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Study on Clinical Use of Serum Blood Lactate Monitoring in Critically ill Patients

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ABSTRACT
Significance of serum blood lactate levels in critically ill patients to help clinicians in risk stratification and to predict mortality. Prospective non-interventional observation study, where concentration of serum blood lactate levels were assessed in 100 critically ill patients at every 6th hour till the patient is deemed clinically stable or deceased, who presented to ED and admitted to critical care unit of SSIMS and RC, Davanagere for a period of two years. Serial serum lactate levels associated with patient outcome and 7 day mortality were compared. A significant finding was that of total 33 patients who did not survive, 32 patients had lactate >5mmol/L. However 67 patients who were survivors, 31 patients whose serum lactate levels >5mmol/L had a longer stay at the hospital for >7 days. High numbers of deaths were seen in sepsis, trauma cases. All respiratory failure cases survived. Survivability was highest in other medical emergencies in MICU where blood lactate levels were <5mmol/L. Decrease in serum lactate levels with time was consistently related with lower mortality rates in every group of patients. Statistically significant difference was observed between serum lactate levels related to length of stay in the hospital and mortality, with serial blood lactate levels measured beyond 6 hours from time of admission. Hyperlactatemia is common in critically ill patients. In critically ill patients, increased glycolysis may be a prime cause of raised blood lactate levels. Nevertheless, the increasing serial blood lactate levels have important significance in predicting morbidity and mortality or longer length of hospital stay in hyperlactatemia patients consistent with our results in this study.

INTRODUCTION

In the emergency care triage, diagnosis and intervention time is critical. In addition to a validated decision process, further analyses are often needed to make decisions concerning priorities, diagnostics and treatment, preferably in close association with the initial medical assessment. In the Emergency Department the relationship between priority and outcomes in patients with high blood lactate is being studied, along with lactate's effect on reassessment[1]. Mainstream adaptation to the diverse Emergency Department environment will require further ED-based studies and observation of lactate utility in routine care of critically-ill and injured patients[2]. One of the main responsibilities of an Emergency Department doctor is to identify those patients who are at highest risk for mortality. Unfortunately, not all critically ill patients will present with abnormal vital signs. Obtaining blood lactate levels can potentially identify those patients in occult shock and helps in reducing mortality by expediting definitive treatment. Several variables estimated in critically ill patients have been used to predict severity of disease, prognosticate morbidity and mortality, to assess costs of therapy and to direct specific treatment and monitor the sufficiency of treatment. Although in our mind firmly related to tissue hypoxia, serum levels shadow many more metabolic processes not connected to tissue hypoxia and, consequently, subject to many interruptions found in different clinical state[3]. The amount and clearance fraction of blood lactate are known useful characteristics in the prognosis of the septicemic patients. In a mixed Critical Care Unit(CCU) setting, there is strong proof for an association between raised lactate levels and increased mortality. As proved in many Meta analyses the dynamic growth of hyperlactatemia over a period of time following ICU admission is an important and self-sufficient indicator of illness gravity, in a mixed CCU setting corresponding to results in septic patients[4]. The half-life of lactate is around 20 min. Even slight increases in lactate concentrations to >1.5mEq/l are related with higher mortality rates[5]. The precise pathophysiologic mechanisms of hyperlactatemia have been much contemplated, because the illness does not always merely reveal the progress of anaerobic metabolism[6]. In sepsis to be specific, metabolic changes can provide to raised blood lactate concentrations, including augmented glycolysis, catecholamine- stimulated Na-K pump activity, variations in pyruvate dehydrogenase activity and decreased lactate elimination mainly as a consequence of liver hypoperfusion. Nevertheless, hyperlactatemia is a hallmark characteristic of shock states[7] and the degree of rise in lactate concentrations is openly linked to the severity of the shock state and to mortality rates[8]. Venous lactate levels are analogous to arterial lactate levels, which refutes the necessity for an arterial puncture when obtaining a lactate measurement.

MATERIALS AND METHODS

The study was conducted on patients arriving to the Emergency Department with clinical suspicion of true emergency according to early warning scoring system at tertiary care and referral hospital of S.S Institute of Medical Sciences and Research Centre Hospital, Davanagere, having a catchment area of approximately 19,50,000 inhabitants. A prospective observational study on critically ill patients where concentration of serial blood lactate levels at emergency department and intensive care unit associated with length of hospital stay and mortality for a period of two years was registered. Duration of study was 2 years.

