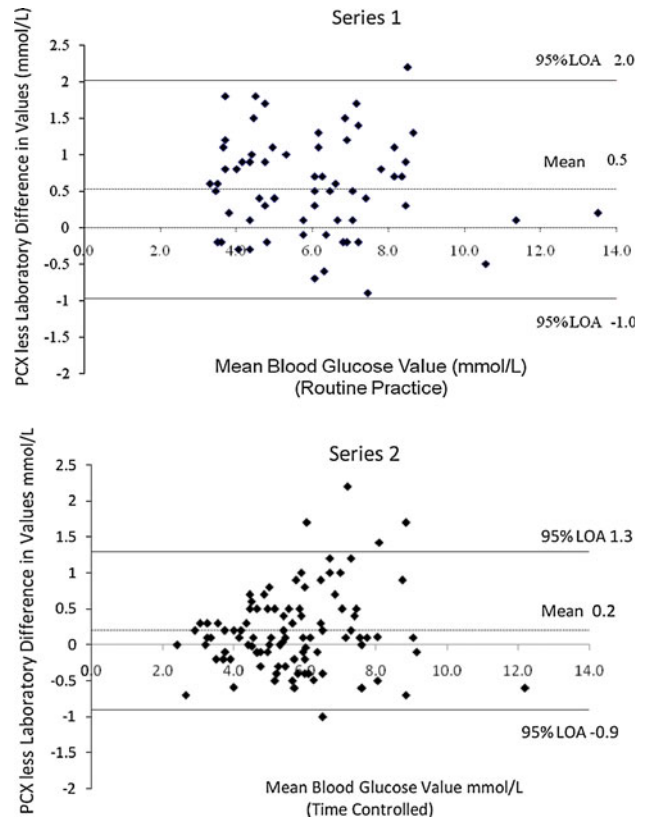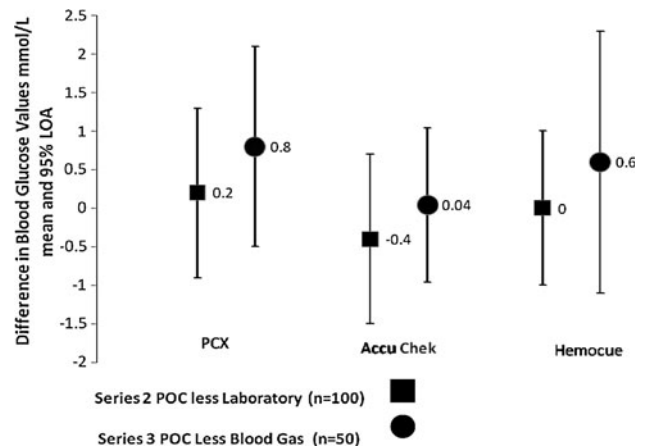

Fig. 3 Comparison of agreement in blood glucose values between pairs of devices; mean and crude 95% limits of agreement are plotted to illustrate trends. The same sample was measured on three point-of-care (POC) devices (PCX, Accu Chek and Hemocue) and by the laboratory (series 2), then a different sample on three POC devices and the blood gas analyser (series 3). Time between tests was controlled to minimise glycolysis
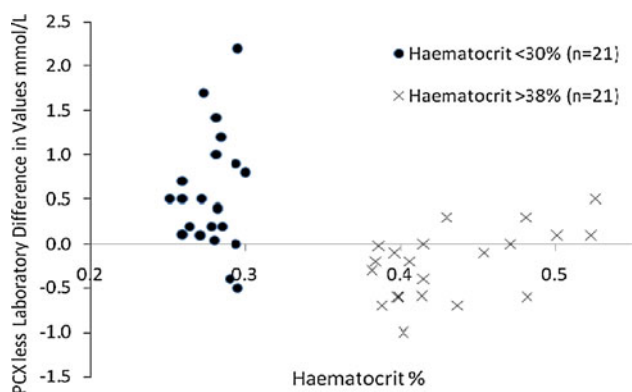
Fig. 4 Difference in blood glucose values for samples with extreme haematocrit values measured on the PCX point-of-care device less laboratory values (mmol/L) for blood samples with haematocrit below 30% compared with samples with haematocrit above 38% (series 2)

$R^2 = 0.084$). Hemocue values did not show an inverse effect ($P = 0.28$, $R^2 = 0.012$). These data have relatively poor correlation (ESM Figs. 6–8).

