Clinica Chimica Acta 468 (2017) 145–149

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Validation of a hand-held point of care device for lactate in adult and pediatric patients using traditional and locally-smoothed median and maximum absolute difference curves

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ARTICLE INFO

Article history:
Received 18 December 2015
Received in revised form 18 February 2017
Accepted 20 February 2017
Available online 21 February 2017

Keywords:
Lactate
Point-of-care
Trauma
Sepsis
Pre-hospital
Validation
Locally-smoothed median absolute difference curve
Locally-smoothed maximum absolute difference curve

ABSTRACT

Background: Lactate is commonly used in septic patients and is a viable biomarker for trauma patients. Its pre-hospital use could assist triaging and managing patients with these conditions.
Methods: We evaluated the analytical performance of the point-of-care (POC) StatStrip Xpress Lactate Meter (Nova Biomedical) and compared it to the ABL 800 (Radiometer). We measured lactate in 250 adult and 250 pediatric whole blood samples in 2 laboratories. The performance of the POC meter was assessed by traditional linear regression and Bland-Altman plots, and locally-smoothed (LS) median absolute difference and maximum absolute difference (MAD and MaxAD) curves.
Results: The StatStrip was linear with acceptable reproducibility at clinically relevant concentrations. Correlation with the ABL800 showed a negative bias for both populations with slope, bias ± SD (% bias) of 0.78, −0.4 ± 0.7 (−14.5%) in children and 0.80–0.3 ± 0.6 (−13.3%) in adults. The proportional bias appeared more significant at concentrations >4 mmol/l (36.0 mg/dl). The StatStrip misclassified 7.6 and 8.8% pediatric and adult samples, respectively, to lower risk categories defined using guidelines driven cut-offs. The LS MAD curves identified one breakout, concentration where the LS MAD exceeds the total allowable error limit of 0.3 mmol/l (2.7 mg/dl), at lactate concentrations of 3.8 and 3.2 mmol/l (34.2 and 28.8 mg/dl) in the pediatric and adult curves, respectively. Breakthroughs, points at which the LS MaxAD curve exceeds the 95th percentile of MaxADs, occur at concentrations above 7.5 mmol/l (67.6 mg/dl) for both populations where the performance of the POC meter became erratic. We concluded that if serial lactate measurements are performed, the same method should be used for baseline and follow up measurements. The LS MAD and LS MaxAD curves allowed visual and quantitative mapping of the performance of the lactate POC meter over the range of concentrations measured.
Conclusions: This approach seems useful for the identification of points at which the performance of a POC meter differs significantly from a comparison method and thresholds of poor analytical performance.

1. Introduction

Lactate is useful in the assessment of septic and injured patients. Early identification and prompt treatment can reduce mortality. When sepsis is suspected, adult national guidelines recommend measuring lactate promptly [1]. Increased lactate is associated with increased morbidity and mortality [2,3]. Injury-related mortality, can be reduced by triaging patients to a trauma center. Lactate is a viable biomarker of severely injured patients. Increased lactate correlates with increased morbidity and mortality [4–7] and adding lactate to trauma triaging could increase sensitivity [6,8].

The increasing availability of point-of-care (POC) lactate devices could facilitate pre-hospital measurement of lactate to guide interventions, assess risk and determine destinations. This study verified the analytical performance of the StatStrip Xpress Lactate Meter (Nova Biomedical), a handheld POC device that could be used in the pre-hospital setting. We studied the correlation of the POC meter and the ABL 800 (Radiometer) in heparinized WB samples and characterized the potential impact of serial lactate measurements for prognosis. Traditional

