Original Research Article

Plasma lactate levels and lactate clearance as predictors of outcome in patients with sepsis and septic shock

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ABSTRACT

Background: Severe sepsis and septic shock are the major causes of admission and deaths in the ICU, killing one in four (and often more) and increasing in incidence. In order to improve the clinical outcomes in these patients, it is crucial to obtain early recognition of patients who are at risk of death and to optimize the clinical decision making in a timely manner. In order to monitor the metabolic consequences of shock and hemodynamic management, plasma lactate levels can be used in critical illness. Objective of the study is to estimate plasma lactate and lactate clearance in sepsis and septic shock patients and to correlate plasma lactate and lactate clearance as predictors of mortality.
Methods: This study is a prospective observational study conducted over 18months. Children with age of 1 month to 18 years admitted to the Paediatric intensive care unit with sepsis and septic shock were enrolled in the study. ABG at admission to document plasma lactate and lactate repeated at 6 and 24 hrs. Lactate clearance calculated at 6 and 24 hrs. The final outcome in terms of survival or death will be recorded.
Results: Majority of the children fall in the class between 1-6 months 51(48.11%). Male comprises 69(65.09%). Among these, Sepsis 36(33.96%); followed by Pneumonia 34(32.07%). Survivors group were 35(33.02%) and non-survivor was 71(66.98%). The Non survivor group was observed to have lower mean values of lactate clearance and found to be statistically significant. Specificity of Lactate clearance was 63.52% and Sensitivity 76.02% respectively. The results were positively associated with lactate level at 24 hours found to be significant effect of survivability when compared to non-survivor.
Conclusions: Lactate clearance is vital and markable sign for screening of septic shock at early stage for therapeutic option. Further, 24-hours lactate estimation (cut off values) clearance appears superior to 6 h lactate clearance in predicting mortality in such patients.

Keywords: Lactate, Lactate clearance, Pediatric sepsis, Septic shock

INTRODUCTION

Successful hemodynamic resuscitation and continued monitoring are key components of the management of sepsis in the emergency department {ED}.[1-3] Unfortunately, traditional methods of monitoring such as noninvasive blood pressure, pulse rate, pulse oximetry and urine output, are insensitive and unreliable markers of ongoing tissue hypoperfusion and hypoxia.[4] It is well documented that microvascular flow alterations and organ hypoxia can exist despite normalization of vital signs.[5,6] In order to monitor the metabolic consequences of shock and hemodynamic management, plasma lactate levels and lactate clearance can be used in critical illness.

Lactate measurement in critically ill patients is practical and can provide information on illness severity and prognosis, because a high lactate level is most frequently,

interpreted as resulting from anaerobic metabolism related to cellular hypoxia and is thought to be an important marker of impaired tissue perfusion in patients with sepsis particularly when associated with metabolic acidosis.[7,8] For this reason, current guidelines on the ED management of sepsis recommend measuring and monitoring serum markers of tissue ischemia.[9-11]

The present study aims to check whether plasma lactate levels and lactate clearance at admission to PICU show any correlation with mortality in critically ill patients and the levels which best correlate with mortality and which could be used prospectively to identify patients who are likely to develop multi-organ failure.

METHODS

This study is a prospective observational study conducted over 18 months. Children with age of 1 month to 18 years admitted to the Pediatric intensive care unit with sepsis and septic shock were enrolled in the study. ABG at admission to document plasma lactate and lactate repeated at 6 and 24 hrs. Lactate clearance calculated at 6 and 24 hrs. The final outcome in terms of survival or death will be recorded.

Inclusion criteria

Children with age of 1 month to 18 years admitted to PICU with suspected sepsis and septic shock. Sepsis + Hypotension (BP<2SD adjusted for the age) Or atleast one manifestation of inadequate perfusion:[1]

- Altered mentation (Irritability/ Lethargy/Coma)
- Hypoxia (PaO2/FiO2 <300)
- Metabolic acidosis (Arterial pH<7.35 or Base deficit>5)
- Oliguria (Urine output <0.5ml/kg/h)
- Along with s/o poor peripheral perfusion (CRT>3s; cyanosis)

Exclusion criteria

- Patients with other causes of shock
  - Hypovolemic shock
  - Cardiogenic shock
  - Anaphylactic shock
  - Neurogenic shock
  - Endocrinological cause
- Known malignancies and immunosuppressive treatment.
- Chronic kidney diseases.
- Post-operative state.
- Sepsis and Septic shock patients succumbed within 24 Hrs.

