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Original Contribution

Lactate clearance and mortality in septic patients with hepatic dysfunction☆

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ABSTRACT

Background: Serum lactate clearance (LC) during initial resuscitation is a potentially useful prognostic marker in patients with severe sepsis or septic shock. However, it is unclear whether LC is also associated with the outcome in septic patients with hepatic dysfunction that may impair lactate elimination, which may contribute to elevated serum lactate levels or decreased LC.
Methods: The relationships between LC measured within 6 and 24 h after initial resuscitation and hospital mortality were evaluated with multiple logistic regression analysis.
Results: Of 770 patients with severe sepsis or septic shock, 208 (27%) with hepatic dysfunction were included in the analysis. The median LC within 6 h in survivors (31.4%) was significantly higher than that of non-survivors (9.3%) ($P = .010$). In addition, the median LC within 24 h was also significantly different between groups (51% vs. 12%, $P < .001$). Low LCs, defined as less than 10% of clearance, at 6 and 24 h were associated with in-hospital mortality. After adjusting for potential confounding factors, low LCs at 6 and 24 h remained associated with hospital mortality (adjusted OR 4.940, 95% CI 1.762-13.854 at 6 h; adjusted OR 5.997, 95% CI 2.149-16.737 at 24 h). However, LC at 24 h (area under the curve of 0.704) had higher discriminatory power to predict hospital mortality than LC at 6 h (area under the curve of 0.608) ($P = .033$).
Conclusions: LC may be useful for predicting outcomes in septic patients with hepatic dysfunction.
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1. Introduction

Systemic imbalances between oxygen delivery and demand cause tissue hypoxia [1], and inadequate tissue oxygenation increases serum lactate via anaerobic glycolysis [2]. Many studies have reported that serum lactate is a potentially useful marker of global tissue hypoxia in patients with circulatory failure, including sepsis [3,4]. Therefore, increased lactate levels have been used as surrogate markers of tissue hypoperfusion and disease severity in patients with severe sepsis or septic shock [3–8]. However, single measurements of lactate level are difficult to interpret, since they represent the balance between lactate production and elimination [9–11]. Therefore, serial lactate measurements are more important than single lactate measurements as outcome prognosticators [12–14] and are useful to guide initial resuscitation [15,16] in cases of severe sepsis or septic shock.

Lactate is primarily cleared by the liver, but the kidneys and skeletal muscles are also involved [2]. In normal individuals, about half of the lactate produced is removed from the circulation by the liver [17]. Therefore, in patients with hepatic dysfunction, impaired lactate elimination may contribute to elevated serum lactate levels or decreased lactate clearance (LC) [18,19]. We recently reported that elevated serum lactate levels are associated with outcome even in septic shock patients with hepatic dysfunction [11], consistent with a previous report that initial serum lactate is associated with mortality independent of organ dysfunction [8]. However, it is unclear whether early LC during the first 6 h of initial resuscitation is also associated with outcome in septic patients with hepatic dysfunction. Therefore, we evaluated early LC measured during initial resuscitation for severe sepsis or septic shock as a potential prognostic marker of mortality even in patients with hepatic dysfunction. In addition, we compared the predictive performance of early LC with that of delayed LC in patients with hepatic dysfunction that may impair lactate elimination.

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2. Materials and methods

We analyzed the sepsis registry at Samsung Medical Center (a 1960 bed, university-affiliated, tertiary referral hospital) to identify patients presenting to the emergency department (ED) who met criteria for severe sepsis or septic shock for whom data were prospectively collected from August 2008 to March 2012. We previously used this registry in studies of severe sepsis and septic shock [20–24]. The study was approved by the Institutional Review Board of Samsung Medical Center to review and publish information obtained from patient records (approval number 2014–08-083). The institutional review board waived the need for written informed consent from the patient because of the observational nature of the study. In addition, patients' information was anonymized and de-identified prior to analysis.

2.1. Study population

We included patients 18 years of age or older who presented with severe sepsis or septic shock. Severe sepsis was defined as sepsis associated with acute organ dysfunction [25]. Septic shock was defined as sepsis with acute circulatory failure characterized by persistent arterial hypotension (systolic arterial pressure <90 mmHg, mean arterial pressure <60 mmHg, or a reduction in systolic blood pressure >40 mmHg from baseline) despite adequate volume resuscitation [25]. Patients who were younger than 18 years old were transferred from another hospital, had limitations on decision-making regarding care, or had poor performance with metastatic cancer unresponsive to chemotherapy or radiation therapy were excluded from this study.