Sample Size: 100 cases.

Modified version of the Early Warning Scoring (EWS) system was used which was first described in 1997 as described below:

Inclusion Criteria: All patients above the age of 18 years presenting to emergency department who were stratified as critically ill according to Early Warning Scoring (EWS) system which comprises of the following:

- Systolic blood pressure <90mmHg.
- Heart rate <40 or >130 beats/min.
- Respiratory rate <8 or >30 breaths/min.
- Peripheral oxygen saturation (SpO2)<90%.
- Sudden decrease in consciousness and/or in tuition/serious concern for the patient

Exclusion Criteria:

- Patients whose serial blood lactate levels were unavailable due to medical errors.
- Patients below 18 years of age.

Data Collection: Patient demographics (age, gender), vital signs (systolic blood pressure, heart rate, respiratory rate and peripheral oxygen saturation) and the reason for the medical emergency -call were collected. Lab results, comorbidity, the event of transfer to the ICU, therapy received (including vaso active agents, mechanically assisted ventilation), length of hospital stay as well as ICU stay and death within 7 days were collected from the medical records department. Blood lactate analysis was performed at our hospital laboratory using ABL 800 Flex Analyzer(Radio meter Medical, Copenhagen, Denmark. Test Range 0.5-15mmol/L). i e, reference range is 0.63-2.44mmol/L and the normal time to get a result was about 15 minutes in total from when the sample is taken.

- Collection of data was by a Proforma.
- Regional ethical committee clearance was obtained.

Triage of the 100 Patients: Of all the patients, they were subdivided into:

- Non-survivors.
- ICU Stay<7days.
- ICU Stay>7days.

Each patient fulfilling the criteria was included in the study and the serum lactate was taken at 0 hours, 6th hour, 12th hour, 18th hour, 24th hour, 48th and 72nd hours. All the seven values were taken into consideration and were studied. Patients were categorized into three lactate groups concurring to serum lactate levels as <2.5mmol/L, 2.5-5mmol/L and >5mmol/L. Correlations of these serum lactate categories were analyzed with length of stay in the hospital and mortality of the patient.

Data was be Analyzed by:

- Mean+ Standard deviation.
- Diagrammatic presentation.
- Using proper statistical test i.e, chi-square test.
- Sensitivity and Specificity.
- P value was obtained.

RESULTS AND DISCUSSIONS

Our study included 23 cases of sepsis and septic shock, 22 cases of trauma, 4 cases of cardiogenic shock, 35 cases of other medical illnesses in medical ICU, 7 cases of abdominal surgical emergencies, 6 cases of post cardiac arrest revived, 3 cases of respiratory failure. Serial blood lactate levels were analyzed to prognosticate and predict mortality. Out of the 100 studied, 14 patients were below 25 years, 52 were between 25 and 50 years of age and 34 patients were above 50 years of age. Among the study population 60 patients were male and 40 patients were females.

Table 1: Distribution of the Subjects Based on Outcome Code

Length of Stay	Frequency	Percent
<7 Days	25	25.0
>7 Days	42	42.0
Dead	33	33.0
Total	100	100.0

Out of 100 patients, 33 patients did not survive, 42 patients had a longer stay of >7 days in the ICU. And 25 patients recovered rapidly and stay was lesser then 7 days. In the study population of 100 patients, 48 patients were on inotropes or vasopressors, among which 25 patients did not survive. Out of 100 patients, 56 patients were on mechanical ventilator support, among which 29 patients did not survive.