After obtaining institutional ethics committee clearance and written informed consent, the admitted patients in paediatric intensive care unit, the department of Paediatrics fulfilling the inclusion criteria were enrolled in the study.

All patients with sepsis and septic shock based to International consensus on Paediatric sepsis according to inclusion criteria, their blood samples were collected for lactate at the time of admission to the PICU. Pre-structured format was used for collection of data. ABG at admission to document plasma lactate, later serial monitoring of the plasma lactate at 6 and 24 hours. The final outcome in terms of survival or death was recorded.

Collected data was analysed by using SPSS 16.50 version, Univariate logistic regression, ROC and paired test was used to test the hypothetical results.

RESULTS

A total 106 cases were prospectively observed during the study period, the mean age of the patient was 10.56 years with SD 1.62 years. The age class was categorized based on the mean and SD of the individual age group. As per the resulted findings, majority of the children were falling on in the age class between 1-6 months 51(48.11%) followed by 2-5years 22(20.75%), 7-12 months 14(13.21%); 11-16 years was 10(9.43%); 6-10 years 7(6.60%) and more than 16 years was 2(1.89%) respectively (Table 1).

Table 1: Demographics.

Demographics	Number	Percentage
Age class		
1-6months	51	48.1%
7-12months	14	13.2%
2-5years	22	20.7%
6-10years	7	6.60%
11-16years	10	9.43%
>16years	2	1.89%
Gender		
Male	69	65.1%
Female	37	34.9%
Diagnosis		
Pneumonia	34	32.07%
Sepsis	36	33.96%
Neuroinfection	30	28.30%
Urosepsis	04	3.77%
Tonsillopharyngitis	02	1.89%

Of which male comprised 69(65.09%) with male: female ratio of 2:1.

Frequency distribution of various types of diagnosis, presenting with sepsis. As per the resulted findings pneumonia 34(32.07%) was the major cause followed by sepsis 36(33.96%); Neuroinfection 30(28.30%); Urosepsis 04(3.77%) and Tonsillophasyngitis 02(1.89%). The results found that,the survivor 35 (33.02%) and non-

survivor was 71(66.98%) (Table 2). Final outcome in association with lactate level with defined time interval, hypothesis was tested by using ROC and logistic regression analysis methods.

Blood lactate significance level correlation with final outcome with defined time interval, this hypothesis was tested by using ROC analysis .The results found that, in case of survivor, the mean lactate level at 0 hours was 2.92±0.88 ; At 6 hours 8.02±0.93 and at 24 hours was 15.98±3.60. Similarly authors have correlated in non-survivor the mean lactate level at 0 hours was 4.04±0.33; at 6 hours was 7.89±1.56; at 24 hours mean lactate was 13.28±4 (Table 3). The results were positively associated with lactate level at 24 hours found to be significant effect of survivability when compared non survivor with good Specificity =95.21%, Sensitivity =84.55%, NPV-53, PPV-88.63, AUC-0.86.

Table 2: Outcome.

Out come	No	Percentage
Survivor	35	33.02
Non Survivor	71	66.98
Total	106	100.00

Table 3: Blood lactate significance level.

Blood lactate	Non survivor (n=35)		Survivor (n=71)		p-Value	AUC
	Mean±SD	CI-95%	Mean±SD	CI-95%		
Lactate 24h	2.92±0.588	1.76-4.07	4.74±0.33	4.04-5.45	≥0.000	0.62
LC6hrs	8.02±0.93	6.10-9.94	7.89±1.56	4.84-10.95	≥0.000	0.71
LC24hrs	15.98±3.6	8.92-23.03	13.28±4.45	4.42-22.14	≤0.000	0.86

The Non survivor group was observed to be associated with lower mean values of lactate clearance and found to be statistically significant, At 24 hours: Specificity =95.21%, Sensitivity=84.55%, NPV-53, PPV-88.63, AUC-0.86 (Relative cut off values lactate clearance 26.52 at 24 hours) (Figure 1).
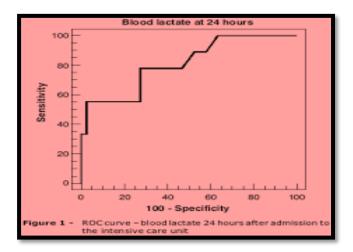

Figure 1: ROC curve blood lactate at 24 hours.

