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Analytical

Analytical performance of three whole blood point-of-care lactate devices compared to plasma lactate comparison methods and a flow-injection mass spectrometry method

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ABSTRACT

Objectives: Point of care (POC) whole blood lactate testing may facilitate rapid detection of sepsis. We evaluated three POC methods against both plasma lactate comparison methods and a flow-injection mass spectrometric (MS) method.

Design and Methods: Nova StatStrip, Abbott i-STAT CG4 + and Radiometer ABL90 POC lactate methods were evaluated against the mean of Cobas Integra 400 and Vitros 350 plasma lactate. POC methods were also compared to a flow-injection mass spectrometric assay measuring lactate in $ZnSO_4$-precipitated whole blood extracts. Intra- and inter-assay precision was determined using quality control material. Method comparison included specimens from normal donors at rest, after exertion, and after spiking with lactic acid.

Results: Intra- and inter-assay coefficient of variation was <5% for i-STAT and ABL90; but ranged from 3.1–8.2% on two StatStrip meters. Mean (±SD) bias between POC and plasma lactate ranged from −0.2 ± 0.9 (i-STAT and ABL90) to −0.4 ± 1.2 (StatStrip) mmol/L. At concentrations >6 mmol/L, all POC methods showed proportional negative bias compared to plasma methods; but this bias was not observed when compared to the MS method. Despite proportional negative bias, all POC methods demonstrated acceptable concordance (94–100%) with plasma lactate within the reference interval (<2.3 mmol/L) and >4 mmol/L, commonly used clinical cut-offs for detection of sepsis.

Conclusions: POC lactate methods demonstrate acceptable concordance with plasma lactate across commonly used clinical cut-offs for detection of sepsis. Due to systematic negative bias at higher lactate concentrations, POC and plasma lactate should not be used interchangeably to monitor patients with elevated lactate concentrations.

1. Introduction

Sepsis is the systemic inflammatory response to infection and is one of the most common causes of in-hospital mortality. Sepsis is associated with increased risk of permanent physical and cognitive impairment, and a more than two-fold mortality risk after hospital discharge [1,2]. From 2001 to 2008 there has been a 70% increase in the incidence of sepsis in the US [3]. While this is undoubtedly a result of increased surveillance efforts, it can also be attributed to an increase in both the number and survival of immunocompromised patients. Not only has the CDC estimated that $14.6 billion was spent on sepsis hospitalizations from 1997 to 2008, but hundreds of billions of dollars have additionally been spent in pharmaceutical development over the years; with unsuccessful translation of findings from animal models into clinical practice [4]. However studies have shown that early sepsis detection can impact overall survival, as survival decreases by 7.6% with every hour delay in initiation of effective antimicrobials [5].

Lactate is instrumental in the early detection and diagnosis of sepsis [6,7] and can identify patients with tissue hypoperfusion who have not yet progressed to a hypotensive state. The sepsis recognition and resuscitation bundle, including point of care (POC) whole blood lactate

Non-standard abbreviations: POC, point of care; ED, emergency department; FDA, United States Food and Drug Administration.

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measurement, has resulted in improved time to start fluid resuscitation in emergency department (ED) patients [8] and improved compliance with sepsis resuscitation guidelines in the ICU [9]; both of which are associated with decreased mortality from sepsis. Early goal-directed therapy using POC lactate has also been shown to improve outcomes after cardiovascular surgery [10]. In light of this and other evidence, the National Academy of Clinical Biochemistry guidelines on Evidence-based Practice for Point of Care Testing conclude that more rapid turnaround time of lactate results in critically ill patients, leads to improved clinical outcomes [11]. The evidence supporting rapid lactate measurement in critically ill patients has stimulated increased interest in the use and accuracy of whole blood lactate assays.

Several studies have examined the accuracy of cartridge-based blood gas analyzers for near-patient measurement of whole blood lactate, finding that these devices correlate well with laboratory methods and are appropriate to use for sepsis detection [12–16]. However, not all of these devices are small enough to be used in all critical care environments, and per test cost is significantly higher than for laboratory measurement. Hand-held, strip-based whole blood lactate meters have been available for some time, but they have primarily been evaluated for use in sports medicine [17]. It was only recently that a strip-based method (Nova StatStrip) received FDA-approval for hospital use in the US. We compared the precision, accuracy and clinical concordance of two handheld single-use POC lactate devices (one strip-based meter and one single use cartridge-based blood gas analyzer) and a near-patient multi-use cartridge-based blood gas analyzer, using the average of two plasma lactate methods as an internal reference method. We also assessed POC whole blood lactate accuracy using a $ZnSO_4$ precipitated whole blood flow-injection mass spectrometry comparison method.

2. Materials and methods

This study included the measurement of POC whole blood lactate on the i-STAT single-use cartridge-based analyzer (Abbott Diagnostics, Princeton NJ), the StatStrip lactate analyzer (Nova Biomedical, Waltham MA), and the ABL90 multi-use cartridge-based blood gas analyzer (Radiometer, Bronshoj Denmark). Measurements were performed in duplicate on two separate StatStrip meters, in duplicate on one i-STAT meter, and in duplicate on one of two ABL90 blood gas analyzers.

Precision of POC lactate methods was assessed by performing 20 measurements within-day and 20 measurements over 10–20 days using two levels of vendor-specific commercial quality control (QC) material. Linearity was assessed by triplicate measurement of commercially available linearity material at four or more levels covering the analytical measuring range of each method. The method precision was evaluated by calculating the percent coefficient of variation (CV) for intra- and inter-assay precision.

