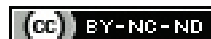


Role of Blood Lactate Clearance in Predicting Outcomes among Septic Patients Admitted to the PICU: A Prospective Cohort Study

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ABSTRACT

Introduction: A crucial metric for evaluating the effectiveness of microcirculation in septic shock is serum lactate. Lactate clearance within the first 24 hours of admission has predictive value for death in Paediatric Intensive Care Unit (PICU) admissions. Higher mortality was observed in septic patients who were unable to clear elevated admission lactate.

Aim: To determine the admission lactate level and to investigate whether failure to clear elevated lactate in septic patients can prognosticate high PICU mortality.

Materials and Methods: This prospective cohort study was conducted from August 2021 to July 2022 at PICU, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India. A total of 75 children, aged two months to 18 years, admitted

to the PICU for sepsis or septic shock, were enrolled in the study. The authors measured blood lactate at Intensive Care Unit (ICU) admission, at 6, 12, and 24 hours. Lactate clearance was calculated, and its association with mortality after 24 hours of PICU stay was measured using the Chi-square test.

Results: Out of the total, 55 survived, comprising 31 males (41.3%) and 44 females (58.7%). When comparing admission blood lactate to lactate clearance >10% at 6, 12, and 24 hours, there was no correlation between the two variables and mortality in PICU patients with sepsis.

Conclusion: Lactate clearance in the first 24 hours of PICU stay was recommended as a parameter associated with the mortality rate among septic patients. However, the authors did not find any correlation.

Keywords: Child, Lactic acid, Paediatric intensive care unit, Prognosis, Septic shock, Sepsis

INTRODUCTION

Paediatric sepsis with shock, one of the most life-threatening conditions, remains the leading cause of mortality and morbidity [1]. The Third International Consensus definitions for sepsis and septic shock classified sepsis as an infection in the presence of Systemic Inflammatory Response Syndrome (SIRS). SIRS comprises temperature dysregulation (core body temperature >38.5°C or <36°C); tachycardia (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); bradycardia (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); respiratory rate dysregulation (mean respiratory rate >2 SD above normal for age); elevated or depressed leucocyte count for age, or >10% immature neutrophils (but not secondary to chemotherapy-induced leukopenia) [1].

The inadequate tissue perfusion causes adverse vascular, inflammatory, metabolic, cellular, endocrine, and systemic responses. Hyperlactatemia, defined as lactate levels greater than or equal to 2 mmol/L, is a cardinal finding in sepsis and septic shock, and is used as a marker for predicting mortality [2]. Blood lactate levels increase significantly during tissue hypoperfusion and can be detected earlier than other changes in haemodynamic parameters, namely a fall in blood pressure, prolonged capillary refilling time, cool extremities, and feeble pulses [3]. Blood lactate clearance can be used to assess the oxygen supply of microcirculation, and blood lactate clearance over a 24-hour period is a more reliable guide for fluid resuscitation in sepsis than measuring single blood lactate levels [4].

Studies comparing the prognostic value of blood lactate level and lactate clearance at six hours after septic shock recognition found that both blood lactate and blood lactate clearance are useful targets in patients with septic shock [5,6].

Most studies [6-10] measuring the association between serum lactate and mortality in sepsis and septic shock have been done on adults, with few paediatric studies [9,11]. The present study was the first study conducted at the PICU of study institute on critically-ill paediatric patients to determine whether low blood lactate clearance (<10%) over 24 hours (compared to admission arterial blood lactate level) increases all-cause mortality.

MATERIALS AND METHODS

This was a prospective cohort study conducted over a period of one year from August 2021 to July 2022 at PICU, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India. The study was conducted with the approval of the Institute Ethics Committee in accordance with the ethical standards (HFW (MC-II) B (12) Ethics/2021-8560).

Inclusion criteria: Age group between 2 months till 18 years [1], who survived >24 hours after PICU admission, had Arterial Blood Gas (ABG) performed and reported within 15 minutes of admission into the PICU, and whose parents/caregivers gave consent to participate in the study were included.

