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Original Research

CRITICAL CARE

Whole Blood Lactate Kinetics in Patients Undergoing Quantitative Resuscitation for Severe Sepsis and Septic Shock

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Background: **We sought to compare the association of whole-blood lactate kinetics with survival in patients with septic shock undergoing early quantitative resuscitation.**
Methods: **This was a preplanned analysis of a multicenter, ED-based, randomized, controlled trial of early sepsis resuscitation. Inclusion criteria were suspected infection, two or more systemic inflammation criteria, either systolic BP < 90 mm Hg after a fluid bolus or lactate level > 4 mM, two serial lactate measurements, and an initial lactate level > 2.0 mM. We calculated the relative lactate clearance, rate of lactate clearance, and occurrence of early lactate normalization (decline to < 2.0 mM in the first 6 h). Area under the receiver operating characteristic curve (AUC) and multivariate logistic regression were used to determine the lactate kinetic parameters that were the strongest predictors of survival.**
Results: **The analysis included 187 patients, of whom 36% (n = 68) normalized their lactate level. Overall survival was 76.5% (143 of 187 patients), and the AUC of initial lactate to predict survival was 0.64. The AUCs for relative lactate clearance and lactate clearance rate were 0.67 and 0.58, respectively. Lactate normalization was the strongest predictor of survival (adjusted OR, 5.2; 95% CI, 1.7-15.8), followed by lactate clearance ≥ 50% (OR, 4.0; 95% CI, 1.6-10.0). Lactate clearance ≥ 10% (OR, 1.6; 95% CI, 0.6-4.4) was not a significant independent predictor in this cohort.**
Conclusions: **In patients in the ED with a sepsis diagnosis, early lactate normalization during the first 6 h of resuscitation was the strongest independent predictor of survival and was superior to other measures of lactate kinetics.**
Trial registry: **ClinicalTrials.gov; No.: NCT00372502; URL: clinicaltrials.gov**

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Abbreviations: IQR = interquartile range; ROC = receiver operating characteristic; $Scvo_2$ = central venous oxygen saturation; SOFA = sequential organ failure assessment

Severe sepsis is a global health problem, resulting in at least 750,000 hospitalizations annually in the United States.[1,2] Approximately 500,000 of these hospitalizations will be treated in US EDs.[3] Early and aggressive quantitative resuscitative care is recommended for the treatment of septic shock[4] and meta-analytic data have shown its efficacy at reducing mortality.[5] However, presently there remains uncertainty about the optimal goals of early resuscitation, particularly regarding the roles of central venous oxygen saturation ($Scvo_2$) and lactate clearance.[6,7]

Elevated serum lactate measurements have been demonstrated to be independently associated with poor outcome in patients in the ED with infection.[8] Previous investigations have documented that a lactate clearance of 10% during early sepsis resuscitation is independently associated with survival, a finding which persists even after adjusting for confounders.[9,10] Previous work by our group found that in patients undergoing quantitative resuscitation for septic shock, achievement of a $Scvo_2 \geq 70\%$ had a similar prognosis as achievement of a lactate clearance of 10%. However, failure to achieve a lactate clearance of 10% was associated with a mortality rate of 41% vs 8% if patients failed to achieve a $Scvo_2$ of 70% (proportion difference 33%, 95% CI, 9%-55%).[11] These data suggest that lactate clearance parameters may have better

For editorial comment see page 1521

characteristics as resuscitation goals; however, it remains unclear which are the optimal lactate parameters to target during resuscitation. Accordingly, we sought to compare the relative value of various measures of whole-blood lactate kinetics to predict survival in patients with septic shock undergoing early quantitative resuscitation.

Materials and Methods

Study Design

We conducted a preplanned analysis of a prospective, parallel group, nonblinded, randomized clinical trial designed to assess the noninferiority of lactate clearance vs $Scvo_2$ as the protocol end point evaluating the adequacy of oxygen delivery during early sepsis resuscitation.[12] The multicenter trial took place from January 2007 to January 2009 at Carolinas Medical Center, Charlotte, North Carolina; Beth Israel Deaconess Medical Center, Boston, Massachusetts; and Cooper University Hospital, Camden, New Jersey, all of which are large, urban, tertiary care hospitals staffed by emergency medicine resident physicians supervised by board-certified emergency medicine attending physicians. The study was approved by the institutional review board of Carolinas Healthcare System (09-06-02A), and all participants or their surrogates provided written informed consent for participation. The trial was registered on clinicatrials.gov, identifier NCT00372502.

