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Research paper

Are point-of-care measurements of glycated haemoglobin accurate in the critically ill?

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ABSTRACT

Introduction: Critically ill patients with type 2 diabetes mellitus (T2DM) and chronic hyperglycaemia may benefit from a more liberal approach to glucose control than patients with previously normal glucose tolerance. It may therefore be useful to rapidly determine HbA1c concentrations. Point-of-care (POC) analysers offer rapid results but may be less accurate than laboratory analysis.
Aim(s): The aim of this study was to determine agreement between POC and laboratory HbA1c testing in critically ill patients with T2DM.
Methods: Critically ill patients with T2DM had concurrent laboratory, capillary-, and arterial-POC HbA1c measurements performed. Data are presented as mean (standard deviation) or median [interquartile range]. Measurement agreement was assessed by Lin's concordance correlation coefficient, Bland–Altman 95% limits of agreement, and classification by Cohen's kappa statistic.
Results: HbA1c analysis was performed for 26 patients. The time to obtain a result from POC analysis took a median of 9 [7, 10] minutes. Laboratory analysis took a median of 328 [257, 522] minutes from the time of test request to the time of report. Lin's correlation coefficient showed almost perfect agreement (0.99%) for arterial- vs capillary-POC and both POC methods vs arterial laboratory analysis. Bland–Altman plots showed a mean difference of 2.0 (3.7) with 95% limits of agreement of −5.4 to 9.3 for capillary vs laboratory, 1.6 (3.4) and −5.1 to 8.4 for arterial vs laboratory, and −0.137 (2.6) and −5.2 to 4.9 for capillary vs arterial. Patient classification as having inadequately controlled diabetes (>53 mmol/mol) showed 100% agreement across all tests.
Conclusions: HbA1c values can be accurately and rapidly obtained using POC testing in the critically ill.

1. Introduction

Type 2 diabetes is a frequent preexisting medical condition in critically ill patients admitted to the intensive care unit (ICU), with prevalence ranging from 15% to 30% worldwide.[1,2] In addition, critical illness frequently causes deterioration in glycaemic control,[3] and this “stress hyperglycaemia” is associated with greater illness

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severity and potentially a long-term predisposition to the development of type 2 diabetes in non-diabetic patients.[4] Despite the prevalence of diabetes in patients admitted to the ICU, the ideal management of hyperglycaemia in this group is uncertain. Acute hyperglycaemia in critically ill patients without diabetes may be harmful, and international guidelines recommend the initiation of insulin therapy to maintain blood glucose <10 mmol/L in this group.[5,6] However, recent observational and preliminary trial data suggest that acute lowering of glucose to <10 mmol/L may be associated with harm in patients with diabetes.[7–9]

Whether a more liberal approach to glucose control is beneficial in patients with diabetes is being evaluated in the Liberal glUcose Control in critically Ill patients with pre-existing type 2 Diabetes (LUCID) trial. LUCID is a 450-patient, prospective, multicentre, parallel group, open label, randomised clinical trial that has been endorsed by the Australian and New Zealand Intensive Care Society Clinical Trial Group (Australian Clinical Trials Registration Number 12616001135404).

Glycated haemoglobin (HbA1c) is produced by non-enzymatic glycation of haemoglobin, and the degree of glycation reflects the mean blood glucose concentration over the life of the red blood cell (2–3 months).[10] HbA1c is used as an objective marker of chronic glycaemia, and a level ≥48 mmol/mol (≥6.5%) is considered diagnostic of diabetes.[11] Based on previous data suggesting that critically ill patients with chronic hyperglycaemia [HbA1c > 53 mmol/mol (>7%)] are most at risk of harm from hypoglycaemia[7,12] it may be useful to rapidly determine HbA1c concentrations in the ICU to identify such patients and to facilitate rapid initiation of targeted insulin therapy. If the LUCID study identifies benefit from liberal glycaemic control in patients with chronic hyperglycaemia, translation of results into clinical practice may be impaired by a lack of a rapid and accurate measurement of chronic glycaemia.[13]