Table 2: Distribution of the Subjects Based on o Hrs Code

0 HRS Code	Frequency	Percent
<2.5mmol/L	6	6.0
2.5-5mmol/L	32	32.0
>5mmol/L	62	62.0
Total	100	100.0

At the time of arrival to the ED, 62 patients had blood lactate levels >5mmol/L, 32 patients had lactate levels between 2.5mmol/L-5mmol/L and only 6 patients had <2.5mmol/L. At 6 hours in to admission to CCU, 67 patients had blood lactate levels >5mmol/L, 26 patients had lactate levels between 2.5mmol/L-5mmol/L and 7 patients had <2.5mmol/L. At 12 hours in to admission to CCU, 78 patients had blood lactate levels >5mmol/L, 21 patients had lactate levels between 2.5mmol/L to 5mmol/L and only 1 patient had <2.5mmol/. At 18 hours in to admission to CCU, 74 patients had blood lactate levels >5mmol/L, 22 patients had lactate levels between 2.5mmol/L-5mmol/L and 4 patients had <2.5mmol/L. At 24 hours in to admission to CCU, 58 patients had blood lactate levels >5mmol/L, 34 patients had lactate levels between 2.5mmol/L-5mmol/L and 8 patients had <2.5mmol/L. At 48 hours in to admission to CCU, 48 patients had blood lactate levels >5mmol/L, 34 patients had lactate levels between 2.5mmol/L-5mmol/L and 18 patients had <2.5mmol/L. At 72 hours in to admission to CCU, 41 patients had blood lactate levels >5mmol/L, 24 patients had lactate levels between 2.5mmol/L to 5mmol/L and 35 patients had <2.5mmol/L. There was no correlation between age and outcome of the patients. As well as no statistically significant difference was established between age and length of stay or mortality of the patient. There was no correlation between gender and outcome of the patients. As well as no statistically significant difference was established between gender and length of stay or mortality of the patient. Six post cardiac arrest revived cases were considered in to this study, three patients did not survive where they had 14.7mmol/L average lactate levels and all others who survived had a longer say of >7 days. At 0 hours, there was no statistically significant difference between higher blood lactate levels with longer stay in the hospital and mortality of the patients. (P=0.73). Patients with blood lactate levels >5mmol/L, 46.8% of people had longer than 7 days stay whereas 32.3% patients did not survive. At 6 hours, there was no statistically significant difference between higher blood lactate levels with longer stay in the hospital and mortality of the patients. (P=0.08). Patients with blood lactate levels >5mmol/L, 43.3% of people had longer than 7 days stay whereas 37.3% patients did not survive. At 12 hours, a statistically significant difference was observed between higher blood lactate levels with longer stay in the hospital and mortality of the patients (P=0.001). Patients with blood lactate levels >5mmol/L, 39.7% of people had longer than 7 days stay whereas 42.3% patients did not survive. At 18 hours, a statistically significant difference was observed between higher blood lactate levels with longer stay in the hospital and mortality of the patients. (P=0.00). Patients with blood lactate levels >5mmol/L, 43.2% of people had longer than 7 days stay whereas 44.6% patients did not survive. At 24 hours, a statistically significant difference was observed between higher blood lactate levels with longer stay in the hospital and

Table 3: Cross-Tabulation of Age and Outcome

Age code	Outcome code			Total
	<7 Days	>7 Days	Dead	
<25	3	2	9	14
	21.4%	14.3%	64.3%	100.0%
25-50	12	24	16	52
	23.1%	46.2%	30.8%	100.0%
>50	10	16	8	34
	29.4%	47.1%	23.5%	100.0%
Total	25	42	33	100
	25.0%	42.0%	33.0%	100.0%
Chi-square value- 8.54				
p value- 0.073				

Table 4: Cross-Tabulation of Gender and Outcome

Gender	Outcome code			Total
	<7 Days	>7 Days	Dead	
Male	15	26	19	60
	25.0%	43.3%	31.7%	100.0%
Female	10	16	14	40
	25.0%	40.0%	35.0%	100.0%
Total	25	42	33	100
	25.0%	42.0%	33.0%	100.0%
Chi-square value-0.14				
p value-0.93				

Table 5: Statistical Analysis Between Lactate Categories of Survivors and Non-Survivors Dependent (Related with) on Diagnoses

Diagnoses	Out come	<2.5Mean±SD	p value	2.5-5.0 Mean±SD	P-value	>5.0Means±SD	P-value
Sepsis	Alive			4.59±0.28		6.98±2.02	0.002
	Dead					10.47±1.90	
Cardiogenic Shock	Alive			3.76±0.11			
	Dead					9.09±1.30	
MICU	Alive	2.09±0.08		3.82±0.58		6.38±1.79	0.012
	Dead					11.22±5.17	
Post Cardiac Arrest	Alive					8.47±2.71	0.429
	Dead					12.11±6.63	
Respiratory Failure	Alive					9.46±2.58	
	Dead						
SICU	Alive			3.46±0.94	0.351	10.66	0.701
	Dead					9.28±2.70	
TRAUMA	Alive			4.10±0.43		6.29±2.41	0.746
	Dead			4.5571		7.56±2.44	