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http://dx.doi.org/10.1016/j.cca.2017.02.015
0009-8981/

method correlation consists of linear regression analysis. Another group has used locally-smoothed (LS) median absolute difference (MAD) and maximum absolute difference (MaxAD) curves for the evaluation of hospital POC glucose meters [9,10]. This approach was used to assess the overall performance of glucose meters not only statistically but also visually, to distinguish the performance of clinically acceptable from clinically unacceptable meters and to pinpoint ranges at which the quality of results of a given meter was below performance specifications. Kost et al. [9] claimed that this set of non-parametric tools could be used to evaluate the performance of other POC tests. We employed this statistical approach to assess the comparability of lactate measured in the handheld POC device and the ABL 800. To accomplish this, we drew LS MAD curves and their non-parametric 95% confidence intervals. We identified the breakout point, the concentration at which the performance of the meter started to deteriorate, using a total allowable error of 0.3 mmol/l (2.7 mg/dl). We also drew LS MaxAD and identified where breakthroughs occur. Breakthroughs are points that demonstrate erratic behavior of the meter, defined here as any point in which the Max AD exceeded the 95th percentile of Max AD.

2. Materials and methods

We measured whole blood (WB) lactate in the ABL800 (Radiometer) and the StatStrip Xpress POC meter (Nova Biomedica). There is no recognized reference method for lactate. Since our standard practice is to measure WB lactate in the ABL800 Flex system, this was used as the reference instrument for this study. Both instruments measure lactate by enzymatic reaction and amperometric detection.

The study used residual and de-identified venous and arterial specimens collected in heparinized syringes and included 250 pediatric (<18 years) and 250 adult (≥18 years) samples sent for blood gas analysis to the Children's Hospital of Wisconsin (CHW) laboratory or to Wisconsin Diagnostic Laboratories (WDL) at Froedtert Memorial Lutheran Hospital, respectively. The study was approved by the Medical College of Wisconsin institutional review board.

Within-day imprecision was assessed using 2 concentrations of StatStrip lactate control material and 3 WB specimens with low, mid and high concentrations, each analyzed 10 times. Between-day and total imprecision were assessed using 2 concentrations of control material, each analyzed in 3 runs per day for 5 days, according to EP-15A3 [11]. Percent coefficients of variation (%CV) were calculated. %CVs were considered acceptable if <5% for concentrations >4.0 mmol/l, as that corresponded to a standard deviation of 0.2 at that concentration and <10% for samples with concentrations <4.0 mmol/l, corresponding to and SD of approximately 0.1 for a sample with concentrations as low as 1.0 mmol/l. The analytical measurement range (AMR) of 0.3 to 20.0 mmol/l (2.7–180.2 mg/dl) was verified using Nova's linearity check materials ranging from 0.6 to 17.0 mmol/l (5.4–153.2 mg/dl). Acceptability criteria for the lowest and highest sample used for the AMR verification required their range of concentrations to be within ±0.5 mmol/l and ±30%, respectively. Accuracy was evaluated by comparing results between the StatStip Xpress POC meter and the ABL800 in the adult and children laboratories. The ranges of concentrations of the samples were 0.4–18.5 mmol/l (3.6–166.7 mg/dl) and 0.3–17.5 mmol/l (2.7–157.7 mg/dl) in pediatric and adult samples, respectively. Upon receipt in the laboratory, samples were tested in the ABL 800 within 15 min of collection, per laboratory policy and then immediately (target of within 2 min) using the POC meter. Adult samples were measured in duplicate using two ABL800s and one StatStrip Xpress meter. Pediatric samples were measured in duplicate on one StatStrip Xpress meter and when possible on the ABL800s. Samples were not allowed to sit to obtain higher lactate results. The pre-defined acceptability criteria used was a total allowable error (TAE) of 0.3 mmol/l. Results were analyzed using EP Evaluator (Data Innovations, LLC).

We calculated median absolute differences (MAD) and maximum absolute differences (MaxAD), and constructed locally smoothed (LS) MaxAD (bandwidth = 0.4 mmol/l) and MAD curves (bandwidth = 1 mmol/l) and reported its non-parametric 95% pointwise confidence intervals as described previously (reference). Calculation of curves was programmed using R 3.3.1 [12]. Breakouts were defined as the point(s) where the MADs exceeded the TAE of 0.3 mmol/l. Breakthroughs represented the concentrations where the MaxADs exceeded the 95th percentile.