2.2. Initial resuscitation and hemodynamic management for severe sepsis or septic shock

A specific protocol for early recognition and management of patients with severe sepsis or septic shock was implemented at our institution. Additionally, to improve compliance with the initial resuscitation bundle and management for sepsis, we revised, approved, and promoted our early goal-directed therapy (EGDT) protocol with an educational program named Emergency Approach to Sepsis Treatment in early 2008 [20]. All patients were managed according to our EGDT protocol, which is an adaptation of the protocol outlined by Rivers et al [26]. Once a patient met the criteria for severe sepsis or septic shock, fluid resuscitation and hemodynamic monitoring were initiated with placement of a central venous catheter with the internal jugular or subclavian vein approach for central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$) monitoring. Broad-spectrum antibiotics were administered as soon as possible. Hemodynamic resuscitation was conducted according to a prespecified treatment plan. First, isotonic crystalloid was administered in boluses to target CVP ≥8 mmHg. Second, systolic blood pressure ≥90 mmHg or mean arterial pressure ≥65 mmHg, if not achieved with fluid administration, was targeted by initiating and titrating vasopressors (preferably norepinephrine as a first-line agent) to achieve this desired blood pressure goal. Finally, $ScvO_2$ ≥70% was targeted after CVP and blood pressure goals were met. If the $ScvO_2$ was lower than 70% and the hematocrit was lower than 30%, packed red blood cells were transfused to achieve a hematocrit of at least 30%. If the $ScvO_2$ remained lower than 70% after the hematocrit was 30% or higher, dobutamine was initiated and titrated in attempts to achieve $ScvO_2$ ≥70% at the treating physician's discretion. Mechanical ventilation was initiated if necessary. However, subsequent lactate measurements after initiation of resuscitation were not used for goal-directed resuscitation.

2.3. Data collection

The following data were obtained from our sepsis registry and electronic medical records: general characteristics of patients including demographic data, infection source, type of shock, and laboratory measurements including serial lactate measurements, amount of fluid administered, and dose of vasopressor. Sequential Organ Failure Assessment (SOFA) scores [27] were calculated to assess the severity of illness at the time of diagnosis of severe sepsis or septic shock from the obtained data. We assessed compliance of resuscitation bundles and interventions by the initiation (yes or no) of particular bundles or interventions, as previously reported [20]. Hepatic dysfunction was defined as a serum total bilirubin >2 mg/dL [8,11,28].

Serum lactate concentration (mmol/L) was measured with a serum-based enzymatic colorimetry method, using a Modulator DDP analyzer (Roche Hitachi, Tokyo, Japan). Initial serum lactate concentrations were measured when patients arrived at the ED (H_0) and subsequent serum lactate measurements were repeated at 6 and 24 h (H_6, H_{24}) after initiation of resuscitation according to our protocol. LCs were defined using the following formula: lactate at ED presentation (H_0) minus lactate at 6 and 24 h (H_6, H_{24}) after initiation of resuscitation divided by lactate at ED presentation, then multiplied by 100, as presented with LC_6 and LC_{24}, respectively. Finally, we documented outcomes of septic patients with hepatic dysfunction including in-hospital mortality and length of stays in the hospital. To determine the relationships between each LC and in-hospital mortality, cutoff value for each LC was defined as a decrease ≥10% from initial based on previously published data [13–15].

2.4. Statistical analysis

Data are presented as medians and interquartile ranges (IQR, 25th and 75th percentiles) for continuous variables and as numbers (percentages) for categorical variables. Data were compared using the Mann-Whitney *U* test for continuous variables and the chi-square or Fisher's exact test for categorical variables.

Multiple logistic regression analysis was used to adjust for potential confounders in the associations between different LCs and hospital mortality [29]. Three models were constructed for LC_6 and LC_{24}, respectively: the first models were adjusted for age, gender, and initial lactate levels; the second models were additionally adjusted for severity of illness assessed by SOFA score, site of infection, and compliances of resuscitation bundles; and the final models additionally included factors with *P* values less than .2 on univariate analyses as confounding factors [30]. To reduce the risk of multicollinearity, one variable from closely correlated variables was a candidate for inclusion in the final model and the variance inflation factor was evaluated. LC_6 and LC_{24} were separately put into regression models. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated in the final models. The Hosmer-Lemeshow test was used to check the goodness-of-fit of the final logistic regression model. The predictive performance of each LC was assessed by calculating the area under each receiver operating characteristic (ROC) curve. Values for the estimated area under the curve (AUC) were compared by using the Hanley-McNeil test [31].

All tests were 2-sided, and $P < .05$ was considered significant. The data were analyzed using IBM SPSS 20 (IBM, Armonk, NY) for descriptive analysis and STATA 11 (STATA Corp, College Station, TX) for ROC analysis.

3. Results

During the study period, a total of 917 patients with severe sepsis or septic shock were entered into the sepsis registry. Of these, 147 patients were excluded according to the exclusion criteria: terminal malignancy (n = 116), signed DNR orders (n = 27) and refused EGDT (n = 4). Finally, a total of 770 patients were eligible for this study. Of the eligible patients, 208 (27%) patients with hepatic dysfunction were included in the final analysis. The baseline characteristics of patients with and without hepatic dysfunction are summarized in Table 1. In the hepatic dysfunction group, liver cirrhosis was more common (25%) compared

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