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Outcomes of patients with severe sepsis after the first 6 hours of resuscitation at a regional referral hospital in Uganda

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ABSTRACT

Introduction: The optimal resuscitation strategy for patients with severe sepsis in resource-limited settings is unknown. Therefore, we determined the association between intravenous fluids, changes in vital signs and lactate after the first 6 hours of resuscitation from severe sepsis, and in-hospital mortality at a hospital in Uganda.
Materials and methods: We enrolled patients admitted with severe sepsis to Mbarara Regional Referral Hospital and obtained vital signs and point-of-care blood lactate concentration at admission and after 6 hours of resuscitation. We used logistic regression to determine predictors of in-hospital mortality.
Results: We enrolled 218 patients and had 6 hour postresuscitation data for 202 patients. The median (interquartile range) age was 35 (26-50) years, 49% of patients were female, and 57% were HIV infected. The in-hospital mortality was 32% and was associated with admission Glasgow Coma Score (adjusted odds ratio [aOR], 0.749; 95% confidence interval [CI], 0.642-0.875; $P < .001$), mid-upper arm circumference (aOR, 0.876; 95% CI, 0.797-0.964; $P = .007$), and 6-hour systolic blood pressure (aOR, 0.979; 95% CI, 0.963-0.995; $P = .009$) but not lactate clearance of 10% or greater (aOR, 1.2; 95% CI, 0.46-3.10; $P = .73$).
Conclusions: In patients with severe sepsis in Uganda, obtundation and wasting were more closely associated with in-hospital mortality than lactate clearance of 10% or greater.

1. Introduction

Severe sepsis and septic shock are leading causes of mortality in hospitalized patients in resource-limited settings (RLSs) such as sub-Saharan Africa. Although the true incidence of sepsis in sub-Saharan Africa is not known, it is estimated that there are 1.2 to 2.2 million cases of sepsis and 6.5 million deaths due to infection annually [1]. In a recent study at Mbarara Regional Referral Hospital (MRRH) in southwestern Uganda, the in-hospital mortality rate was 10% for patients with sepsis, 34% for patients with severe sepsis, and 59% for patients with septic shock [2].

Resuscitation and monitoring of patients with severe sepsis during the critical first 6 hours of resuscitation remains a significant challenge in RLS. Recent guidelines from the Surviving Sepsis Campaign (SSC) recommend many interventions and monitoring strategies that are impractical in most RLS [3–5]. The World Health Organization has also provided recommendations for management of septic shock and severe respiratory distress in RLS, but these guidelines also require intensive clinical monitoring and have not been validated [6,7]. However, point-of-care blood lactate concentration predicts mortality in patients with severe sepsis in Africa [8,9]. Lactate clearance of at least 10% is associated with improved outcomes in resource-rich settings and is a targeted end point in the SSC guidelines [4,10]. Accordingly, although monitoring SSC-recommended end points such as central venous pressures and mixed venous oxygen saturation may not be possible in RLS, serial assessment of vital signs and lactate may be a more feasible method of monitoring patients being resuscitated from severe sepsis [8,9,11].

Therefore, the objective of this study was to describe the current management strategies used during the first 6 hours of resuscitation of patients with severe sepsis in a regional referral hospital in Uganda. We aimed to determine whether improvements in measurable physiological parameters were associated with improved in-hospital mortality. We were particularly interested to know whether lactate clearance of at least 10% was associated with improved in-hospital mortality.

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2. Materials and methods

2.1. Description of the study site

This study was conducted at the medical emergency department (ED) and the adult general medical ward of MRRH. MRRH has 600 beds and serves as the main referral center for all the districts in southwestern Uganda as well as neighboring parts of Rwanda and the Democratic Republic of Congo. It is also the teaching hospital for the Mbarara University of Science and Technology Faculty of Medicine. Patients 14 years or older with sepsis and other nonsurgical emergencies are initially resuscitated and stabilized in the ED before being transferred to the adult general medical ward. The ED has 8 monitored beds and is staffed by 1 nurse.

2.2. Patient recruitment process

We consecutively enrolled patients at least 14 years of age with severe sepsis presenting to the ED between October 2014 and May 2015. Severe sepsis was defined by: (1) a clinically suspected infection; (2) at least 2 systemic inflammatory response syndrome criteria including an axillary temperature of at least 38°C or less than 36°C, heart rate higher than 90 beats/min, respiratory rate higher than 20 breaths/min, or white blood cell concentration greater than 12 000 cells/μL or less than 4000 cells/μL; and (3) signs of end-organ dysfunction including a systolic blood pressure (SBP) of 90 mm Hg or lower, thrombocytopenia (< 100 000 cells/μL), or a Glasgow Coma Scale (GCS) score lower than 15 [2]. Patients were excluded if they required triage to a surgical or obstetrics and gynecology ward, had received any antibiotics or intravenous fluids prior to recruitment, or had a history suggestive of other diagnoses associated with lactic acidosis such as diabetic ketoacidosis, acute coronary syndrome, or chronic liver disease.