Accuracy studies were performed by collecting specimens from normal donors at rest ($n = 15$), after exertion ($n = 41$) and with lactic acid-spiked samples ($n = 25$) for a total of 81 samples with lactate concentrations ranging from 0.3 to 17.3 mmol/L. Each normal donor, either at rest or after exertion, had blood collected into a 10 mL plain non-anticoagulant syringe, a 3.0 mL lithium heparin syringe and two 2 mL grey-top sodium fluoride/potassium oxalate (grey-top) plasma Vacutainer tubes (BD, Franklin Lakes NJ). The lithium heparin syringe used for i-STAT, ABL90 and StatStrip methods was run within 5 min of collection. Grey-top tubes were centrifuged at 4000 $\times g$ for 3 min for plasma lactate analysis. To minimize pre-analytical effects of ongoing glycolysis despite potassium oxalate inhibition, plasma lactate measurement was completed within 2 h of blood draw. For each donor, 1 mL of the remaining non-anticoagulated whole blood was precipitated with 2 mL of 0.1 mmol/L ZnSO4, then centrifuged at 14,000 $\times g$ for 5 min and frozen at −70 °C for later testing by the mass spectrometry method.

For the lactic acid-spiked samples, 20 mL whole blood was collected from normal donors into a plain syringe and spiked with various concentrations of lactic acid prepared in 0.9% saline. After mixing the whole blood was then quickly transferred to one 3.0 mL lithium heparin syringe, two 2 mL grey-top tubes, and (1 mL) of whole blood was precipitated with 2 mL of 0.1 mmol/L $ZnSO_4$ as described above for MS testing. The study design was approved by the Mayo Clinic Institutional Review Board.

The lack of a consensus reference method for lactate measurement poses a significant problem for comparison studies. The Vitros LAC slide (Ortho Clinical Diagnostics, Rochester NY) assay was originally validated by the manufacturer against an ion exclusion chromatography method. It showed excellent agreement with this non-enzymatic method (slope 0.99, intercept 0.02 mmol/L, correlation coefficient 1.00, samples ranged from 1.0–13.6 mmol/L). The Roche Lactate Gen.2 assay (Roche Diagnostics, Indianapolis IN) was validated by the manufacturer by comparing results to the same reagent run on a Hitachi 917 analyzer, and by comparing to results of a previous generation lactate assay run on the Integra [13]. Commercial QC material analyzed daily in our laboratory at lactate concentrations of 1–5 mmol/L demonstrated precision (CV) of <3% for Vitros and Integra plasma lactate.

We previously found that Vitros LAC and Roche Lactate Gen.2 assays correlate very well (slope 0.95, r [2] 0.99), and have 99% concordance for classification of sepsis. Based upon these results, we proposed use of the average of Vitros LAC and Roche Gen.2 lactate as a plasma reference method for POC comparisons [13]. Mean bias (± standard deviation) between whole blood lactate methods and the plasma lactate was determined. Linear regression was performed to determine the relationship between POC whole blood and plasma lactate concentrations

Since there are no generally accepted reference methods for lactate measurement, POC whole blood lactate accuracy was also assessed by comparison to $ZnSO_4$ precipitated lactate measured by a flow-injection mass spectrometry method (MS lactate). MS lactate was determined following treatment with $ZnSO_4$ and centrifugation at 14,000 $\times g$ for 5 min. 10 μL of whole blood extract was added to 100 μL of acetonitrile containing 1 mmol/L $^{13}C_3$-lactate then centrifuged for an additional 5 min at 14,000 $\times g$. For analysis 5 μL of this prepared specimen was injected into mobile phase consisting of 80% acetonitrile at a flow rate of 300 μL/min. Mass spectrometric analysis was performed with an Applied Biosystems 3200 QTRAP (SCIEX, Framingham MA, USA) operating in negative ion mode, coupled to an Agilent 1200 series HPLC system (Agilent, Santa Clara CA, USA). Precursor/product pairs were 89/43 and 92/45 for lactate and $^{13}C_3$-lactate, respectively. The assay was calibrated with each run at concentrations of 0.25, 1.0, 5.0, and 10.0 mmol/L and analysis was performed using Analyst software (Version 1.4.2, SCIEX, Framingham, MA, USA). Precision was determined by triplicate analysis of plasma pools over 5 days (deproteinized on each day of analysis) and ranged from 5–10% CV at concentrations of 0.25, 1.0, and 4.5 mmol/L ($n = 45$). Accuracy was confirmed by comparison with an enzymatic (LDH) technique generating NADH monitored at a wavelength of 340 nm. Regression of the MS lactate assay vs. the enzymatic technique ($n = 21$) with lactate concentrations from 1–5 mmol/L yielded the following regression equation: $y = 1.04x - 0.21$ with an $r^2 = 0.88$ correlation coefficient (Data Supplement A). POC whole blood lactate methods were compared to the average of two replicate measurements by the MS method, using both linear regression and mean bias (± standard deviation) to assess accuracy.

Precision and accuracy criteria for whole blood lactate measurements were derived from a previous study that used standard deviation of duplicates to assess the biological variability of lactate both within the normal range and at elevated lactate concentrations [18]. The biologic variability within the normal range was found to be quite high (~20%), such that significant analytic error could be tolerated for normal lactate values. These findings support the use of a generous error tolerance (30%), as used by previous investigators to assess whole blood lactate accuracy at lower concentrations [15]. However, biological variability at higher (>4 mmol/L) lactate was only ~10% in this study [18], suggesting a need for better precision and accuracy at higher