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LABORATORY PREPAREDNESS FOR EBOLAVIRUS

Evaluation of point-of-care testing in critically unwell patients: comparison with clinical laboratory analysers and applicability to patients with Ebolavirus infection

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Summary

Data on the performance of point-of-care (POC) or near-patient devices in the management of critically unwell patients are limited, meaning that there are demands for confirming POC test results in the routine clinical laboratory and so potentially leading to delay in treatment provision. We evaluated the performance of the i-STAT CHEM 8+ and CG4+, Hemochron Signature Elite, HemoCue Hb 201+ and WBC Diff Systems on whole blood collected from medical and surgical patients admitted to the intensive care unit at an Australian tertiary care hospital. Measurements obtained for haematology, coagulation, biochemistry and arterial blood gas parameters using POC devices were compared against clinical laboratory analysers (XE-5000, STA-R Evolution, Dimension Vista 1500 and ABL800 FLEX). Bland–Altman and Passing–Bablok regression plots were constructed to assess agreement. Good correlation was defined as a bias of <10% between the POC device and the reference method. Forty arterial blood samples were collected from 28 patients. There was good correlation demonstrated for sodium, potassium, chloride, ionised calcium, glucose, urea, haemoglobin and haematocrit values (i-STAT Chem 8+); pH, pCO_2, bicarbonate and oxygen saturation (i-STAT CG4+); haemoglobin, white cell, neutrophil count and lymphocyte counts (Hemocue); and internationalised normal ratio (INR; Hemochron Signature Elite), but not creatinine, anion gap, pO_2, base excess, lactate, eosinophil count, prothrombin and activated partial thromboplastin time. POC devices were comparable to clinical laboratory analysers in measuring the majority of haematology, biochemistry and coagulation parameters in critically unwell patients, including those with infections. These devices may be deployed at the bedside to allow 'real-time' testing to improve patient care.

Key words: Biochemistry, coagulation, diagnostics, haematology, point-of-care.

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INTRODUCTION

Point-of-care (POC) testing is the fastest growing sector in the clinical *in vitro* diagnostic market, and is increasingly being used to improve patient outcomes by providing faster turnaround times (TAT). Traditional POC testing methods using immunochromatography and wire-guided droplet microfluidics for physiological measurements have been further complemented by multicore processors, microchips, high-resolution cameras and wireless communication to advance POC testing in areas of infectious diseases, cancer and cardiac care.

POC devices have the advantage of not requiring specialised laboratory equipment or expertise to operate, making them suitable for near patient deployment to provide rapid results in 'real-time' which translates to improved clinical decision-making and quality of care, and potentially lower healthcare costs. Confirmation of a clinical diagnosis by POC testing further obviates unnecessary testing and allows the timely provision of specific therapies. In the example of Ebolavirus infection or other diseases in remote settings, POC testing may be an alternative where routine laboratory services are unavailable, or when use of laboratory analysers may be inappropriate.

Data are limited on the performance of POC devices in critically unwell patients, particularly 'in the field'. Some POC devices were developed for specific populations in specific settings, and may not be fit for purpose when used outside these instances. Herein, we evaluate the performance of several POC devices in measuring haematology, coagulation, biochemistry and arterial parameters in critically unwell patients, and compare results obtained to clinical laboratory analysers.

METHODS

Clinical samples

Arterial blood samples were collected from medical and surgical patients admitted to the intensive care unit (ICU) at Westmead Hospital, a tertiary-level hospital with trauma, solid organ and high-risk haematopoietic stem cell transplantation services, and placed into the appropriate blood tubes [BD Vacutainer K2E (EDTA), LH PST II (lithium heparin) and Citrate tubes (3.2% sodium citrate; Becton Dickinson, USA)].

Samples were collected in duplicate, and tested immediately after collection in four separate POC devices: (1) i-STAT (Abbott Point of Care, USA), (2) Hemochron Signature Elite (ITC, USA), (3) HemoCue Hb 201+, and (4) HemoCue WBC Diff System (HemoCue, Sweden). Table 1 details the tests

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Table 1 Tests performed on the point-of-care devices

Instrument	Measurands
i-STAT CHEM 8+	Sodium, potassium, chloride, ionised calcium, glucose, creatinine, urea, haemoglobin, haematocrit and anion gap
i-STAT CG4+	pH, pCO_2, pO_2, base excess, bicarbonate, oxygen saturation and lactate
HemoCue Hb201+	Haemoglobin
HemoCue WBC Diff System	White blood cells, neutrophils, lymphocytes and eosinophils
Hemochron Signature Elite	Prothrombin time (PT), international normalised ratio (INR) and activated partial thromboplastin time (APTT)

performed by each device. In parallel, samples were also tested using the routine analysers XE-5000 (Sysmex, Japan), STA-R Evolution (Stago, France), Dimension Vista 1500 (Siemens, Germany) and ABL800 FLEX (Radiometer, Denmark).

