Original Article

Serum Lactate Variability as Predictor of Mortality in Septic Shock: An Experience of Intensive Care Unit of Dhaka Medical College Hospital, Bangladesh

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ABSTRACT

Background: *Observation of variability of lactate levels instead of mean lactate level in critically ill patients with sepsis act as more efficient mortality factor.*

Objective: *To determine whether lactate levels measured at different intervals can predict mortality more effectively than that of mean lactate level for septic patients in intensive care unit (ICU).*

Methods: *This cross-sectional study was done in the Department of Anaesthesia, Analgesia, Palliative and Intensive Care Medicine, Dhaka Medical College Hospital, Bangladesh, between July and December of 2019. Purposively selected 147 septic patients with multiple organ failure in Intensive Care Unit were observed prospectively. Serum lactate levels at different intervals were assessed within the first twenty-four hours of recruitment of septic patients. The assigned patients were divided into three lactate variable groups: Group I (mild variable group) – when less than 2 values were not within the target lactate level; Group II (moderate variable group) – when 2-3 values were not within the range; Group III (more variable group) – when more than 3 values were not within the range.*

Results: *The mean age of the study participants was 48.3±12.5years. Among them, 82 (55.78%) were male and 65 (44.22%) were female. Number of survivors and non-survivors in Group I (mild) were 37(84.09%) and 7(15.91%) respectively, while in Group II (moderate) 48(71.64%) and 19(28.36%) respectively and in Group III (more) 13(36.11%) and 23(63.89%) respectively. A highly significant difference (P=0.001) was existed between three blood lactate variability groups with respect to mortality. Logistic regression analysis demonstrated that more lactate variability group had predicted higher mortality rate with a P value of 0.007 and an odds ratio of 16.0. Result is significant. On the other hand, significant effect of moderate lactate variability group on mortality was not found with a P value of 0.665 and an odds ratio of 0.667.*

Conclusion: *The septic patients having more serum lactate variability were reported to have higher mortality rate than that of moderate and less lactate variability in Intensive Care Unit. Our study suggests that serum lactate variability should be included as a future approach to see prognosis and predict mortality in septic patients.*

Keywords: *Serum lactate variability, septic shock, multi-organ failure, intensive care unit, mortality.*

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INTRODUCTION

Sepsis is very common worldwide resulting in an estimated 8 million deaths annually; however, a rapid detection and treatment can reduce the number of deaths[1]. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, as described in the Sepsis-3 definition[2]. The mortality rate of patients with sepsis has decreased during the past several decades; unfortunately, the incidence of sepsis has steadily increased, and the mortality rate remains e"20%[3-5]. The situation is worse in low-income countries.[6] Sepsis syndromes span a clinical continuum with variable prognoses. Septic shock, the most severe complication of sepsis, carries high mortality[7]. The etiopathogenesis of the syndromes is complex – a dysregulated host response to infection. In response to any inciting agent, e.g. various viral/bacterial components, including LPS, peptidoglycans, lipoteichoic acid and sometimes exotoxins, an intense, potentially lethal host response occurs; pro-inflammatory and anti-inflammatory arms of the immune system are activated in concert with the activation of monocytes, macrophages, neutrophils and/or T cells that interact with the endothelium through pathogen recognition receptors to release high levels of inflammatory response mediators e.g. cytokines, proteases, kinins, reactive oxygen species, and nitric oxide[8,9]. Those cells play important roles in the cascade of events leading to this condition. Until recently, septic shock was diagnosed as of three components together: systemic arterial hypotension, tissue hypoperfusion associated with organ dysfunction, and hyperlactatemia[10]. However, in newer definition, patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) e"65mmHg and serum lactate level >2 mmol/L (or >18mg/dL) in the absence of hypovolemia[2].

The efficacy of serum lactate as a marker for diagnosis of sepsis and response to resuscitative therapies in septic patients has demonstrated a clear association with clinical outcomes including mortality[11]. As per recommendation of the Surviving Sepsis Campaign guidelines, serum lactate levels should be measured within 3 hours of admission in the hospital and if elevated repeated within 6 hours[12]. That allows for the implementation and evaluation of effective hemodynamic management of the septic patient as early as possible, increasing the chances of survival and better prognosis. However, in other literature, it was stated that lactate measurements beyond 24h from the initiation of resuscitation continue to have predictive and prognostic utility[13]. Thus, controversies prevail in literature. Moreover, in our country, only few reports are available on utility of lactate levels in prognosis and mortality in sepsis. Hence, we proposed this study to measure serum lactate levels at different duration and evaluate the impact of serum lactate variability as predictor of mortality for septic patients in one of the largest Intensive Care Unit (ICU) facilities in the country.