The decision to start insulin at 7 mmol/L would have altered due to the differences in values for 33% of the pairs of samples depending on which method was used in a TGC protocol. Each sample in series 1 ($n = 95$) produced a pair of values for the PCX (POC) and laboratory, of which 60 pairs were consistently <7 mmol/L (group A), 11 pairs were mixed values ±7 mmol/L (2 pairs <1 mmol/L difference were excluded) and 22 pairs were consistently >7 mmol/L (group C). Groups B and C included one value >7 mmol/L in each pair that would trigger insulin, and 33% (11/33) of these pairs produced mixed values above and below 7 mmol/L.

Discussion

Glucose concentration estimates vary when different methods are used in clinical practice, which may mask hypoglycaemia and influence decisions to control hyperglycaemia. Inconsistent measurements between devices would lead or would have led to different ranges being targeted, and the resulting clinical decisions lead to misclassification of data, making it difficult to distinguish between the control and intervention group, particularly in multicentre trials. These data show that the glucose value is dependent on many factors, including device standards and methods (including enzymes utilised in the method), which are influenced by the blood sample, haematocrit and glycolysis.

This evaluation has shown consistent variation between each device or sample source. As a result a different decision to start insulin at 7 mmol/L would have been made for 33% of the paired samples and suggests this degree of error

may occur with each adjustment of insulin. Although trends are evident, the values are affected by other factors, therefore not sufficiently consistent to apply a constant adjustment. PCX values are higher than the Accu-Chek and GAS, and the Hemocue had close agreement with the laboratory but poor agreement with the GAS. Agreement was closer between all three POC and laboratory values than with GAS values (Fig. 3), which may suggest that the GAS reads lower than the laboratory or that variation diminished after a longer period of glycolysis. Direct comparison between the laboratory and a blood gas analyser with both in the laboratory is required. Arterial samples have been shown to be more reliable; venous blood may be contaminated by glucose infusions, producing a different concentration throughout the sample, and capillary samples may be affected by poor perfusion [4, 18].

POC devices are not designed to adjust to the extreme clinical variables that occur in PICU or to achieve the level of precision essential to implement a TGC protocol [9]. ISO standards allow wider variation for POC devices (20%) than for laboratories (10%) [19]. To achieve correct insulin dosing 95% of the time requires the bias and coefficient of variation (CV) of the meter to be <2%; a 10% total error led to 16–45% insulin dose errors [20]. The College of American Pathologists found wide variation between the CV of glucose meters (12–14%) and bias of as much as 41%, considerably higher than for laboratories CV 2.5–4.3% and bias <11%, (cited by [9, 13]).

Most glucose values fell in the normal range (5–7 mmol/L) for both the control and intervention group; at 7 mmol/L, 20% variation would result in a range of values between 5.6 and 8.4 mmol/L, therefore data will overlap. In series 1, 39% of pairs of samples had >20% difference. In TGC, the intervention group targets glucose below 7 mmol/L, but the control group data are also *often* below 7 mmol/L and only *occasionally* between 7 and 12 mmol/L. As a result, a clinical trial using different devices or sources is unlikely to generate data that accurately represent the control and intervention group to determine outcomes. Measurements generated by a single device with a consistent bias would allow comparison of the control and intervention group (even though it may not be accurate). This may explain why single-centre studies using single devices observed a reduction in mortality [1, 3]. In contrast, the NICE Sugar Study did not demonstrate improved outcomes; the protocol did not specify the device to be used in the 41 centres [21].

Devices that over-estimate glucose levels may mask hypoglycaemia; studies have been stopped due to safety [22–24]. TGC substantially increases the risk of hypoglycaemia reported as 25% in paediatrics [1], 5% in adult surgical [3] and 18.7% in adult medical studies [25], compared with 2.3% in children in PICU not receiving insulin [26]. The ISO standard for POC allows ± 0.83 difference at low values <4 mmol/L; this would allow a range between 1.37 and 3.03 for hypoglycaemia at 2.2 mmol/L [20].

Undetected hypoglycaemia may have adverse consequences that outweigh the benefits of TGC and, given the use of different devices in some of the main TGC trials, may have contributed to adverse study outcomes.

Low haematocrit may lead to higher glucose values, depending on the device. Glucose concentration is higher in plasma, as it dissolves in the aqueous part of the sample and plasma has higher water content (0.93) than erythrocytes (0.71) and whole blood (0.84), corresponding to a ratio of plasma to whole blood of 1.11 [7]. The IFCC standard requires a constant adjustment factor of 1.11 to convert whole-blood concentration to plasma equivalent values on POC devices [8]. This ratio does not then readjust to the wide range of haematocrit the wide range of haematocrit (24–53%) in PICU (series 2), resulting in an inverse relationship between haematocrit and glucose error. A change in haematocrit from 0.4 to 0.7 will change the ratio from 1.1 to 1.38, an error of 26% [6]. The GAS analyser is not affected by haematocrit, as it measures molality of glucose (glucose per unit water mass) rather than concentration (glucose quantity per unit volume). The difference between the molality value on a GAS analyser (0.99) and glucose concentration on POC (0.84) is 18% (0.99/0.84); as such both devices require a constant adjustment to plasma equivalent laboratory values (0.93) [7].