Point-of-care (POC) HbA1c analysers may offer a viable solution for the rapid determination of pre-existing glycaemic control.[14] Previous studies have demonstrated the use of HbA1c POC analysers to be feasible in the emergency and outpatient settings.[12,15–17] However, POC HbA1c analysers may be less accurate and associated with more errors than laboratory analysis,[18,19] therefore not satisfying clinical needs.[20] In addition, finger prick capillary blood samples may be particularly affected during critical illness.[21] The feasibility and accuracy of HbA1c POC testing in the ICU setting have not been studied. Therefore, we sought to determine agreement between POC and laboratory HbA1c testing in critically ill patients with type 2 diabetes. Secondary aims were to establish the feasibility of POC testing in the ICU setting and to determine agreement between arterial and capillary POC HbA1c results.

2. Methods

We conducted a prospective single-centre study in a mixed medical-surgical university–affiliated ICU. The study received approval for a waiver of informed consent from the Royal Adelaide Hospital Human Research Ethics Committee. Critically ill patients with known type 2 diabetes and an intra-arterial catheter in situ had concurrent laboratory, capillary POC, and arterial POC HbA1c tests conducted. Patients who had undergone recent HbA1c testing within the same ICU admission with no clinical reason for repeat testing were excluded. Arterial blood samples for laboratory and POC testing were collected from intra-arterial catheters in ethylenediaminetetraacetic acid–containing 4-mL tubes, and capillary samples for POC testing were collected by finger-tip lancing. Capillary samples were analysed first, and the corresponding arterial sample was stored on ice for analysis immediately after the capillary sample. Analysis was performed using the Siemens Vantage POC analyser by monoclonal antibody agglutination reaction (Siemens Healthcare, Australia) and the Bio-Rad variant II by high-pressure liquid chromatography (Bio-Rad Laboratories, Australia) for laboratory analysis. The Siemens Vantage POC analyser was calibrated and operated as per the manufacturer's protocol.[22]

Haemoglobin and bilirubin levels on the day of HbA1c testing were obtained from the hospital's electronic record of laboratory results. Anaemia was defined as haemoglobin levels ≤132 g/l for men and ≤122 g/l for women.[23]

Data are presented as mean (standard deviation) or median (interquartile range [IQR]), and HbA1c is presented in International Federation of Clinical Chemistry (IFCC) units (mmol/mol) from conversion of National Glycohemoglobin Standardization Program (NGSP) units (%) by NGSP = [0.09148*IFCC]+2.152. Measurement agreement was assessed by Lin's concordance correlation coefficient, Bland–Altman 95% limits of agreement (LOA), and classification by Cohen's kappa statistic. Patient classification as having poorly controlled diabetes was set at HbA1c > 53 mmol/mol *a priori*.

3. Results

HbA1c analysis was performed on a convenience sample of 26 patients. The baseline characteristics of the cohort are outlined in

Table 1
Baseline characteristics of the cohort.

Characteristic	All participants, n = 26
Mean age, years (SD)	63 (12)
Men, n (%)	14 (53)
Median APACHE II score [IQR]	22 [15, 26]
Median ICU length of stay, days [IQR]	6 [3, 11]
Mechanically ventilated at the time of test, n (%)	9 (35)
Received vasopressors/inotropes during admission, n (%)	17 (65)
Mean peak vasopressor dose, noradrenaline equivalent mcg/min (SD)	18 (14)
Received renal replacement therapy[a], n (%)	6 (23)
Received blood transfusion before testing, n (%)	8 (30)
Median blood transfusion, units [IQR]	0 [0, 2]
Mean haemoglobin, g/L (SD)	98 (16)
Mean bilirubin, μmol/L (SD)	17 (20)
Median peak blood glucose in the first 24 h of ICU admission, mmol/L [IQR]	12 [10, 16]
Median blood glucose nadir in the first 24 h of ICU admission, mmol/L [IQR]	6 [5, 8]
Renal failure[b], n (%)	14 (54)
Liver failure[b], n (%)	2 (8)

APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.
[a] Defined as continuous veno-venous haemodiafiltration in the ICU.
[b] As documented in the medical record.