METHODS

This cross-sectional study was done in the Department of Anaesthesia, Analgesia, Palliative and Intensive Care Medicine, Dhaka Medical College Hospital, Bangladesh, between July and December of 2019. Purposively selected 147 septic patients with multiple organ failure in Intensive Care Unit were observed prospectively. Serum lactate levels at different intervals were assessed within the first twenty-four hours of recruitment of septic patients. A detailed history of the patient's current illness, previous history of surgery, drug allergy, other comorbid illnesses (if present, treatment they are taking and the severity of the comorbidity) were recorded along with baseline vitals. Investigations including complete hemogram, serum electrolytes, renal function test and coagulation parameters were recorded as per standard institute protocol. Sequential Organ Failure Assessment score (SOFA) and Acute Physiology And Chronic Health Evaluation II (APACHE II) were calculated for each patients. ICU monitoring consisted of electrocardiogram (ECG), oxyhemoglobin saturation (SpO2), systolic and diastolic blood pressure (IBP) and temperature. Arterial blood gas analysis was done to establish baseline and subsequent lactate levels in each patient. The assigned patients were divided into three lactate variable groups: Group I (mild variable group) – when less than 2 values were not within the target lactate level; Group II (moderate variable group) – when 2-3 values were not within the range; Group III (more variable group) – when more than 3 values were not within the range. Fluid and vasopressor management was guided by invasive arterial, central venous pressure, blood gas with lactate and point of care ultrasound monitoring. Broad spectrum antibiotics were initiated at presentation as per institute protocol and appropriate cultures (blood, urine, abdominal fluid and tracheal aspirate whenever suitable) were sent. Patients were followed up daily till 28 days or death or discharge from the hospital, whichever was earlier. Following parameters were collected daily for all patients: urine output, serum

creatinine, requirement of renal replacement therapy, development of acute respiratory failure, need for mechanical ventilation, vasopressor requirement, type of nutritional support, and the length of ICU stay.

Student's t-test, Chi-square test, and multiple logistic regression analysis were performed. The level of significance was at 95% confidence interval and a P-value <0.05 was considered as significant. Data were analyzed using SPSS (Statistical package for Social Sciences) version 22.0. The study was approved by the Ethical Review Committee of Dhaka Medical College, Dhaka, Bangladesh.

RESULTS

The mean age of the study participants (n=147) was 48.3±12.5years. Among them, 82 (55.78%) were male and 65 (44.22%) were female. However, there is no difference in age and sex of the participants (P>0.05) (Table-I). Among survivors (n=98) and non-survivors (n=49), systolic blood pressure were found 106.1±30.8 and 107.4±33.4 mmHg and diastolic blood pressure 65.6±51.6 and 65.9±23.2 mmHg respectively. Mean respiratory rates were 21.3±2.1 and 22.7±3.4 per minute respectively, while pulse rates were 103.8±30.3 and 108.0±34.2 per minute respectively. Body temperatures were found 37.1±1.4°C and 37.5±1.3°C respectively. SOFA scores were 10.0 (8.0–13.0) and 13.0 (11.0–16.0), while APACHE II scores were 2.0 (1.0-2.0) and 6.0 (5.0-6.0) respectively. Lactate area scores were 38.8 (22.7–58.0) and 57.0 (33.9–98.0) respectively (Table-II). Number of survivors and non-survivors in Group I (mild) were 37(84.09%) and 7(15.91%) respectively, while in Group II (moderate) 48(71.64%) and 19(28.36%) respectively and in Group III (more) 13(36.11%) and 23(63.89%) respectively. A highly significant difference (P=0.001) was existed between three blood lactate variability groups with respect to mortality (Table-III). Logistic regression analysis demonstrated that more lactate variability group had predicted higher mortality rate with a P value of 0.007 and an odds ratio of 16.0. Result is significant. On the other hand, significant effect of moderate lactate variability group on mortality was not found with a P value of 0.665 and an odds ratio of 0.667 (Table-IV).

Table I: *Demographic characteristics of the study population (n=147)*

Characteristics	Survivor (n=98)	Non-survivor (n=49)	P value
Age group			
18-30 years	12 (66.67%)	6 (33.33%))	>0.05
31-45 years	31 (77.5%)	9 (22.5%))	
46-60 years	29 (64.44%)	16 (35.56%)	
61 years and above	26 (59.09%)	18 (40.91%)	
Mean±SD	48.3±12.5		
Sex			
Male	56 (66.4)	26 (67.8)	>0.05
Female			
	42	23	

Values were presented as mean±SD, and number (%) as applicable.
P value reached from Student's t-test and Chi-square test respectively.