3. Results

Control materials with average concentrations of 0.8 and 5.8 mmol/l (7.6 and 52.1 mg/dl) were used to determine reproducibility of the StatStrip Xpress in 10 consecutive runs. The meter shows %CVs of 11.5% and 4.8% for QC concentrations 1 and 2, respectively. WB samples with lactate concentrations of 1.0, 3.7 and 14.0 mmol/l (8.1, 33.5 and 125.8 mg/dl) had inter-run %CVs for of 12.4%, 4.9% and 1.8%, respectively. Samples with lower lactate concentrations showed higher imprecision, unrelated to potential increases of lactate over time in WB samples, as QC material and WB samples showed similar impression. Assessment of imprecision over time using CLSI EP-15A3 guidelines, showed total %CVs of 10.6% and 4.2%. The reproducibility at the low end is comparable to the manufacturer claim of %CV of 9.1% at a mean of 0.8 mmol/l and within the TAE for imprecision. The imprecision observed at higher concentrations is within the %CV of 5% defined as acceptable.

The lactate StatStrip method was linear over the analytical measurement range. The least-squared linear regression of the measured versus expected concentrations had a slope of 0.84 and intercept of 0.38. The materials used for verifying linearity and AMR had target concentrations ranging from 0.6 to 17.0. Triplicate measurements resulted in concentrations ranging from 0.8 to 14.7 (5.4–132.4 mg/dl), with percent recoveries going from 125% to 87%, with increasing material concentrations.

Deming regression analyses (Fig. 1) for each population showed the following slope and intercept with their respective 95th confidence interval (CI), and coefficient of determination (R^2): Children: slope = 0.78 (0.77–0.80), intercept = 0.22 (0.16–0.28), R^2 = 0.97 (Fig. 1A). Adults: slope = 0.80 (0.79–0.82), intercept = 0.20 (0.14–0.25), R^2 = 0.98 (Fig. 1B).The mean bias ± SD (% bias) between methods was −0.4 ± 0.7 (−14.5%) in children and −0.3 ± 0.6 (−13.3%) in adults. Correlation between the two methods in the subrange of concentrations up to 4 mmol/l had a slope of 0.87 in children and 0.90 in adult samples. The bias (% bias) in that subrange was −0.1 (−8.7%) in children and −0.1 (−7.1%) in adults. In contrast, the bias (% bias) in the subrange >4.0 mmol/l was −1.4 (−20.9%) in children and −1.3 (−20.0%) in adults. The samples were classified into risk categories, low (≤2.0 mmol/l), intermediate (2.1–3.9 mmol/l) and high (≥4 mmol/l) to assess the clinical relevance of these differences (Table 1) [13]. Low risk categorization between the methods agreed in 99% and 100% of the pediatric and adult samples and ranged from 78 to 88% for the intermediate and high risk categories. The POC method classified 19 (7.6%) pediatric samples into lower risk categories (high to moderate risk-7 samples, moderate to low risk-12 samples) and 1 sample (0.4%) into a higher risk group. Twenty-two (8.8%) adult samples were classified into lower risk categories (high to moderate risk and moderate to low risk-11 samples each). The lactate medical decision points of 2 and 4 mmol/l for the ABL800, represented in Fig. 1 by dotted lines, were calculated as 1.8 and 3.4 mmol/l for the StatStrip Xpress (CI = 1.8–1.8 and 3.4–3.5 for adult and 1.7–1.8 and 3.3–2.4 for pediatric samples). Using these cut-offs for risk assessment in the StatStrip Xpress, discrepant classifications into lower risk categories decreased to 2 (0.8%) and 8 (3.2%) pediatric and adult samples, respectively, at the expense of a slight increase in samples classified into higher risk groups (8 (3.2%) and 3 (1.2%) pediatric and adult samples, respectively).

Fig. 2 displays the integrated LS MAD and MaxAD curves for lactate over the range of lactate concentrations measured in pediatric