Table 1. More than a third of the patients were mechanically ventilated at the time of HbA1c testing. Before ICU admission, 7 (27%) patients were receiving insulin, 14 (54%) were receiving oral hypoglycaemic medications, and 4 (15%) were receiving both therapies. Twenty-five (96%) patients were anaemic with a mean haemoglobin level of 98 (17) g/L at the time of HbA1c testing. While haemoglobin electrophoresis was not performed as part of this study, no patient had previously been diagnosed with a haemoglobinopathy.

Lin's correlation coefficient showed almost perfect agreement (0.99%) for arterial vs capillary POC analysis and both POC methods vs arterial laboratory analysis (Fig. 1). Bland–Altman plots showed a mean difference of 2.0 (3.7) mmol/mol with 95% LOA of −5.4 to 9.3 for capillary POC vs laboratory testing, 1.6 (3.4) mmol/mol with 95% LOA of −5.1 to 8.4 for arterial POC vs laboratory testing, and −0.137 (2.6) mmol/mol with 95% LOA of −5.2 to 4.9 for capillary vs arterial POC testing (Fig. 2). Patient classification as having

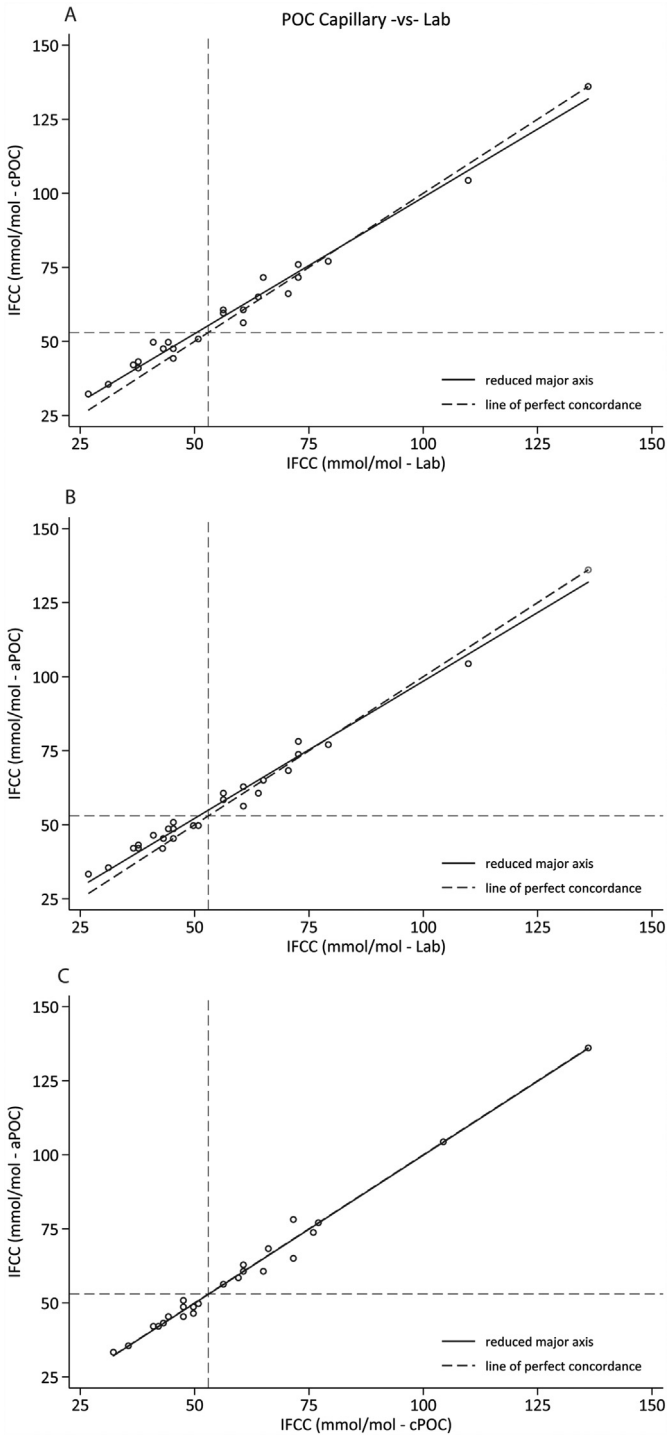

Fig. 1. Lin's correlation coefficient for point-of-care (POC) capillary (cPOC) vs laboratory, POC arterial (aPOC) vs laboratory and cPOC vs aPOC testing. IFCC, International Federation of Clinical Chemistry.