Table II: *Baseline characteristics of the study population (n=147)*

Vital signs	Survivor (n=98)	Non-survivor (n=49)	P value
Systolic blood pressure (mmHg)	106.1±30.8	107.4±33.4	>0.05
Diastolic blood pressure (mmHg)	65.6±51.6	65.9±23.2	>0.05
Respiratory rate (rates/min)	21.3±2.1	22.7±3.4	>0.05
Pulse rate (beats/min)	103.8±30.3	108.0±34.2	>0.05
Body temperature (°C)	37.1±1.4	37.5±1.3	>0.05
SOFA score	10.0 (8.0–13.0)	13.0 (11.0–16.0)	<0.001
APACHE II	2.0 (1.0-2.0)	6.0 (5.0-6.0)	<.0001
Lactate area score	38.8 (22.7–58.0)	57.0 (33.9–98.0)	<0.001

Values were presented as mean±SD or median (interquartile range) as applicable.
SOFA: Sequential Organ Failure Assessment. P value reached from Chi-square test.

Table III: *Status of the patients among lactate variability groups*

Lactate variability group	Survivor	Non-survivor	X^2	P value
Group I (mild)	37(84.09%)	7(15.91%)	14.56	0.001
Group II (moderate)	48(71.64%)	19(28.36%)		
Group III (more)	13(36.11%)	23(63.89%)		
Total	98(66.67%)	49(33.33%)		

Values were presented as mean±SD, number (%), or median (interquartile range) as applicable.
P value reached from Chi-square test.

Table IV: *Effect of Blood lactate variability on mortality*

Lactate variability groups	OR	P value
Group I (mild) (Reference)		0.004
Group II (moderate)	0.667	0.665
Group III (more)	16.000	0.007

Multiple logistic regression analysis was done.

DISCUSSION

Severe sepsis and septic shock are the biggest cause of mortality in critically ill patients[3-6]. A simple infection can rapidly develop into sepsis a life-threatening condition which requires on-the-spot diagnosis and treatment while the condition is still in its early stages. The major pathways that lead to sepsis-induced coagulopathy and DIC include activation of coagulation, platelets, and other inflammatory cells (e.g., neutrophils, lymphocytes) and vascular endothelial injury[8,9]. Traditionally, lactic acidosis in sepsis is attributed to anaerobic glycolysis due to inadequate oxygen delivery. However, it has become clear that the mechanism of hyperlactatemia in sepsis is multifactorial and due to factors beyond hypoxic tissue injury alone[15-18]. Evidence have shown that lactate levels are known to be predictors of survival or mortality in patients of sepsis in ICU settings[19-23]. A normalization of serum lactate with aggressive treatment within the first 24 hours of the diagnosis has a favourable outcome, as shown in several studies[19,21]. Aggressive treatment includes timely resuscitation, antibiotics, surgical management, vasopressor and inotropic drugs, ventilatory support, and dialysis as deemed fit. The aim of all interventions remains patient survival. However, the patient presents with a pre-existing set of variables of morbidity that affect his response to an insult and hence the result of these interventions differs between patients.

Our study demonstrated that more lactate variability had predicted higher mortality in septic patients. Several evidence demonstrated serial serum lactate measurements at different intervals for >72h in ICU patients and concluded that the duration of hyperlactemia is a reliable indicator of morbidity and mortality following trauma, which is in congruence with our study.[21-23] However, Krishna et al. suggested that lactate values probably need to be followed for longer periods of time in critical patients even when they have tided over the present crisis. The utility of regular lactate analysis in those patients depends on factors such as availability and cost of tests as well, especially in resource-poor settings[21].

Our study has several limitations. It belongs to observational study design and lacks randomization. Our sample size is small and a single centre study; therefore, the findings derived from this study hardly generalize to the reference population. Moreover, the selective biomarker used in this study was only able to show the picture of an adult ICU, as we spared paediatric group.

CONCLUSION

Our data suggest that variability of lactate levels at different intervals instead of mean lactate level in critically ill patients with sepsis act as more efficient mortality factor. The septic patients having less lactate clearance predicted mortality more than that of drastic lactate clearance therapy in ICU setting. When we know about the propensity of death from the serum lactate clearance of septic patients within the first 24 hours of detection of sepsis, it will be easy to treat the patient and easily improve the outcome of sepsis. However, further studies with larger sample and

multi-centre trials along with combination of more biomarkers are recommended.

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