Table 6: Serum Lactate Levels Associated with Survival According to Diagnoses

Diagnosis		Lactate			Total
		≤2.5	2.5-5	>5	
Sepsis	Alive		5	8	13
	Dead		0	10	10
Cardiogenic shock	Alive		2	0	2
	Dead		0	2	2
MICU	Alive	3	15	11	29
	Dead	0	0	6	6
Post Cardiac Arrest-Revived	Alive			3	3
	Dead			3	3
Respiratory Failure	Alive			3	3
SICU	Alive		3	1	4
	Dead		0	3	3
TRAUMA	Alive		8	5	13
	Dead		1	8	9
Total	Alive	3	33	31	67
	Dead	0	1	32	33

mortality of the patients. (P=0.00). Patients with blood lactate levels >5mmol/L, 36.2% of people had longer than 7 days stay whereas 56.9% patients did not survive. At 48 hours, a statistically significant difference was observed between higher blood lactate levels with longer stay in the hospital and mortality of the patients. (P=0.00). Patients with blood lactate levels >5mmol/L, 42.0% of people had longer than 7 days stay whereas 33.0% patients did not survive. At 72 hours, a statistically significant difference was observed between higher blood lactate levels with longer stay in the hospital and mortality of the patients. (P=0.00). Patients with blood lactate levels >5mmol/L, 42.0% of people had longer than 7 days stay whereas 33.0% patients did not survive. A statistically significant difference was observed in sepsis (p value=0.002) and other MICU cases (p value=0.012). Hence it can infer that a relationship is evident between serial blood lactate levels and length of stay and mortality in these categories. A significant finding was that of total 33 patients who did not survive, 32 patients had lactate >5mmol/L. However 67