2.3. Data collection

At enrollment, each patient underwent a physical examination including measurement of their vital signs and mid-upper arm circumference (MUAC), which was obtained at the midway point between the olecranon and acromion processes as previously described [12,13]. We obtained blood for laboratory testing including random glucose concentration, complete blood cell concentration, HIV serostatus, CD4 + T-cell concentration (if HIV infected), peripheral blood bacterial cultures, and point-of-care lactate as previously described [2,13]. We obtained lactate concentration in duplicate and recorded the mean value. Six hours after the admission lactate measurement, we repeated vital signs and lactate measurements. The study team provided all vital signs and laboratory data to the admitting clinicians but was not directly involved in the management of the patients. We defined the initial time point of resuscitation as the time of initial lactate acquisition. We recorded the antibiotics, blood products, and volume of intravenous fluids administered to each patient during the first 6 hours of resuscitation. We followed up each patient throughout their hospital stay until discharge or death.

2.4. Statistical analysis

To calculate our sample size, we set α at .05 or less and power at 80%. Based on previously published data, we assumed that 30% of patients would clear lactate by at least 10% and that the in-hospital mortality for patients that cleared or did not clear lactate by at least 10% would be 25% and 45%, respectively [2,10]. Using these parameters, we determined that 199 patients would provide enough power to determine a statistically significant difference in in-hospital mortality between the 2 groups (PASS 13 Power Analysis and Sample Size Software; NCSS, LLC, Kaysville, Utah, 2014). Factoring in a dropout rate of 10% gave us an additional 19 patients for a total sample size of 218 patients. Data were recorded using Epi-Info (Centers for Disease Control, Atlanta, Ga, 2011) and analyzed using SPSS software (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, New York). We summarized patient characteristics as frequency with percentage for categorical variables and median with interquartile range (IQR) for continuous variables. We determined relationships between clinical and laboratory variables and outcomes using logistic and linear regression with significance set at $P < .05$. For the multivariable logistic regression models, we required that there be at least 10 outcome events for every included predictor variable [14]. In addition, we did not include predictor variables that were correlated with each other either clinically (eg, GCS and ambulatory status) or statistically as defined by a Pearson correlation P value < .05, or if the associated P value in the univariate analysis was .2 or greater. However, given our a priori hypothesis that lactate clearance of at least 10% would predict in-hospital mortality, this variable was included in the final multivariable in-hospital mortality model even if the P value in the univariate analysis was .2 or greater.

2.5. Ethical considerations

The study was approved by the Faculty Ethics Review Committee and the Institutional Ethical Review Committee at Mbarara University of Science and Technology as well as the institutional review board at the University of Virginia. All patients provided informed consent prior to enrollment in the study. If a patient could not provide informed consent, then an accompanying family member or friend provided it for them.

3. Results

3.1. Patient characteristics and resuscitation

We enrolled 218 patients and had data after 6 hours of resuscitation for 202 patients. The median (IQR) age was 35 (26-50) years, 49% of patients were female, and 57% were HIV infected, of whom 73% were receiving antiretroviral therapy (Table 1). The median (IQR) duration of illness preceding hospitalization was 14 (4-53) days and was highly correlated with low MUAC (Pearson correlation < .001). The most common presenting focus of infection was the chest (44%) followed by the gastrointestinal tract (30%) and the central nervous system (20%). MUAC was a strong predictor of HIV infection (odds ratio [OR], 0.931; 95% confidence interval [CI], 0.870-0.995; $P = .035$). Patients spent a median (IQR) of 8 (5-16) hours in the ED. The median (IQR) volume of intravenous fluids administered to patients was during the first 6 hours of resuscitation was 1.5 (1-2) liters and 89% of patients received antibiotics with a median (IQR) time to administration of 30 (14-60) minutes. For every unit increase in admission lactate, the patients received an increase of 73 mL in administered intravenous fluid (95% CI, 28-117; $P = .002$). For every unit decrease in admission oxygen saturation and mean arterial pressure (MAP), the patients received an increase of 170 mL (95% CI, 100-240; $P < .001$) and 130 mL (95% CI, 80-180; $P < .001$), respectively, in administered intravenous fluid. For every liter of administered intravenous fluid, lactate clearance increased by 10% (95% CI, 2-18; $P = .014$) and MAP increased by 5 mm Hg (95% CI, 2-9; $P = .002$). Blood pressure, heart rate, respiratory rate, and lactate were improved after 6 hours of resuscitation, but there were no improvements in temperature or oxygen saturation (Table 2). The median (IQR) lactate clearance was 24% (7%-41%), and 72% of patients achieved lactate clearance of at least 10%. In the univariate analysis, duration of illness, admission MUAC, and the total volume of administered fluids were all associated with lactate clearance of at least 10% (Table 3). In the multivariable analysis, the total volume of administered fluids remained an independent predictor of lactate clearance of at least 10% (Table 3).