DISCUSSION

The present study confirms the association between Lactate level and Lactate clearance [LC] with mortality in Sepsis and septic shock patients. This study demonstrated to know the correlation between lactate levels and lactate clearance (relative cut off values 26.52 at 24 hours).

A separate group was categorised based on the mortality viz survivor and non-survivor group, for each group ROC analysis was done to obtain the relevancy of the study parameters. Importantly, this is very important paediatric study to demonstrate that a relative estimation of LC, lactate normalisation within the 0-24 hours of treatment strongly predicts survival rate by using statistical methods.

Zhang Z, Xu X, et al, conducted meta-analysis clearly depicted that, a consistent lower mortality associated with LC cut off values (24.55 at 24 hours, specificity 95.0% p=0.002). This study is comparable to this study intervention, the present study describes blood lactate level was found to be significantly correlated with survivor and insignificant correlation was found in non-survivor. The results were strongly associated with lactate level at 24 hours found to be significantly affect the survivability when compared to non-survivor group with good Specificity =78.21%, Sensitivity =80.09.55%, Negative Predictive Value -76, Positive Predictive Value -63.21, AUC-0.72.[12]

Another global study reported by Krishna et al, measured a serial lactate concentrations during 24 hours in 115 children with severe malaria in Gambia, concluding that sustained high lactate was the most powerful prognostic indicator of fatal outcome.[13-17]

Another study done by Kim et al, in 65 children admitted in a paediatric intensive care unit (PICU) with septic shock, the results found that the area under the curve (AUC) of serial lactates measured during the first 24h

had a strong predictive power of mortality at 28 days (ROC AUC -0.828).[18-21]

In this study, the serial lactate was estimated and analysed by ROC, the results proved that lactate level was correlated with different time period and mortality (p<0.01).

Authors observed to correlate this results with another study done by Munde et al, recently reported that a relative LC <30% at 6 h predicted mortality in PICU children in India comparably to the more complex Paediatric Risk of Mortality (PRISM) score, standard in paediatric intensive care.[22-27] LC could serve as valid surrogate end point of clinical trials of malaria, aiming to improve mortality, as recently demonstrated by Jeeyapant et al, in a large cohort of adult patients with malaria.[21]

To date two multicentre randomised trials have assessed the clinical value of resuscitation strategies that included LC as a target in adults admitted to intensive care units, showing that quantitative resuscitation based on LC was non-inferior or even superior to that based on ScvO2 alone, and the most recent Surviving sepsis Campaign guidelines suggest targeting resuscitation to lactate normalisation in adult septic patients, although weak evidence exists for this recommendation.[14,15,28]

A recent study conducted in 218 adult patients with severe infection at a regional referral hospital in Uganda questioned whether serial assessment of vital signs combined with point-of-care lactate at 6 hr could be a feasible method of monitoring patients being resuscitated from severe sepsis or malaria in a resource-poor setting.[24] Despite an improvement in vital signs and lactate values at 6 h of resuscitation, the authors could not demonstrate an association between an LC ≥10% and improved in-hospital mortality.[25,26]

Many literatures revealed that, more extreme or loose definition could have yielded slightly different results. Moreover, the fact that LC in the FEAST trial was calculated at 8h after randomisation for all participants, prevents one from determining the precise moment when lactate normalisation occurred for each individual. If some of the participants cleared their lactate significantly earlier than 8-24 hours and that was associated with a better outcome, the true effect of lactate normalisation/LC on survival could be underestimated.[21-23]

This study had certain limitations to correlate PRISM score in accordance with standard operating protocol due to time lag and resources. Despite the optimal LC threshold or the LC rate not having been clearly defined, many studies on LC in sepsis have used a relative clearance rate of 10–20% in repeated samples measured at 2 -3 hours intervals during the first 0-24 hours of morbidity. Unfortunately, this prospective observational study design does not allow one to answer whether targeting resuscitation to achieve a specific Lactate clearance improves outcomes in severely ill children in this context.

CONCLUSION

Lactate clearance is a simple, valid and cost-effective risk stratification tool, potentially more reliable than absolute lactate values alone. It may as well be a potential therapeutic target to guide resuscitation in children in resource-poor settings. Furthermore, it is not limited to children with specific diagnoses, but rather covers different presentation syndromes, which reflects the population of children presenting to hospital.

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