Exclusion criteria: Patients with shock not due to sepsis, e.g., cardiogenic, oligemic, anaphylactic, neurogenic, endocrinological, and dengue shock, patients with known malignancies and on immunosuppressive treatment, postoperative patients, those whose ABG could not be done within 15 minutes of PICU admission due to logistic reasons, patients taking drugs nucleoside reverse transcriptase inhibitors for the treatment of Human Immunodeficiency Virus (HIV), metformin for diabetes mellitus, steroids, linezolid, and sodium bicarbonate, patients admitted with ethylene glycol and methanol intoxication, known cases of liver dysfunction, gut ischaemia, thiamine deficiency, mitochondrial dysfunction, inborn errors of metabolism, and those whose parents/guardians refused consent to participate were excluded.

Sample size calculation: A total of 193 patients were admitted to the PICU, out of which 75 patients diagnosed with sepsis in the age group between two months to 18 years were enrolled.

Study Procedure

The primary outcome was survival or death at the end of the hospital stay. Demographic data were collected from hospital records, including age, sex, treatment including oxygen, ventilation, blood gas, and outcome. ABG from the right radial artery (0.5 mL blood sample) was taken into a heparinised syringe and analysed on the Opti CCA Blood gas and electrolyte analyser machine in all eligible patients with a diagnosis of sepsis within 15 minutes of PICU admission, and repeated at 6 hours, 12 hours, and 24 hours after admission. In a previous study, low lactate clearance (<10%) within the first 6 hours accurately predicted death two-thirds of the time in 111 adult patients with sepsis and septic shock [12]. Blood lactate clearance was calculated using the formula: {(lactate initial-lactate delayed)/lactate initial}×100 [8]. Patients were managed for sepsis with antibiotics, fluid resuscitation, inotropes, and source identification according to the standard guidelines [13]. The outcome of the patient was recorded as survived and discharged alive or dead.

STATISTICAL ANALYSIS

The data was entered in Microsoft excel and analysed using Epi Info version 7 software. The Chi-square test was used to compare among the survivors and those who died. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Among a total of 75 patients diagnosed with sepsis in the age group between two months to 18 years who were enrolled, there were 31 males (41.3%) and 44 females (58.7%), resulting in an M:F ratio of 1:1.4. Out of these, 55 (73.3%) survived. Among them, 45 (60%) were aged <5 years [Table/Fig-1].

Characteristics		n (%)
Sex	Male	31 (41.3)
	Female	44 (58.7)
Age	<5 years	45 (60)
	>5-18 years	30 (40)
Ventilation received	Yes	31 (41.3)
Only free oxygen	Yes	20 (26.6)
Non invasive respiratory support	Yes	24 (32)
Inotrope support	Yes	60 (80)
Outcome	Discharged	55 (73.3)
	Dead	20 (26.7)
Mean admission lactate	2.5±0.2 mmol/L	
Mean lactate at 6 h	2.0±0.1 mmol/L	
Lactate clearance at 6 h	<10%	36 (48)
	>10%	39 (52)
Mean lactate at 12 h	1.9±0.2 mmol/L	
Lactate clearance at 12 h	<10%	28 (37.3)
	>10%	47 (62.7)
Mean lactate at 24 h	1.8±0.3 mmol/L	
Lactate clearance at 24 h	<10%	20 (26.7)
	>10%	55 (73.3)

[Table/Fig-1]: Characteristics of patients admitted in PICU with sepsis.

A total of 55 patients had admission blood lactate below 2 mg/dL in ABG, among them 33 patients (60%) survived. At six hours of admission, among 36 patients with lactate clearance of <10%, 28 (77%) survived. At 12 hours of admission, among 28 patients with lactate clearance <10%, 22 (78.7%) survived. At 24 hours of

admission, out of 20 patients with lactate clearance <10%, 15 (75%) survived. There was no association between lactate clearance >10% and mortality at 6, 12, and 24 hours of PICU admission [Table/Fig-2].

Variables		Discharged alive, n (%)	Died, n (%)	p-value
Age	<5 yrs	30 (66.7)	15 (33.3)	0.182
	>5 yrs	25 (83.3)	5 (16.7)	
Male:Female		1:1.4	1:1.5	1.00
Admission blood lactate	<2 mg/dL	33 (80.5)	12 (35.3)	0.2
	>2 mg/dL	22 (19.5)	8 (64.7)	
Lactate clearance at 6 h of PICU admission	>10%	27 (69.3)	12 (30.7)	0.56
	<10%	28 (77.7)	8 (22.3)	
Lactate clearance at 12 h of PICU admission	>10%	33 (79.1)	14 (29.89)	0.6
	<10%	22 (78.9)	6 (21.2)	
Lactate clearance at 24 h	>10%	40 (72.73)	15 (27.27)	0.91
	<10%	15 (75)	5 (25)	
Duration of PICU stay		13±2 days	10±3	0.6

[Table/Fig-2]: Association between lactate clearance and survival in PICU.

