Lactate clearance versus lacate levels in sepsis

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Abstract Objectives: 1) To study the role of blood lactate levels in sepsis. 2) To compare blood lactate levels and lactate clearance in sepsis in relation to survival outcome. Materials and Methods: This is an observational cohort study done in 67 patients admitted to R.L. Jalappa Hospital. Subject's history and clinical examination suggestive of sepsis satisfying the inclusion and exclusion criteria were taken into the study. Arterial Blood lactate levels were measured at the time of admission, 12 hours, 24 hours and 36 hours by using epoc blood gas analyzer. Relevant investigations including haemogram, blood gas analysis, blood urea, serum creatinine, electrocardiogram and x-ray were done. The patients were followed till the time of discharge or death. Results: The mean arterial blood lactate levels at the time of admission, 12 hours, 24 hours, 36 hours in sepsis patients who survived are 3.56 ± 3.16 , 2.96 ± 2.86 , 2.30 ± 1.52 , 2.04 ± 0.88 mmol/lit respectively and mean blood lactate levels in non survivors are 5.53 ± 3.83 , 4.80 ± 3.30 , 3.78 ± 2.05 , 3.43 ± 2.76 mmol/lit at the time of admission, 12 hours, 24 hours, 36 hours respectively. There was a significant association between blood lactate levels and outcome. The mean values for lactate clearance at first 12 hours, 12 to 24 hours and 24 to 36 hours are 15.78 ± 12.92 , 13.26 ± 20.01 , 7.59 ± 15.30 in the survived and 14.75 ± 48.49 , 36.12 ± 50.07 , 12.91 ± 39.37 in the non survived. The lactate clearance was significant only for first 12 to 24 hours. At admission sensitivity and specificity for lactate in predicting mortality is 76.5% and 30% respectively. Lactate levels at 24 hours has got much higher sensitivity of 77.8% and specificity of 32% in predicting mortality. The sensitivity and specifity for lactate clearance were very less in comparison with lactate levels Conclusion: Arterial blood lactate is elevated in sepsis patients and there is an increased risk of mortality if the elevation is above 4 mmol/lit. Lactate levels are better predictor of mortality than lactate clearance.

Key Words: Sepsis, arterial blood lactate, prognostic marker.

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INTRODUCTION

Sepsis is a systemic response to infection.^{1,2} It is heterogeneous syndrome characterized by wide spread inflammation and continuum ranging from sepsis to severe sepsis and septic shock. It is a lethal incapacitating syndrome, with a high mortality rate that is an important burden to the health care system. Severe sepsis is the most common cause of death in non-coronary intensive care units.³ Even with advanced medical care in

developed countries mortality is around 20% for severe sepsis and increases to 50% for those group with septic shock^{4,5} Lactate is a product of anaerobic metabolism secondary to tissue hypoperfusion and is also seen in aerobic metabolism due to extensive inflammation.⁶ Blood lactate levels rise early because of increased glycolysis as well as impaired clearance of the resulting lactate and pyruvate by liver and kidney. Before the vasodilatory phase of septic shock, a hypodynamic period exists during which the blood lactate concentration is elevated.⁷ Lactate levels can be elevated in hemodynamically stable patients who have normal vital signs.⁸ Hyperlactatemia is a marker of stress response, its severity and duration are related to mortality in critical ill.⁹ Timely identification of ongoing events before they take an ominous turn is essential in the management of the patient in shock.^{10,11} A normalization of serum lactate with aggressive treatment within 24 hours of the insult has been shown to have a favorable outcome.^[11] Many studies have shown the relation between lactate values and sepsis since the identification of lactate in human blood. Its relation with survival outcome has been documented in very fewer studies. This study helps in providing further information regarding blood lactate levels in sepsis and its role in prognosis of patients with sepsis.

MATERIALS AND METHODS

Source of data: The study was conducted in 67 patients admitted to R.L. Jalappa hospital and research centre,Kolar, who satisfied the criteria of SIRS, sepsis, severe sepsis or septic shock. It is a prospective observational cohort study. The "Ethics committee" of the institution approved the study.

Inclusion Criteria: Age > 18 years and patients meeting criteria for sepsis.

Exclusion Criteria: Patients with known Ischemic heart disease, Congestive heart failure, Renal failure, Malignancy, Acute alcohol ingestion, Toxic compounds consumption, Chronic medication for diabetes with Metformin, AIDS, Inborn errors of lactate metabolism