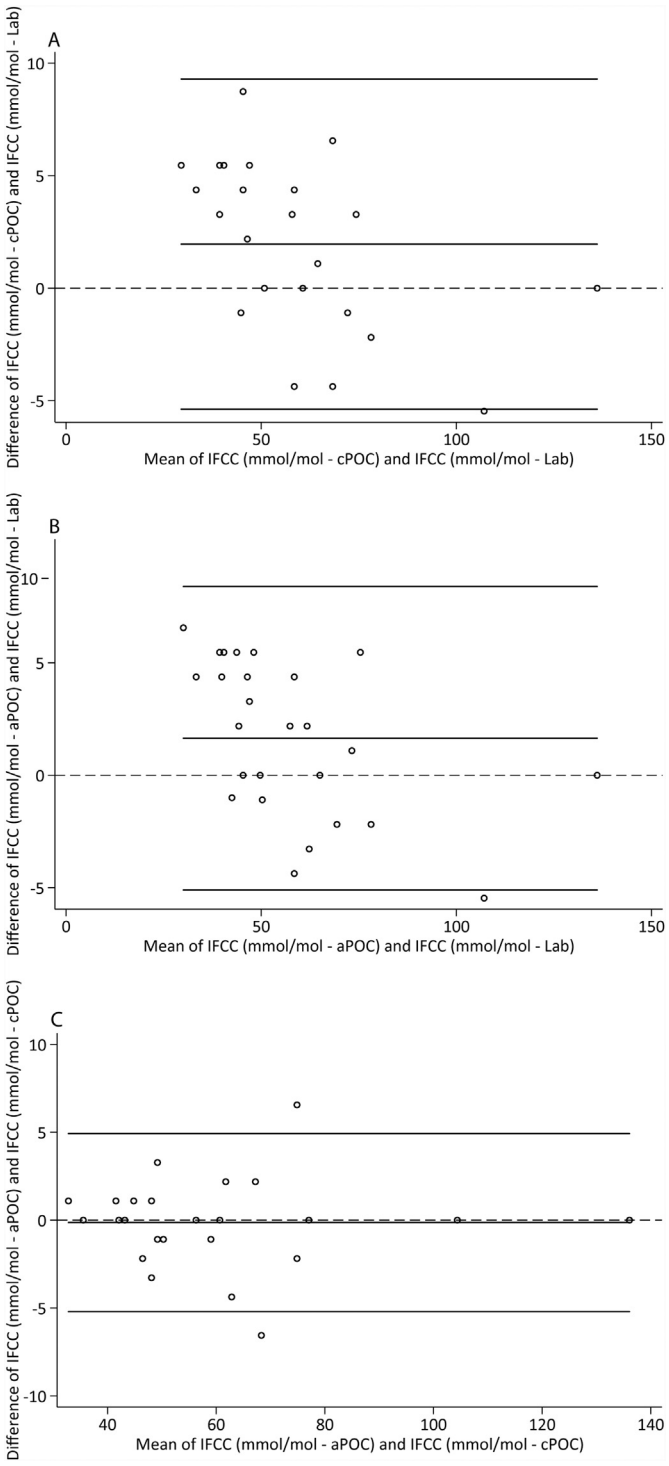

Fig. 2. Bland–Altman plots for point-of-care (POC) capillary (cPOC) vs laboratory, POC arterial (aPOC) vs laboratory, and cPOC vs aPOC testing. IFCC, International Federation of Clinical Chemistry.

inadequately controlled diabetes (HbA1c > 53 mmol/mol) showed 100% agreement across all tests.

The Siemens DCA Vantage POC analyser took a median [IQR] of 9 [7, 10] minutes to measure HbA1c in each blood sample from the time of sample acquisition to the time of result reporting. Laboratory analysis took a median time of 328 [257, 522] minutes (5 h 28 min [4 h 17 min, 8 h 42 min] hours) from the time of test request to the time of result report, with delays of up to 36 hours during weekends. POC analyser technical errors occurred five times in four patients (9.6% of all tests); all but one error occurred with the use of capillary samples. The four technical errors in capillary samples were reported by the Siemens DCA Vantage analyser as due to low total haemoglobin. The single error affecting an arterial sample was due to excessive filling of the POC analyser with blood.

