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A Study to Assess Lactate Clearance for Death Prediction in Severe Sepsis or Septic Shock Patients in Intensive Care Unit-KIMS Hospital, Bengaluru

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Abstract
Aims and Objective: *To determine the significance of lactate clearance in sepsis and its association with morbidity and mortality in sepsis, at KIMS Hospital Bengaluru.*
Materials and Methods: *A total of 100 patients with age more than 18 years with sepsis in the duration of 18 months (December 2016 - May 2018) were included in this retrospective observational study. Other causes of shock not due to sepsis were ruled out, serial Arterial Blood Gas Analysis and 0,6 and 24 hours were drawn respectively. Lactate clearance, Acute Physiology and Chronic Health Evaluation was calculated and the outcome was observed.*
Measurements and Main Results: *One hundred patients were enrolled with mean age 52±10yrs, overall in-hospital mortality rate 32%. Baseline APACHE II score was 18±4and lactate 6.6±3.6 mmol/L. Survivors compared with nonsurvivors had a lactate clearance of 36.1±30 vs. 10.0±40.8 respectively (p =.005). Multivariate logistic regression analysis of statistically significant univariate variables showed lactate clearance to have a significant inverse relationship with mortality (p =0.04). There was an approximately 14% decrease likelihood of mortality for each 10% increase in lactate clearance. Patients with a lactate clearance >10%, relative to patients with a lactate clearance <10%, had a greater decrease in APACHE II score and mortality.*
Conclusions: *Patients with higher lactate clearance after 6 hrs of intensive care unit intervention have improved outcome compared with those with lower lactate clearance.*
Keywords: *Lactate clearance, septic shock, resuscitation, hypoxia, severe sepsis.*

Introduction

Severe sepsis and septic shock is the common cause of ICU admission and is associated with high morbidity and mortality worldwide. This study impacts the predictor of mortality in severe sepsis and septic shock with lactate clearance.(1) Elevated blood lactate levels provide an insight into the presence of impaired tissue perfusion. In

the recent years, lactate has been studied as a biomarker for sepsis and septic shock.

In addition reduced lactate clearance may reflect globally impaired renal and hepatic metabolic function, both of which normally contribute to systemic lactate disposal. Thus, lactate clearance biologically reflects homeostasis of the host and provides more meaningful data about the overall adequacy of the resuscitative processes.[(2)]

The survival sepsis campaign recommends lactate normalization as a target of resuscitation for patients with severe sepsis and septic shock with a recent update.

Materials and Methods

Source of data: Patients admitted with severe sepsis and septic shock at KIMS hospital ICU, Bengaluru.

Duration of study: 18 months (December 2016 - May 2018)

Sample size: 100 subjects

Type of study: Retrospective study

Inclusion criteria:

1. Age >18 years.
2. Sepsis was defined as clinical or laboratory evidence of infection in the presence of more than 2 of the following findings:

a) Temperature more than 38℃ or less than 36℃.

b) WBC counts abnormalities (i.e., >12000 cells/mm^3, <4000 cells/mm^3 or 10% immature neutrophils).

c) Heart rate >90/min

d) Respiratory rate >20/min

Exclusion criteria

1. Patients with other causes of shock not due to sepsis, eg: cardiogenic, oligaemic, neurogenic, anaphylactic, endocrinological.
2. Patients with known chronic liver disease, malignancies and immunosuppressant treatment.
3. Post operative cases.

Method of collection of data

- Information will be collected through structured proforma for each subjects.
- Study will be carried out on subjects with sepsis.
- Qualified subjects will be undergoing detailed history, clinical examination including relevant investigation.
- Serial ABGs at presentation to hospital at0,6 and 24 hours respectively.