Study Methodology: After taking an informed consent, a detailed clinical history including demographic data, chief complaints, past medical history, personal and family history was taken. A general physical examination was done and axillary temperature, heart rate, blood pressure, respiratory rate and oxygen saturation were recorded. Systemic examination of cardiovascular, respiratory, abdomen and nervous system was done. Arterial Blood was drawn for measuring lactate levels. Blood was drawn from radial artery in a 2ml-heparinized syringe. Heparinized syringe was prepared by first filling the barrel of syringe until 1ml marking and then flushing out all the heparin solution and air 4 times so that no visible heparin solution was left in syringe. Modified Allen's test was performed before drawing blood from radial artery. The femoral artery sampling was done in patients who presented with shock and in whom there was difficulty in

obtaining radial arterial blood sample. Once the sample was obtained it was analyzed within 5 minutes in epoc blood gas analyzer, with CT-1004-00-00 epoc BGEM Test Card. Lactate was measured by amperometry. The sensor comprises an immobilized enzyme first layer coated onto a gold electrode of the electrode module, with diffusion Lactate clearance was calculated according to formulae [(lactate_{initial} - lactate_{delayed})/lactate_{initial}] X 100. Lactate clearance was calculated at 12, 24 and 36 hours Haemogram, arterial blood gas analysis, serum creatinine, blood urea, ECG, chest X-ray.Above investigations were done and recorded. Diagnosis was made clinically and based up on relevant other investigations. Treatment was given as required and no intervention was done. Patients were followed till the time of discharge or death.

Statistical Methods: Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square was used as test of significance. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two groups. Receiver-operating characteristics (ROC) curves and area under the curve (AUC) were computed. For mortality prediction, cut off values for lactates, lactate clearance, and were chosen to correspond to the best respective sensitivity and specificity.

RESULTS

67 subjects whomet the inclusion criteria for sepsis were included in the study Mean age of subjects was 45.34 ± 18.39 yrs. Majority of them were males (52.2). There was no significant difference in gender and age between two groups. There was significant association between mortality and Skin involvement, ARF, MODS in the study (Table 1).

Table 1: Profile of subjects in the study with respect to the Outcome								
Outcome								
	Survivor n=50		Non survivor n = 17		Total		P value	
Sex	22	/28	1()/7	32/35 (47.8%/52.2%)		0.200	
F / M	(44.0%	%/56%)	(58.8%	/41.2%)			0.270	
Age (yrs) Mean ± SD	46.04	18.50	43.29	18.47	45.34	18.39	0.599	
System Involved								
Respiratory system	26	52%	13	76.5%	39	58.2%	0.077	
Hepatobiliary and GIT	8	16.0%	3	17.6%	11	16.4%	0.874	
Skin	1	2.0%	3	17.6%	4	6.0%	0.019*	
Nervous system	1	2.0%	1	5.9%	2	3.0%	0.416	
ARF	2	4.0%	12	70.6%	14	20.9%	<0.001*	
MODS	6	12.0%	12	70.6%	18	26.9%	<0.001*	
Dengue	8	16.0%	2	11.8%	10	14.9%	0.672	
Unknown	11	22.0%	1	5.9%	12	17.9%	0.134	

The mean arterial blood lactate levels at the time of admission, 12 hours, 24 hours, 36 hours in sepsis patients who survived are 3.56 ± 3.16 , 2.96 ± 2.86 , 2.30 ± 1.52 , 2.04 ± 0.88 mmol/lit respectively and mean blood lactate levels in non survivors are 5.53 ± 3.83 , 4.80 ± 3.30 , 3.78 ± 2.05 , 3.43 ± 2.76 mmol/lit at the time of admission, 12 hours, 24 hours, 36 hours respectively. There was a significant association between blood lactate levels and outcome. The mean values for lactate clearance at first 12 hours, 12 to 24 hours and 24 to 36 hours are 15.78 ± 12.92 , 13.26 ± 20.01 , 7.59 ± 15.30 in the survived and 14.75 ± 48.49 , 36.12 ± 50.07 , 12.91 ± 39.37 in the non survived. The lactate clearance was significant only for first 12 to 24 hours.

Table 2: Lactate levels and Lactate clearance between survivors and non	survivors
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	Outcome						
	Survivor		Non survivor		Total		P value
	Mean	SD	Mean	SD	Mean	SD	
Lactate levels (mmol/litre)							
At admission	3.56	3.16	5.53	3.83	4.06	3.42	0.039*
At 12 hours	2.96	2.86	4.80	3.30	3.38	3.04	0.039*
At 24 hours	2.30	1.52	3.78	2.05	2.53	1.67	0.014*
At 36 hours	2.04	.88	3.43	2.76	2.21	1.31	0.007*
Lactate clearance							
First 12 hours	15.78	12.92	14.75	48.49	15.52	26.35	0.891
12 to 24 hours	13.26	20.01	36.12	50.07	19.06	31.71	0.009*
24 to 36 hours	7.59	15.30	12.91	39.37	8.94	23.56	0.425

Mean levels of lactate was significantly higher in non survivors from admission till 36 hours Where as lactate clearance was significantly higher in deceased subjects in 12 to 24 hours value.