An individual value that over-estimates the level of glucose is more important clinically than the combined statistical effect. A child with 24% haematocrit had glucose levels of 7.4 mmol/L PCX, 5.5 mmol/L laboratory and 5.6 mmol/L GAS; insulin would have been started based on the PCX result (series 1). Multiple factors contribute to this variation, but these data suggest caution with haematocrit <30%, as glucose values may be higher on POC, leading to over-treatment with insulin or masking of hypoglycaemia. The inverse relationship between haematocrit and glucose error for the PCX and the Accu-Chek shown by regression analysis had relatively poor correlation (also with quadratic regression), which may be explained by the co-existence of other interferences that increase or decrease values simultaneously.

POC devices use different enzymes and methods known to be influenced by interferences in the sample from substances that often co-exist in intensive care, including high bilirubin, hyperlipidaemia, paracetamol, uric acid, maltose, galactose and high and low oxygen saturation [4]. Tang et al. [27] found, at high glucose concentrations, that low pH decreased and high pH increased blood glucose. The GAS analyser is specifically designed for intensive care and uses reference and interference measuring electrodes to minimise the effect of common interfering substances.

Laboratory values were lower due to glycolysis that occurred during transfer. The positive bias of 0.5 mmol/L (series 1) was initially interpreted as the PCX over-reading, but reduced to 0.2 mmol/L (series 2) when controlling the time between tests (Fig. 2). Sidebottom et al. [5]

demonstrated that glucose decreased more rapidly within 1 h for an infant (by 24%, Hct 0.81) possibly due to their higher mean cell volume, compared with an adult (12.3%, Hct 0.75). Posthouwer et al. [28] found that values decreased by 0.2 mmol/L after 10 min and 0.6 mmol/L after 60 min ($P < 0.01$). Chan et al. [29] demonstrated that glycolysis was similar in both fluoride oxalate (6.30 ± 1.21 mmol/L) and lithium heparin (6.32 ± 1.23 mmol/L) during the first hour; after 4 h, fluoride oxalate had stabilised the sample (6.12 ± 1.20 mmol/L), whereas lithium heparin samples decreased (5.00 ± 1.19 mmol/L). These findings suggest that standard hospital laboratory testing is not suitable for glucose monitoring due to the time between sampling and measurement, even with glucose inhibitors.

This evaluation strengthens the argument to standardise the device method and sample source in TGC protocols. There may be advantages to using arterial samples on blood gas analysers, as specified in the trials that reduced mortality [1, 3]. Blood gas analysers in different centres use similar methodology, as opposed to the diverse range utilised by different models of POC. Values are provided quickly, allowing rapid protocol adjustments and minimising glycolysis when based in PICU. They minimise the effect of interfering substances and are unaffected by haematocrit, reducing the risk of undetected hypoglycaemia. Griesdale's subgroup analysis demonstrated improved outcomes for surgical patients [10]; Van den Berghe suggests that this may be because surgical patients are likely to have central venous access and arterial samples measured on blood gas analysers [11]. In contrast Van den Berghe's study of medical patients did not improve mortality and used a Hemocue POC device and different sample sources [25].

A further study is required to compare agreement between the blood gas analyser based in the laboratory and the laboratory clinical chemistry analyser and between blood gas analysers in participating centres before future trials. This is troublesome, as they are not portable and when located in the laboratory may not include a glucose sensor. The Yellow Springs Instrument has been used as a portable 'gold standard', but unless the sample is plasma the value is affected by haematocrit [6]. The variation found in this series would not be expected when using POC for patients who are not exposed to extreme interferences such as otherwise healthy diabetic patients. Agreement does not equal accuracy but simply illustrates the variation that occurs between methods in clinical practice.

Conclusions

Variation in blood glucose values due to different devices, sample and source are evident when monitoring critically ill children and risks masking hypoglycaemia. The potential benefits of controlling hyperglycaemia are lost when

variation between methods prevents consistent adherence to glucose targets. The resulting misclassification of treatment decisions may have led to different study outcomes, contributing to the conflicting results of TGC studies. Future studies should standardise the measurement techniques in TGC protocols. The efficacy of TGC must be established before the effectiveness of TGC can be truly assessed.

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