Lactate clearance at 6 hours after admission as a predictor of mortality in children with clinically suspected sepsis

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Abstract

Background: Causes of death in children with severe sepsis include septic shock, end organ damage and multiple organ dysfunction syndrome (MODS).

Objective: To ascertain whether lactate clearance predicts outcome of children with sepsis

Method: Prospective observational study was carried out among 100 children aged between 1 month and 12 years with clinical features of clinically suspected sepsis (Proven or suspected infection fulfilling at least two of the four criteria of Systemic Inflammatory Response Syndrome (SIRS)). Relevant investigations were carried out.

Results: The mean age of the children was 2.55 years. The incidence of death among the lactate non-clearance group was 84.2%, significantly more compared to 17.8% among survivors. About 91.6% of the area was under curve which was statistically significant with a cut off value of lactate clearance less than or equal to 12.7%. The sensitivity at this level was 84.2%, specificity was 91.3%, positive likelihood ratio was 8.7, and negative likelihood ratio was 0.17. Lactate at zero hours and six hours was significantly more among non-survivors compared to survivors.

Conclusions: The serum lactate clearance level at 6 hours of admission demonstrated that it is a sensitive and specific marker in prediction of the mortality.

(Key words: Lactate clearance, Admission, Predictor, Mortality, Children, Sepsis)

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Introduction

Causes of death in children with severe sepsis include septic shock, end organ damage and multiple organ dysfunction syndrome (MODS)[1]. Resuscitation efforts are based on improvement in clinical parameters such as peripheral perfusion, capillary refill <3 seconds, heart rate appropriate for age and mental status, along with clearance in lactate (<2 mmol/L) and normalization of central venous oxygen saturation (>70%) as per surviving sepsis guidelines[2]. In situations of sepsis, hypoperfusion leads to global tissue hypoxia, pyruvate no longer entering mitochondria for aerobic metabolism but being preferentially reduced to lactate, resulting in lactate accumulation in the blood[3]. It was noted that patients whose lactate levels decreased with therapy had better outcome than those with persistent elevated lactate levels[3]. Hence the lactate level was useful as a diagnostic, monitoring and prognostic biomarker. To date, no lactate clearance cutoff value has been agreed upon. A study used a cutoff point of >10% within the first 6 hours of treatment, and reported that any increase in lactate clearance by 10% reduced mortality in adults with sepsis[4]. Increased serum lactate level is indicative of anaerobic metabolism caused by tissue hypoxia, and is a good marker to assess tissue perfusion in sepsis. A state of hyperlactataemia (serum lactate >2 mmol/L) is a cardinal sign of sepsis[5]. However, the majority of research with serum lactate and lactate clearance in sepsis has been conducted in adults and paediatric data is scarce.

Objectives

To ascertain whether lactate clearance predicts outcome of children with sepsis.

Method

A prospective observational study was carried out among 100 in-patients of the paediatric department, Chacha Nehru Bal Chikitsalaya, Delhi from January 2018 to December 2019.

Sample size: Assuming the mortality in lactate non–clearance group as 60% in patients with severe sepsis[6], sample size estimation was done based on sample size (n) = Z^2 p (1-p)/d^2

Z = Z value (e.g. 1.96 for 95% confidence level); p = prevalence (06); d = precision (10%)

$(1.96)^2$ x 0.6 x (1-0.6)/ $(0.1)^2$ = 92

Assuming attrition rate of 10%, we planned to recruit 100 cases.

Inclusion criteria: Children aged between 1 month and 12 years with features of clinically suspected sepsis (Proven or suspected infection fulfilling at least two of the four criteria of Systemic Inflammatory Response Syndrome (SIRS).

Exclusion criteria:

- Severe dehydration.
- Patients with diabetic ketoacidosis.
- Known case of chronic liver disease
- Known case of chronic kidney disease

All children with clinically suspected sepsis were enrolled in the study. Sepsis was suspected in those children with proven or suspected infection fulfilling two or more of the 4 SIRS criteria.