4. Discussion

We found that POC HbA1c measurements showed excellent agreement with laboratory analysis in critically ill patients, regardless of whether capillary or arterial blood samples were used. POC testing was feasible in the ICU setting, in terms of both rapid availability of results and overall low technical error rate.

The Siemens DCA Vantage HbA1c POC analyser uses a 1-μL sample of capillary or whole blood.[24] However, capillary sampling is not always feasible in the ICU given that many critically ill patients experience poor peripheral perfusion or even digit ischaemia.[21,25,26] Capillary glucose measurements are known to be inaccurate in the setting of shock.[27] Furthermore, because the majority of critically ill patients, at least acutely, have an

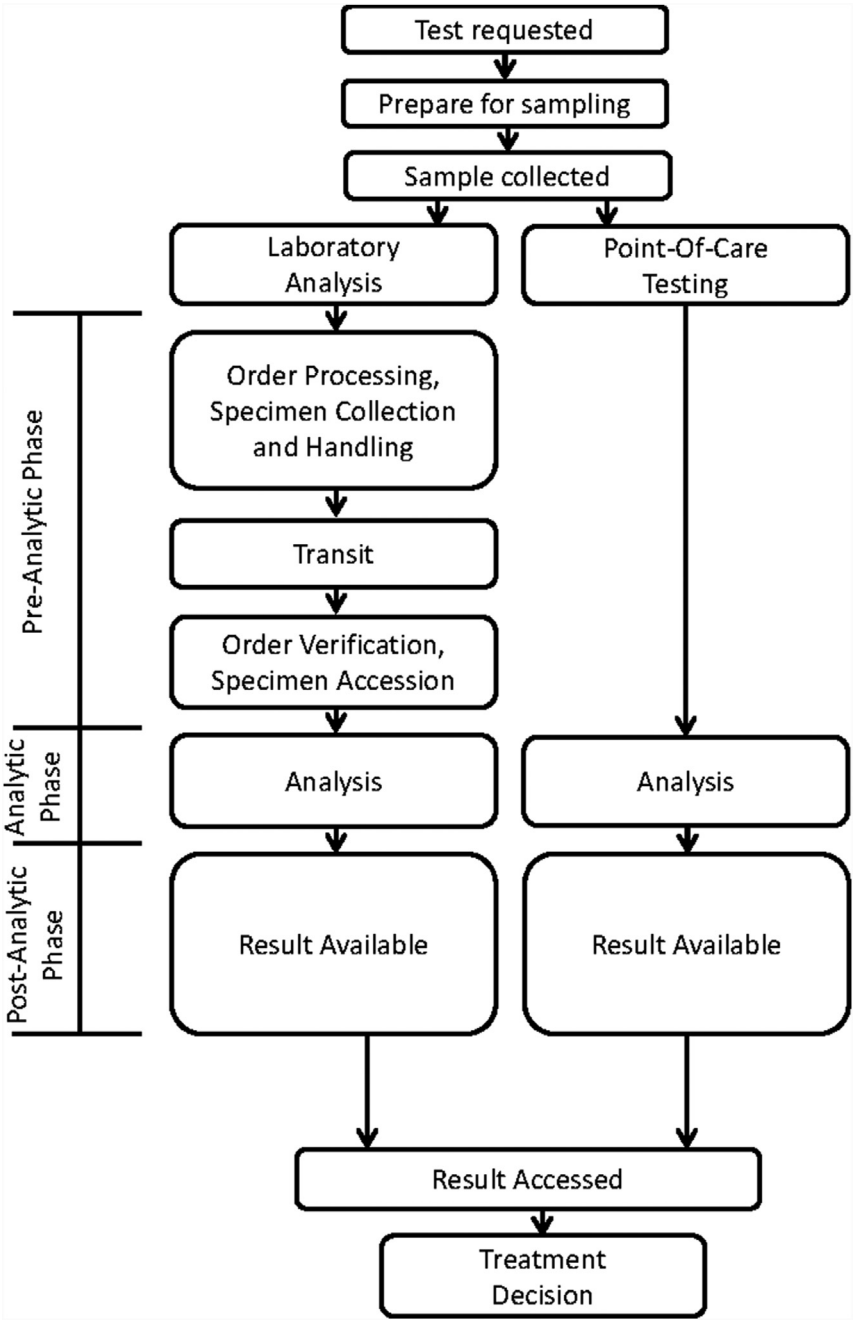

Fig. 3. Flow chart of laboratory and point-of-care testing work flow.