Data analysis

Reference values were defined as measurements obtained using routine analysers. The difference between measurements obtained using laboratory analysers and POC devices were determined by subtracting the values obtained using the laboratory analyser from the POC device (POC measurement – laboratory analyser measurement). A positive bias indicates that the measurement obtained using the POC device was greater. By contrast, a negative bias indicates that the measurement obtained using the laboratory analyser was greater. Good correlation was defined as a bias of $<10\%$ between the POC device and the reference method.

Bland–Altman and Passing–Bablok regression plots were constructed using MedCalc Statistical Software version 15.2.2 (Belgium) to assess agreement between POC devices and routine laboratory analysers.

The Bland–Altman plot represents a scatter diagram of the differences of the two methods plotted against the averages of the two measurements.[1] The solid horizontal line shows the mean difference, whilst the interrupted horizontal line shows the limits of agreement, defined as the mean difference plus or minus 1.96 times the standard deviation of the differences. In brief, the mean, standard deviation, upper and lower limits of the differences between values obtained by POC devices and standard laboratory analysers were determined.

The Passing-Bablok regression plot shows the regression between the two methods.[2] The solid line represents the regression line, the dashed lines the confidence intervals (CIs) for the regression line and the dotted line indicates the identity line. Intercept and slope coefficient values and 95% CIs are presented. 95% CIs of intercept values that include 0 indicate the absence of systematic differences, whilst 95% CIs of the slope coefficient that include 1 indicate that there are no proportional differences.

RESULTS

Forty arterial blood samples were collected from 28 ICU patients (19 medical and 9 surgical) with diagnoses that included sepsis, shock (from sepsis and other causes), stroke, cardiac and/or respiratory failure and major trauma. The cohort included patients that had undergone haematopoietic stem cell or solid organ transplants (kidney and simultaneous pancreas-kidney).

Tables 2–4 detail the reference mean, reference range and the mean, standard deviation, upper and lower limits, intercept and slope coefficient of the differences between measurements obtained by POC devices and standard laboratory analysers. Figure 1 shows a representative Bland–Altman plot of sodium measured on the i-STAT Chem 8+ and Dimension Vista 1500. Figure 2 shows a representative Passing–Bablok plot of haemoglobin measured on HemoCue Hb 201+ and XE-5000.

In the samples tested in the present study, there was good correlation demonstrated for blood sodium, potassium, chloride, ionised calcium, glucose, urea, haemoglobin and haematocrit values for the i-STAT Chem 8+ device compared to the clinical laboratory analyser. Similarly, there was good correlation for pH, pCO_2, bicarbonate and oxygen saturation for the i-STAT CG4+ device. The Hemocue devices were comparable to the clinical laboratory analyser for haemoglobin, white cell, neutrophil count and lymphocyte counts. International normalised ratio (INR) was comparable on the Hemochron Signature Elite device.

A lack of correlation between POC devices and laboratory analysers were observed for creatinine and anion gap (i-STAT Chem 8+); pO_2, base excess and lactate (i-STAT CG4+); eosinophil count (HemoCue WBC Diff System); PT and activated partial thromboplastin time (APTT; Hemochron Signature Elite).

DISCUSSION

POC devices, by their nature, are instruments that provide rapid results at or near the bedside, obviating the need for formal diagnostic testing in many circumstances. They are particularly of value where specimens require inactivation prior to testing for safety reasons (such as those collected from patients with Ebolavirus infection or viral haemorrhagic fevers), since testing inactivated specimens in standard analysers may yield inaccurate results.[3]

In Australia, the magnitude of acceptable bias to determine if a POC device is accurate and therefore fit for purpose has not been defined. Evaluation of POC devices against an established reference method requires the testing of at least 40 samples covering a clinically meaningful range of the measurand, construction of a Bland–Altman plot and performance of a regression analysis of the results.[4] The Royal College of Pathologists of Australasia Quality Assurance Program (RCPA QAP) defines the allowable limits of performance for laboratory analysers,[5] but this does not specifically apply to POC devices. By contrast, acceptable performance limits for some measurands per the United Kingdom National External Quality Assessment Service (UK NEQAS) and United States' Clinical Laboratory Improvement Amendments (CLIA) require that all results should be within 10–15% compared to the reference measurement.[6] The present study defined an acceptable bias as $<10\%$ between the measurements obtained by the POC device compared to the reference method.

Evaluations of POC devices should not necessarily be based on absolute values of the measurands but the clinical impact of the magnitude of the observed differences, as methods that use percentage differences alone to assess agreement have been shown to correspond poorly with clinical decision-making.[7] As data on the performance of POC devices in critically unwell patients are limited, we assessed whether such devices are fit for purpose in this setting, including in the potential care for seriously ill patients with Ebolavirus disease.

The results herein showed good overall correlation with standard analysers for all the devices tested, with the exception of measurements of creatinine, anion gap, pO_2, base excess, lactate, eosinophil count, activated partial thromboplastin and prothrombin time. HemoCue systems have been previously shown to be comparable with clinical laboratory analysers for measuring haemoglobin and leukocyte counts on venous and capillary blood.[8] Concurrent with the report from Bäck *et al.*,