patients who were survivors, 31 patients whose serum lactate levels >5mmol/L had a longer stay at the hospital for >7 days. High numbers of deaths were seen in sepsis, trauma cases. All respiratory failure cases survived. Survivability was highest in other medical emergencies in MICU where blood lactate levels were <5mmol/L. Consistently regardless of diagnoses the raising blood lactate levels were documented in all the non-survivors and in the patients who had a longer stay of >7 days. It was crucial finding that once blood lactate levels reached >5mmol/L the non-survivors succumbed to death with in next 12 hours. This indicates that raising lactate levels are strongly linked to mortality. In this study more than 50% of patients were between ages of 25-50 years, among which majority were males. However age and gender had no significant impact (p value=0.073) on patient outcome consistent with findings of Acharya[9]. Patients with sepsis, trauma and other medical illnesses in MICU contributed to foremost study population in this study. There are several elements that affect mortality in critically ill patients and these causes are not well studied. Many scholars reported that lactate level elevation could be a valuable guide for determination of disease acuity; prognosis and the mortality risk. Broder *et al.* narrated that mortality rate is 89% in patients with consistently raised lactate levels in the 24-hours. Vincent *et al.* reported that the top indicator of the prognosis after resuscitation of shock is reduced lactate level following within one hour[10]. Duke *et al.* narrated that mortality risk of patients could be established in 12 and 24 hours with lactate levels[11]. Many researchers discovered that the organ failure is related with lactate levels in sepsis, trauma, burns and severe acute pancreatitis patients. Fredriksson K *et al.* found that first measured lactate levels are linked with mortality in severe sepsis patients without organ failure in the emergency department[12]. In disparity, Hatherill *et al.* described that lactate levels was a faint prognosticator of mortality and not beneficial in practice. In our study, regardless of diagnoses, statistically significant difference was found between all the lactate groups associated to their length of hospital stay and being a survivor or non-survivor. Patients with lactate levels >5mmol/L either had a prolonged length of hospital stay or they did not survive the illness. As well as there was a statistically significant difference between lactate group of survivors and non-survivors with sepsis, trauma and other groups after 6 hours from time of admission to ICU. In our study, a total of 23 cases were critically ill due to sepsis and septic shock. 10 patients did not survive whereas other 8 patients had a longer stay in the hospital of >7 days (p value=0.002). Among the non-survivors all the cases had a serum lactate levels of >5mmol/L with an average of 14.65mmol/L. Moreover patients who survived had average high blood lactate level of 6.56mmol/L at different intervals, however levels decreased gradually and were least after 7 days of stay at the hospital. A substantial finding was that none of the patients with sepsis or septic shock had lesser than 7 days of admission. This implies that serial blood lactate levels are crucial in sepsis and septic shock to prognosticate and predict mortality. Consistent with Aiyappa *et al.* MODS had strong correlation between the serum lactate levels and outcome. But MODS can be documented only after organ failure sets in. Comparatively serum serial lactate levels quickly predict the impending shock and MODS so that we can manage patients effectively. A total of 22 cases of trauma were critically ill in this study, among which 8 patients did not survive and 4 patients had a longer stay (>7 days). The non-survivors had an average lactate level of 7.61mmol/L. Patients with hemorrhagic shock secondary to trauma had a swift raise in serum lactate levels. Pritvishree *et al.* found that the patients with arterial lactate value >/=4mmol/L and base deficit >/=12mEq/L had statistically significant higher ICU admission. (222) Patients with higher arterial lactate and base deficit were also found to have a higher injury severity score. Patients with higher levels of arterial lactate and base deficit at ED admission had a higher mortality, requirement of blood transfusion and ICU admission at 24 hours. Consistent with the above, our study demonstrated similar correlation between blood lactate levels and outcome, which was significant and promising. Four patients in cardiogenic shock were considered in the study. Two cases did not survive with an average lactate level 11.6mmol/L. And the other two recovered with a longer ICU stay (>7days). According to many studies increase in serial blood lactate was secondary to increased lactate production due to tissue hypoxia and hypotension rather than decreased clearance of lactate. Hence raising lactate levels in cardiogenic shock should warn the clinicians to be aggressive in management or change the mode the intervention. Medical ICU provides enormous variety of different cases who are critically ill. Even though not all the illnesses have similar outcome but the raise in blood lactate levels are reliable, once the disease or illness has attained decompensated phase with clinical shock. A total of 35 patients with illnesses such as kidney disease, liver disease, poisoning, cerebrovascular accident, obstructive shock, hanging, diabetes etc. were considered into the study group. Six patients did not survive with average lactate >5mmol/L. A statistically significant difference was documented in MICU cases (p value=0.0012). Two patients with liver dysfunction who didn't survive demonstrated an abrupt raise in blood lactate levels and clinical deterioration was unpredictable. Since liver is the prime organ associated with lactate clearance, dysfunction of the liver due to clinical shock could also