DISCUSSION

The global burden of sepsis is substantial. Recent scientific publications have estimated about 48.9 million cases with 11 million sepsis-related deaths worldwide, which accounted for almost 20% of all global deaths [14]. Almost half of these cases occurred among children under five years of age, with an estimated 20 million cases and 2.9 million global deaths [15,16]. Sepsis and septic shock are characterised by dysfunctional tissue circulation and decreased oxygen and nutrient supply [2,15]. In tissue hypoxia, anaerobic glycolysis causes an excess of lactate to be generated, which is underutilised because of compromised mitochondrial oxidation [17]. Impaired perfusion at the microcirculation level further impairs lactate clearance in sepsis [4,6,12]. Blood lactate clearance over a period of 24 hours can also be used to assess oxygen delivery during resuscitation to assess its effectiveness [18].

Lactate clearance typically occurs in the liver (60%), followed by the kidney (30%), and to a lesser extent by other organs (such as the heart and skeletal muscle) [3]. Lactate clearance cannot overcome lactate production during sickness and in critically-ill patients. Septic shock with liver dysfunction and acute kidney injury elevates lactate because of reduced lactate clearance. Compared to the initial blood lactate level, lactate clearance at any discrete time point is a significant predictive factor in sepsis [4].

Randomised controlled trials with 647 patients evaluated lactate-guided resuscitation of patients who had septic shock [6]. Results showed that mortality was reduced in patients who received lactate-guided resuscitation compared with those who received resuscitation without lactate monitoring (risk ratio, 0.67; 95% Confidence Interval (CI), 0.53-0.84) [6]. However, the authors did not find any association between lactate clearance and PICU mortality.

Munde A et al., in their study, enrolled 45 patients and found 90% of deaths in the PICU among those with delayed/poor clearance (clearance <10%) compared to 8.5% in those with good clearance (p<0.001) [11]. In the present study, out of a total of 20 deaths, the authors identified that 12 patients had high admission lactate, among whom eight patients failed to reduce admission lactate by more than 10%. However, the p-value was not significant among those who died and lactate clearance over 24 hours.

Gulla K et al., enrolled 43 patients and found that serum lactate ≥2.6 mmol/L at 24 hours predicted early PICU mortality [7]. A retrospective study by Gündoğan U et al., evaluated the predictive value of the anion gap and lactate clearance after 6 hours of PICU admission for mortality in paediatric patients and found increased

mortality with failure to clear elevated lactate [19]. Choudhary R et al., also found that failure to clear elevated lactate in paediatric septic shock patients predicts higher mortality [12]. Moustafa AA et al., concluded in a prospective study among critical PICU admissions that lactate clearance after six hours of admission can predict mortality in critically-ill children [20]. The findings from the present study could not identify failure to clear elevated lactate at admission to be significantly associated with increased mortality among septic patients admitted to our PICU.

Limitation(s)

The present study had a small sample size. Additionally, parameters such as PICU mortality scores, patient sickness, quality of care, nurse-patient ratio, care bundles, etc., should have been taken into consideration for mortality, as sepsis is only one of many processes that might affect lactate clearance.

CONCLUSION(S)

The present study was conducted to examine the effect of low blood lactate clearance (<10%) over 24 hours on mortality among septic patients admitted to the PICU. However, the authors did not find any significant association of lactate clearance over a 24-hour duration in predicting mortality in septic paediatric patients in the PICU. In many studies, among paediatric patients admitted to the Intensive Care Unit (ICU), high admission lactate as well as a delay in lactate clearance was a significant independent predictor of mortality. However, the present study was unable to replicate this finding. Further research evaluating the role of lactate kinetics during sepsis management is required to guide physicians in their management of septic patients and improve clinical outcomes.

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AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

PLAGIARISM CHECKING METHODS: [Jaain H et al.]

- Plagiarism X-checker: Jul 21, 2023
- Manual Googling: Oct 13, 2023
- iThenticate Software: Jan 09, 2024 (14%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

Date of Submission: Jul 20, 2023
Date of Peer Review: Oct 10, 2023
Date of Acceptance: Jan 11, 2024
Date of Publishing: Mar 01, 2024