The detailed methods of the study have been described previously.[12] In brief, consecutive patients presenting to one of the participating EDs were eligible for enrollment if they were aged > 17 years, had confirmed or suspected infection, two or more systemic inflammatory response criteria,[13] and hypotension after fluid challenge or a blood lactate concentration of ≥ 4 mM. After enrollment, patients were randomly assigned to one of two groups. Each group received structured quantitative resuscitation while in the ED with iterative steps of IV crystalloid to achieve a central venous pressure > 8 mm Hg, followed by vasopressors to obtain a mean arterial pressure > 65 mm Hg, and finally packed RBC transfusion or administration of inotropes to achieve a $Scvo_2$ ≥ 70% or a lactate clearance of 10%, depending on treatment group assignment. The study protocol was continued until all end points were achieved or for a maximum of 6 h. The published results of this study showed a 6% (95% CI, −3% to 14%) in-hospital mortality difference favoring the lactate clearance group, confirming the primary hypothesis of noninferiority between the two resuscitation end points.[12]

As a part of the study protocol, research staff was instructed to perform blinded measurements of lactate clearance if patients were randomized to the $Scvo_2$ arm. Blinded lactate measurements were performed by the research coordinator on a bedside point-of-care device, and results were printed onto a hard copy that was immediately gathered by the research coordinator. Measurements were performed using a deidentified patient identification number, which did not synchronize with the electronic medical record, and the treating clinicians had no way to access the data. At the suggestion of our hospital regulatory board, the simultaneous blinded measurements were encouraged, but not mandated, and, therefore, we expected they would not be performed on all subjects. Initial point-of-care lactate measurements were typically performed on the first blood draw, prior to any resuscitation except prehospital fluids. For the present study, we included patients with an abnormal initial lactate (≥2 mM) who received at least two lactate measurements in the first 6 h of resuscitation in the ED.

Data Analysis and Outcomes

The primary outcome was in-hospital survival. Demographics and baseline characteristics of survivors were compared with those of nonsurvivors. Continuous data were compared using *t* tests or Mann-Whitney tests, and categorical data were compared using χ^2 or Fisher exact tests, as appropriate.

Normalization of lactate was defined as a lactate decline to < 2.0 mM. Absolute clearance (initial value minus delayed value), relative clearance (absolute clearance divided by initial value and the result multiplied by 100), and clearance rate (relative clearance divided by clearance time) were calculated. Receiver operating characteristic (ROC) curves were constructed for the ability of initial lactate, absolute clearance, relative clearance, and clearance rate to predict survival, and the area under the curve was calculated. Based on the ROC curves, lactate clearance cutoffs maximizing sensitivity and specificity were selected. Data were analyzed and ORs predicting survival between groups meeting and those failing to meet these various predefined lactate clearance parameters were calculated using Fisher exact tests with 95% CI.

To account for potential confounders, a multivariate logistic regression model was created using in-hospital survival as the dependent variable. Candidate variables were selected based on known predictors of mortality and differences in survivors and nonsurvivors in the bivariate analysis, and the model was refined using reverse stepwise elimination. Adjusted ORs were calculated and are presented with 95% CIs. A post hoc subgroup analysis was performed in patients receiving catecholamine infusion vs patients who did not. Catecholamine infusion was defined as administration of dopamine or norepinephrine at any dose for any period of time while the patient was undergoing resuscitation in the ED and serial lactate measurements were being measured. As patients could have been enrolled in the study with hypotension but without an elevated lactate level, a portion of patients in our study had a lactate level between 2 mM and 4 mM, thus, a post hoc analysis evaluating measures of lactate clearance was conducted in this subgroup as well. All statistical tests were two sided with $P < .05$ considered significant. Data were analyzed using commercially available statistical software (StatsDirect 2.7.7; StatsDirect Ltd and Stata 10.0; StataCorp LP).

Results

Of 272 patients who had two serial lactate measurements, an initial lactate level ≥ 2 mM was present in 187 (69%), which composed the final study group. The

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