***SIRS criteria*[7]:**

1. Abnormal temperature or leucocyte count [Leucocyte count elevated or depressed for age (not secondary to chemotherapy-induced leucopenia) or 10% immature neutrophils].
2. Core body temperature >38.5°C or <36°C.
3. Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli or otherwise unexplained persistent elevation over a 0.5- 4-hour time period or for children <1 year old. Bradycardia was defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, beta-blocker drugs, or congenital heart disease or otherwise unexplained persistent depression over a 0.5-hour time period.
4. Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.

Lactate clearance was calculated at 6 hours of admission and depending on lactate clearance children were divided into two groups as lactate non-clearance and lactate clearance.

- Lactate clearance=lactate decreased by 12.7% or greater from admission lactate level
- Lactate non-clearance= lactate decreased by less than 12.7% from initial or non-reduction of lactate from admission lactate level.

Other tests performed: Complete blood count with differential count, renal function tests, liver function tests, serum lactate level (at admission and after 6 hours), blood culture, venous blood gas analysis (at 0 and 6 hours).

Sample was collected for above mentioned blood tests and necessary parameters were noted; 8-10 ml of venous blood was collected and distributed as per standard guidelines. Repeat serum lactate at 6 hours for lactate clearance calculation was done.

Other parameters noted: Glasgow coma scale, systolic and diastolic blood pressure.
Patients were followed till death or hospital discharge and final outcome was taken as survival or non-survival.

Definitions:

- Lactate clearance[8]: defined as the percentage change in lactate levels after six hours from a baseline measurement in the emergency department (ED).
- Sepsis[4]: defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Severe sepsis[5]: defined as sepsis associated with organ dysfunction or tissue hypoperfusion.
- Fluid-refractory shock: No response to initial fluid resuscitation of up to 60 ml/ kg of isotonic crystalloid/colloid bolus administered in a 15 minutes period.
- Reversal of shock: Attainment of normal pulses, capillary refill time (CRT), mean arterial pressure (MAP), central venous pressure (CVP), urine output and mental status. Normalization of metabolic parameters – lactate clearance, increase in central venous oxygen saturation > 70%.

Ethical issues: Ethics clearance was granted by the Institutional Ethics Committee, Chacha Nehru Bal Chikitsalaya, Geeta Colony, Delhi, India (No. F1/IEC/CNBC/03/01/2019/2469). Written informed consent of parents was taken before enrolling children into study.

Data analysis: Categorical variables were presented in number and percentage and continuous variables were presented as mean± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected, then a non-parametric test was used. Quantitative variables were compared using Independent t-test / Mann-Whitney test (when the data sets were not normally distributed) between the two groups. Qualitative variables were correlated using Chi-Square test. Receiver operating characteristic curve was used to find out cut-off point of lactate clearance for predicting mortality. A p value <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

The mean age of the children was 2.55 years, the mean duration of hospitals stay was 6.9 days, mean lactate at 0 hour was 3.96 and at 6 hours was 3.32 mmol/L. The mean lactate clearance was 17.19±10.51% and the mean platelet count was 200,270/microlitre (Table 1). The incidence of death among the lactate non-clearance group was 84.2% compared to 9.6% among the lactate clearance group. This association was found to be statistically significant ($p<0.05$). The odds ratio of death was 49.78 (95%CI=14.81-167.3) among those children with lactate non-clearance ($p<0.05$) (Table 2)

Table 1

Distribution of study group according to age, duration of hospital stay, lactate levels and platelet count (n=100)

Variable	Mean ± SD	Median	Min-max	Inter-quartile range
Age (years)	2.55 ± 2.61	1.6	0.12-11	0.50-4
Duration of hospital stay (days)	6.9 ± 3.67	6	1-20	4-9
Blood lactate at zero hours (mmol/L)	3.96 ± 1.41	3.6	2.1-8	2.75-4.95
Blood lactate at six hours (mmol/L)	3.32 ± 1.4	2.85	1.6-8.9	2.2-4.3
Lactate clearance (%)	17.19 ± 10.51	16.6	-11.2-45.9	10-25.5
Platelet count / microlitre	200,270 ± 117,729	178,000	40,000-640,000	116,000-247,500