intra-arterial catheter in situ, the use of arterial blood samples for POC testing is often more practical than capillary sampling. Our results demonstrate that there is 0.99% agreement between arterial and capillary HbA1c POC results in the ICU. Our findings validate the use of arterial blood samples for HbA1c POC analysis in the ICU setting.

It is possible that the "low haemoglobin" technical errors that occurred with the use of capillary samples could be user derived, including excessive "milking" of the capillary sample puncture site in patients with poor peripheral perfusion or oedema, causing contamination by interstitial fluid and sample haemolysis.[28] As no arterial samples were reported to have caused a similar error, we hypothesise that the capillary source and user method of lancing are the likely causes of the technical errors.

Laboratory and POC analysis demonstrated 100% agreement in patient classification as having "inadequate glycaemic control" (HbA1c > 53 mmol/mol). However, there was a small degree of systematic bias; the POC analyser tended to overestimate HbA1c at levels >53 mmol/mol and underestimate at levels <53 mmol/mol, when compared to laboratory analysis (Fig. 1). We therefore advise against relying solely on the use of POC HbA1c for the purposes of diagnosing diabetes in the ICU setting, but it may provide a complementary "screening" estimate.[29] However, the use of POC HbA1c testing to determine premorbid glycaemic control in patients with known diabetes appears acceptable.

HbA1c measurements can be deemed unreliable in a number of clinical scenarios including in patients with anaemia,[30,31] haemoglobin variants,[32] and carbamylated haemoglobin due to chronic renal failure.[33] However, Sanchez-Mora et al.[33] reported that carbamylated haemoglobin does not have an effect on the Siemens DCA Vantage analyser. An additional study by Szymezak et al.[34] reported that heterozygous haemoglobin variants had no effect on the Vantage POC system. This may not be true of other HbA1c POC analysers. Although conditions that reduce mean red blood cell lifespan, such as chronic kidney failure and haemodialysis,[18] may affect HbA1c measurements, we demonstrated almost perfect agreement (0.99%) between POC and laboratory analysis in a cohort that included many patients with anaemia and renal failure.

Laboratory analysis can be associated with significant delays in turnaround time.[35] The median laboratory turnaround time of 328 min (5 h 28 min) in this study, when compared to the 9-min time frame with the POC analyser, could adversely delay clinical decision-making about insulin therapy in the ICU. In addition, the POC analyser could offer more rapid recruitment in the clinical trial setting. Laboratory turnaround time has been described as involving three phases[36] as shown in Fig. 3. POC testing enables shortening of these phases, allowing earlier determination of pre-existing glycaemic control and therefore potentially more rapid initiation of targeted insulin therapy in critically ill patients with type 2 diabetes.

Our study had a number of strengths. We studied a diverse cohort of critically ill patients who had significant illness severity. We also collected capillary and arterial POC and laboratory blood samples simultaneously, thereby eliminating any errors due to differences in time of sample collection. Study limitations include the small sample size and the fact that the majority of patients studied had relatively well-controlled type 2 diabetes; 12 (46%) patients had an HbA1c $\leq$ 48 mmol/mol. Also, it is important to emphasise that the POC intervals were from the time of sample acquisition to the time of result reporting. However, for laboratory analysis, the intervals were from the time of request to the time of result reporting. Therefore, the interval reported for laboratory analysis is an underestimation as it does not include the sample acquisition to laboratory arrival interval.

5. Conclusion

Measurement of glycated haemoglobin can be accurately and rapidly obtained using POC testing in the ICU. POC testing appears to be a feasible method to determine pre-existing glycaemic control in critically ill patients with type 2 diabetes.

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