Lactate Clearance Definition: Lactate clearance (percent) was defined using the following formula: lactate at ED presentation (hour 0) minus lactate at hour 6, divided by lactate at ED presentation, then multiplied by 100. A positive value denotes a decrease or clearance of lactate, whereas a negative value denotes an increase in lactate after 6 hrs of ED intervention.

$$\text{Lactate clearance}^{(3)} = \frac{(\text{Lactate}^{(\text{ED Presentation})} - \text{Lactate}^{\text{Hour6}}) \times 100}{\text{Lactate}^{\text{ED Presentation}}}$$

Statistical Analysis

The Statistical Analysis System software (SPSS software) was used for data analysis. Statistical significance was defined as p =0.05. Univariate in-hospital mortality comparisons (survivors vs. nonsurvivors) were made using either two-sample Student's *t*-tests or Wilcoxon rank sum tests for the continuous variables and either chi square tests or Fisher's exact tests for the categorical variables. The variables with univariate comparison $p=0.05$ were then included in a multivariate logistic regression analysis of in-hospital mortality rate.

Results

A total of 100 patients, 57 men and 43 women were enrolled for a one and half year's period (December 2016 - May 2018). The majority admitted subjects were pneumonia and UTI being the causes for sepsis. Vital signs, laboratory

values, and Acute Physiology and Chronic Health Evaluation (APACHE) II score, Arterial Blood Gas Analysis were obtained at hour 0 hour (ICU presentation), 6 hours, and over the first 24 hrs of hospitalization. Logistic regression analysis was performed to determine independent variables associated with mortality. One hundred patients were enrolled with mean age 52±10 yrs, and overall in-hospital mortality rate 32%. Baseline APACHE II score was 18±4 and lactate 6.6±3.6 mmol/L. Survivors compared with nonsurvivors had a lactate clearance of 36.1±30 vs. 10.0±40.8 respectively (p = 0.005). Multivariate logistic regression analysis of statistically significant univariate variables showed lactate clearance to have a significant inverse relationship with mortality (p =0.04). There was an approximately 14% decrease likelihood of mortality for each 10% increase in lactate clearance. Patients with a lactate clearance >10%, relative to patients with a lactate clearance <10%, had a greater decrease in APACHE II score over the 24-hr study period.

In severe sepsis patients, those with high lactate clearance had significantly lower mortality rate than patients with low clearance. There were significantly fewer septic shock patients with high lactate clearance; however, there was a trend toward decreased mortality rate in these patients compared with the septic shock patients with low lactate clearance.

Discussion

Lactate is formed through the reduction of pyruvate which is the end product of glycolysis. This reaction is driven by the enzymatic action of lactate dehydrogenase. Under aerobic conditions, pyruvate is oxidized via pyruvate dehydrogenase (PDH) to acetyl-CoA, which in turn enters

The Kreb's cycle. If the action of PDH is inhibited, as in the anaerobic milieu, pyruvate will be converted to lactate.[2]

Thus, tissue hypo perfusion will lead to a cellular hypoxia which causes accumulation of lactate. Hypo perfusion with its associated ischemia/ reperfusion phase, may prime cells to produce cytokines responsible for the events leading to MODS.[3]

It appears that the normalization of arterial serum lactate may be an efficacious and simple marker to gauge end points of resuscitation.[4] The longer the lactate clearance time the higher the patient mortality. Failure to clear lactate within 96 hours was predictive of certain mortality. In our unit, lactate continues to be utilized as a marker of resuscitation.[5] An elevated lactate is interpreted as generally reflective of ongoing hypo perfusion at the tissue/cellular level.

The most important change in the revision of the SSC bundles is that the 3-h and 6-h bundles have been combined into a single "hour-1 bundle" with the explicit intention of beginning resuscitation and management immediately.[6]

The elements included in the revised bundle are:

- Measure lactate level. Remeasure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administration of broad spectrum antibiotics.
- Begin rapid administration 30 ml/kg crystalloid for hypotension or lactate >4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP > 65 mm of Hg.[7]

Bundle Elements with Strength of Recommendations and Under-Pinning Quality of Evidence: [8]

Bundle Element	Grade of Recommendation and Level of Evidence
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure ≥ 65 mm Hg	Strong recommendation, moderate quality of evidence

Conclusion

When oxygen delivery fails to meet tissue oxygen demand in critical illness, there is a compensatory increase in oxygen extraction. Through this study we would like to reinforce early resuscitation using lactate clearance as a marker in severe sepsis and septic shock predicts the mortality in ICU patients.

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