SD: standard deviation, Min-max: Minimum-maximum

Table 2: ***Mortality in lactate clearance and non-clearance groups***

Lactate clearance status	Non-survivors	Survivors	Chi square	p-value	Odds ratio	95% CI
≤ 12.7% (non-clearance)	32 (84.2%)	06 (17.8%)	52.45	< 0.0001	49.78	14.81-167.3
> 12.7% (clearance)	06 (09.6%)	56 (90.4%)				
Total	38 (38.0%)	62 (62.0%)				

About 91.6% of the area was under curve which was statistically significant with a cut off value of lactate clearance less than or equal to 12.7%. The sensitivity of lactate clearance at this level was 84.2%, specificity was 91.3%, positive likelihood ratio was 8.7, and negative likelihood ratio was 0.2 (Table 3).

Table 3: ***Area Under Curve (AUC), cut off value and predictive accuracy of lactate clearance as predictor of mortality in children with sepsis***

Parameter	AUC	Standard error	95% CI	P value	Cut off value
Lactate clearance (%)	0.916	0.03	0.844-0.962	< 0.0001	≤12.7
Parameter	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**+likelihood ratio (95% CI)**	**Negative likelihood ratio (95% CI)**	**positive predictive value (95% CI)**
Lactate clearance (%)	84.21 (68.7 - 94.0)	90.32 (80.1 - 96.4)	8.7 (4.0 - 18.8)	0.17 (0.08 - 0.4)	84.2 (68.7 - 94.0)

CI: confidence interval

Blood lactate at zero hours and six hours was significantly higher among non-survivors compared to survivors. Duration of hospital stay and albumin levels were significantly less among non-survivors compared to survivors.

Discussion

There were 100 patients who met the inclusion criteria. Overall death rate was 38%. The mean age of the children was 2.55 years and the predominant age group was 1-5 years; 54% were males. Aramburo A, *et al*[9] observed similar findings. In a study by Nazir M, *et al*[10], 46% of the children were males. In our study the mean duration of hospital stay was 6.9 days; mean lactate at zero hour was 3.96 and at six hours was 3.32 mg/dL. The mean lactate clearance was 17.19±10.51% and mean platelet count was 200,270/cu mm. In a study by Aramburo A, *et al*[9], the median age was 24 months among all children, the mean lactate at the time of admission was 3.8 mmol/L. In a study by Nazir M, *et al*[10], the median age was 22 months, the lactate at the time of admission was 6.1 mmol/L; the percentage of lactate clearance was 57.9% within 6 hours.

In our study a lactate clearance cut off of 12.7% had maximum sensitivity plus specificity for predicting hospital mortality. After six hours intervention, a lactate clearance of 12.7% had a sensitivity of 84.2% and a specificity of 90.3%. Patients were then categorized into the non-clearance group (<12.7% clearance) and clearance group (>12.7% clearance). In a study by Saputra DK, *et al*[11], the outcome between patients with lactate clearance of less than or equal to 34.7% and more than 34.7% was statistically significant. This difference may be due to the different cut-off points chosen in these two studies. In our study of 100 patients, 62 had lactate clearance and 38 had lactate non-clearance; mortality was 84.2% in the lactate non-clearance group versus 9.6% in the lactate clearance group ($p<0.001$).

In our study, mean ages of the children with lactate clearance (>12.7%) vs non-clearance (<12.7%) groups were 2.51 years and 2.62 years respectively which was not statistically significant. In a study by Nazir M, *et al*[10], the median age among the survivors was 22.8 months and 24.2 months among the non survivors. Among lactate clearance group 50% were male and 50% were female and in non-lactate clearance group 34.2% were female and 65.8% were males. There was no statistical significance of gender in lactate clearance (p=0.123). No studies compared these results.

There are some limitations to the study. This is a non-experimental observational study and as such can detect only the association between lactate clearance and mortality but cannot establish cause and effect. Performing serial lactate measurement in patients with sepsis is not a mandatory practice in our centres and measurements are performed at the discretion of the clinician, so this could potentially represent a source of selection bias

Conclusions

The serum lactate clearance level at 6 hours after admission is a sensitive and specific marker in prediction of mortality. A lactate clearance cut off of 12.7% had the maximum sensitivity plus specificity for predicting hospital mortality.

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