be source of lactate production. Hence blood lactate levels rapidly increase along with other comorbidities. However rapid lyraising lactate levels in live rdys function indicates the treating clinician that clinical deterioration and mortality of patients is imminent. Four patients were considered in the study with toxins (poisoning). Toxin induced critical patients are challenging to manage due to different toxic levels of the poisons wherein the treatment methods and time of presentation to the ED also matters. Nevertheless serial blood lactate levels were crucial in the cases to predict the mortality. More and more studies are essential in toxin-induced illnesses to stratify the needed management options. In our study serum lactate levels were useful in predicting mortality in all the critically ill poisoning patients. Post cardiac arrest revived patients were considered in this study. There are several factors responsible for rapid increase in serum lactate levels in post arrest period, however it was observed that the patients who survived did not demonstrate a substantial variation in lactate levels on a daily basis, hence there was no correlation between lactate levels with ICU stay and mortality. Additionally in those who did not survive showed a raising lactate levels at repeated samples, indicating that mortality was inevitable. As demonstrated by cox *et al.* blood lactate levels in diabetic ketoacidosis had no correlation with outcome of the patient. Similarly among the only three patients with no mortality were considered in this study also did not demonstrate any significant correlation with outcome and they were not helpful in predicting mortality. Factors responsible for this needs more attention and large sample size study needs to be performed to clearly explain the relationship between lactate and diabetic ketoacidosis. Jeng *et al.* revealed lactate levels are to be a solid prophet of outcome in patients with burns or smoke inhalation. Similarly in this study the burns patients showed a significant correlation between serum lactate levels and outcome of the patient[13]. Consistent with study by Kamolz *et al.* lactate levels of lesser than 2mmol/L showed rapid lactate elimination with decreased mortality. Our study demonstrated that raising or falling serial serum lactate levels could be a good predictor of mortality or recovery respectively. However role of lactate as resuscitation end point in burns cases needs further study and significance is doubtful. Three Patients with respiratory failure were studied, among who an apt association between serum lactate levels and length of stay in ICU was observed. Since serum lactate levels are very well linked to tissue hypoxia in absence of other comorbidities, it appeared a solid association between lactate levels and outcome was appreciated. Surgical emergencies with abdominal pathologies were studied for association between lactate and outcome. It was appreciated that raising lactate levels indicated probable mortality unless surgical correction was performed. Serial lactate levels demonstrated an association with length of hospital stay., hence they could prove good predictor of outcome in surgical emergencies, however similar to other illnesses further studies are indispensable. In a recent publication, Meregalli[14] have shown that despite similar hemodynamic variables, serum lactate values can categorize post surgical patients into survivors and non-survivors within 12 hours of ICU admission. They came to the conclusion that lactate, especially when hemodynamic variables were taken into consideration, seemed to have a similar value in identifying survivors as the SAPS and APACHE II scoring systems and offered even better relevant bedside clinical information in terms of patient condition at the moment". In our study a statistically significant difference was not observed between serum lactate levels with length of hospital stay and mortality at the time of presentation to the ED (p value=0.73) and at 6 hours from time of admission (p value=0.08). This implies that in the initial hours of evaluation of the patients in the ED, a definitive diagnosis with appropriate treatment could not have been established. However factors such as delay in the patient's arrival to the ED, missed diagnosis and inappropriate treatment at a different medical care, non-compliance with daily treatment regimen of chronic illnesses, non availability of complete history etc. May have played the role in initiating the precise treatment. This also directs us to be more swift and thorough in our approach to treat our patients. However there was statistically significant difference evident in the further serum lactate levels drawn 6 hours after from time of arrival to ED. This implies that serial serum lactate levels become crucial to prognosticate and stratify the management strategy of the critically ill. Additionally serum serial lactate levels are strongly correlated with length of Stay in the hospital and mortality. Our study corroborates that a single measurement of serum lactate would only indicate the current status of the critically ill patient, whereas serial measurements help clinicians in predicting mortality. Several factors influence the outcome of the critically ill patients in the ED., hence the time interval between consecutive serum lactate levels drawn from the patients to stratify our treatment are to be scheduled judiciously. This study considered blood lactate levels every 6 hours, whereas several other studies considered at different time intervals. Even though there was no significant difference in these studies, every study justified that serial blood lactate levels are promising in prognostication and predicting mortality. A significant p value was evident in two categories of patients in this study, which are sepsis and other medical illnesses at MICU. Hence it can be warranted that serial blood lactate levels are essential, primarily in these two

categories of patients to help emergency physicians. It was observed in our study that >95% of the patients who did not survive had blood lactate levels >5mmol/L. And 31% of patients who had serum lactate levels >5mmol/L had a longer stay of >7 days. It was evident that non-survivors died with in next 12 hours after serum lactate levels surpassed 5mmol/L. However among survivors, according different diagnoses the dropping serial serum lactate levels had varied time as well as varied recovery time independent of length of stay at the hospital.

CONCLUSION

Our observational study has stipulated the following answers to our original objectives. Firstly, indication of a recovering prognosis with falling lactate concentrations are seen all through the study populations and raising lactate levels were observed in those who did not survive or they had longer hospital ICU stay. Secondly, these observations are not exclusive to sepsis and trauma patients, but relate to all collective circumstances of higher serum lactate levels and in heterogeneous patient populations. Thirdly, the variations are relatively slow in some populations and very swift in other populations and it is challenging to specify recommendations about the swiftness of increase or decrease in lactate levels in the varied disorders. Undoubtedly repeating measurements every 6 hours can largely stratify those patients who will recover well from those patients who are likely not to survive, but shorter time intervals may be beneficial.

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