Table 3: Area under	the ROC curves	for lactate levels and	lactate clearances
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	AUC	CI 9	5%	P value	Threshold	Sensitivity %	Specifity%
Lactate							
At admission	0.702	0.546	0.858	0.013*	2.500	76.5%	64%
At 12 hours	0.701	0.543	0.858	0.019*	2.500	60%	66%
At 24 hours	0.744	0.570	0.919	0.020*	2.500	55.0%	82%
At 36 hrs	0.646	0.359	0.933	0.215	2.500	57.1%	88%
Lactate clearance							
First 12 hours	0.474	0.268	0.680	0.751	13.96	47.1%	52%
12 to 24 hours	0.558	0.363	0.752	0.480	7.32	52.9%	52%
24 to 36 hours	0.477	0.304	0.651	0.779	-0.55	82.4	30%

Though AUC was Area under the curve was highest for lactate levels at 24 hours i.e. 0.744 and threshold of 2.5 had highest sensitivity and specificity. This observation was statistically significant. Were as lactate clearance had no significant AUC. Hence lactate levels can be used as better predictors of mortality.

Table 4: Comparison of various characters observe	d in sepsis in both su	rvivors and non-survivors
Character	Survivors	Non-Survivors
Duration of stay	6.86 ± 3.31 days	3.35 ± 2.37 days
Temperature in degree Fahrenheit	99.42 ± 1.61 ⁰ F	98.06 ± 1.71 ⁰ F
Pulse rate (beats per min)	92 ± 18	106 ± 24
Systolic blood pressure(SBP) in mm of Hg	114 ± 24	96 ± 24
Diastolic blood pressure(DBP) in mm of Hg	74 ± 12	70 ± 14
Respiratory rate per minute	30 ± 22	36 ± 10
O ₂ saturation percentage	92 ±12	85 ± 7
pH	7.36 ± 0.11	7.25 ± 0.11
Bicarbonate in mmol/lit	20.65 ± 4.20	15.87 ± 7.36
PCO ₂ in mm of Hg	35.63 ± 9.45	38.34 ± 16.32
PO_2 in mm of Hg	130.42 ± 72.32	82.07 ± 22.75
White blood cells (WBC) / mm ³	12800±8570	15575±5943
Platelets / mm ³	161176±134699	152529±108959
Random blood sugar (RBS) in mg/dl	144.46±105.59	180.47±98.62
Blood urea in mg/dl	38.80±24.33	84.88±42.77
Serum creatinine in mg/dl	1.03±0.35	2.41±2.04

Table 4 depicts the various characteristics taken in study and compared. There is a significant difference in values noted for temperature, pulse rate, systolic blood pressure, O₂ saturation, pH, bicarbonate, PCO₂, PO₂ blood urea and creatinine.

DISCUSSION

Sepsisis defined as he presence (probable or ocumented) of infection together with system icmanifestations of infection.¹² Hyperlactatemiaisone of the diagnostic criteria of sepsis.¹³ Current guidelines from the SSC advocate lactate measurement in patients within fectionand possible severe sepsistohelpidentify patients at high risk of death who should be treated aggressively.¹² Lactateis derived from glycolysis, an increased glucose turnover implies that increased lactate production, regardless of any "anaerobic" state. In sepsispatients there is increase in both glucoseandinsulin blood concentration. Insulin resistance favors glycolysis and glucoselactatecycling, thus fostering lactateproduction and perpetuatinghyperlactatemia.⁹ The incidence and prevalence of sepsisvaries from regiontoregion. In the present study, mortality was 25.4% [n=17] where as it was 46.3% in the study by Chatterjeeetal³ in India. Kaukenetal⁴ reported mortality of 18.4% in a study of sepsis conducted in Australia and Newzealand. The threshold of eligibility for treatment differs by time and country, with different cultural approaches to end-oflifecare, different availability of acute hospital and ICU beds, varying levels of universal health insurance, and other cultural and economic factors.¹⁴ Varied treatment modalities and other factors may affect mortalityin sepsis. The rise of lactate production after initialresuscitation effort could be duetoactivation of glycolyticpathway triggered by mechanism such as Na+/K+-ATP as eratherthantheimpactoftissuehypoxia¹⁵ It was also suggested that ahighinitial lactate levels had caused irreversibleor gandamage¹⁶ A significant reductionin lactate levels in survivor sindicatesthatan aggressive therapy for treating the cause of sepsis and thus lowering of lactate levels could reduce the mortality With progression of time there is lowering of lactate value with high sensitivity in predictingmortality. However the lactate levels at 24 hours with 1.83 mmol/lithasgot highest sensitivity and specificity with maximum area under ROC curve which indicates that lactatelevels >1.83 mmol/lit at 24 hours is a better prognostic marker than at the time of admission. This finding is in accordance with the study by Smithetal.¹⁷ where the RO Careaunder curve was more at 24 hours than at admission. It was observed that in patients whose blood lactate evelsremain high even after 24 hour soft treatment had higher mortality, soprobably lactate levels at 24 hours has got better prognostication than at admission.

CONCLUSION

Arterial blood lactate levels are elevated in sepsis. The mean arterial blood lactate values were always more in non-survivors as compared with survivors. Lactate levels at 24 hours are a better prognostic indicator than lactate levels at admission. Lactate clearance does not have significant association with mortality.

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