ORIGINAL RESEARCH

To determine the significance of serum lactate clearance in predicting the likelihood of death and complications in neonatal sepsis

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ABSTRACT

Background: Neonatal sepsis remains a significant cause of mortality and morbidity in newborns worldwide, accounting for a substantial proportion of neonatal deaths, particularly in low- and middle-income countries. Serum lactate is produced as an end product of anaerobic metabolism, and its accumulation reflects an imbalance between oxygen delivery and consumption, often due to impaired tissue perfusion and cellular hypoxia. Elevated serum lactate levels have been associated with increased mortality in various critical care settings, including adult and pediatrics sepsis. **Aim and Objectives**: To determine the significance of serum lactate clearance in predicting the likelihood of death and complications in neonatal sepsis. **Materials and methods**: The present prospective cohort study was conducted on 100 neonates diagnosed with sepsis and admitted to the SNCU and NICU during the study period were included. Neonates were categorized into two cohorts: positive lactate clearance (lactate clearance > 0) and negative lactate clearance (lactate clearance < 0). Both cohorts were monitored until discharge or death to track their clinical course. Patient particulars, including demographic parameters (age, gender, gestational age, birth weight, initial presentation, early/late onset sepsis), Results of conventional markers of sepsis, including: Sepsis screen, blood culture and antimicrobial sensitivity pattern, serum procalcitonin levels, cerebrospinal fluid studies, urine routine examination and culture sensitivity, Initial and final lactate levels and lactate clearance, Mortality rate were measured. **Results**: The mortality rate was significantly lower in the positive lactate clearance group (6.67%) compared to the negative lactate clearance group (28.57%), with a p-value of 0.008. The duration of oxygen requirement was shorter in the positive lactate clearance group (3.5 ± 1.2 days) than in the negative group (6.8 ± 2.0 days), with a p-value of <0.001. Similarly, the duration of fluid support was shorter in the positive group (4.0 ± 1.0 days) compared to the negative group (7.5 ± 1.5 days) ($p < 0.001$). The duration of NPM was also shorter in the positive group (2.5 ± 0.8 days) versus the negative group (5.2 ± 1.2 days) ($p < 0.001$). The duration of hypoglycaemia was shorter in the positive group (1.5 ± 0.5 days) compared to the negative group (3.5 ± 0.9 days) ($p < 0.001$). Persistent hypoglycaemia occurred in 4.44% of the positive group and 22.86% of the negative group, which was statistically significant ($p = 0.016$). The duration of ventilation was shorter in the positive group (2.0 ± 0.7 days) compared to the negative group (4.5 ± 1.5 days) ($p < 0.001$). The mode of ventilation showed significant differences, with more neonates in the positive group on CPAP and NIV, while more neonates in the negative group required invasive ventilation ($p = 0.037$). **Conclusion**: In conclusion, the study demonstrates that serum lactate clearance is a valuable predictor of mortality and morbidity in neonatal sepsis. Higher lactate clearance is associated with significantly better clinical outcomes, including lower mortality rates and reduced duration and severity of illness. These findings emphasize the need for incorporating lactate clearance measurements in the management and prognosis of neonatal sepsis, alongside conventional sepsis markers.

Keywords: Serum lactate clearance, Death, Neonatal sepsis.

INTRODUCTION

Neonatal sepsis remains a significant cause of mortality and morbidity in newborns worldwide, accounting for a substantial proportion of neonatal deaths, particularly in low- and middle-income countries. Despite advances in neonatal care, early diagnosis and effective management of neonatal sepsis continue to pose considerable challenges to clinicians. Conventional markers of sepsis, such as white blood cell count, C-reactive protein (CRP), and procalcitonin, though widely used, often lack the sensitivity and specificity required for early and accurate prognostication in neonates. This has necessitated the search for additional biomarkers that can reliably predict outcomes and guide therapeutic interventions. Among these, serum lactate levels and lactate clearance have emerged as potential indicators of tissue hypoxia and overall metabolic distress, offering promise as prognostic tools in neonatal sepsis.[1]Serum lactate is produced as an end product of anaerobic metabolism, and its accumulation reflects an imbalance between oxygen delivery and consumption, often due to impaired tissue perfusion and cellular hypoxia. Elevated serum lactate levels have been associated with increased mortality in various critical care settings, including adult and paediatric sepsis. However, static lactate measurements can be influenced by numerous factors and may not always correlate with clinical outcomes. In contrast, lactate clearance, defined as the rate of decrease in serum lactate levels over time, provides dynamic information about the resolution of metabolic acidosis and the restoration of adequate tissue perfusion. Several studies have highlighted the prognostic significance of lactate clearance in adult and paediatric populations, but its utility in neonatal sepsis warrants further exploration.[2,3]The pathophysiological basis for lactate clearance as a prognostic marker lies in its reflection of the body's ability to recover from septic shock and restore tissue perfusion. During sepsis, systemic inflammation and microbial invasion lead to widespread endothelial dysfunction, capillary leak, and impaired microcirculation, resulting in inadequate oxygen delivery to tissues. The subsequent shift to anaerobic metabolism causes lactate accumulation. Effective therapeutic interventions, such as fluid resuscitation, antibiotics, and vasoactive medications, aim to reverse these hemodynamic disturbances, thereby enhancing oxygen delivery and promoting lactate clearance. Consequently, a higher rate of lactate clearance indicates a favourable response to treatment and a better prognosis.[4]

Despite its potential, the clinical application of lactate clearance in neonatal sepsis has been limited by several factors. Neonates, particularly preterm infants, exhibit unique physiological characteristics that influence lactate metabolism, including immature organ systems, variable metabolic rates, and differential responses to hypoxia. These factors can affect baseline lactate levels and clearance rates, necessitating age- and gestation-specific reference ranges for accurate interpretation. Moreover, the optimal timing and frequency of lactate measurements remain areas of active research, with studies suggesting that early and frequent monitoring may enhance the predictive value of lactate clearance.[5]

AIM AND OBJECTIVES

To determine the significance of serum lactate clearance in predicting the likelihood of death and complications in neonatal sepsis.

MATERIALS AND METHODS

A prospective cohort study was conducted in the Special Newborn Care Unit (SNCU) and Neonatal Intensive Care Unit (NICU) at the Department of Paediatrics, Gouri Devi Institute of Medical Sciences & Hospital, Rajbandh, Durgapur, West Bengal, India, for a period of one year (March, 2019 – February, 2020) among 100 neonateswith a confirmed diagnosis of neonatal sepsisin the paediatric department after obtaining ethical clearance from the Institutional Ethical Clearance Committee.The present study was conducted on both genders and those who met the specified criteria for inclusion and exclusion criteria. Written informed consent was obtained from the parents or guardians of the neonates enrolled in the study.

Inclusion Criteria

- All neonates with a confirmed diagnosis of neonatal sepsis, as evidenced by one or more of the following tests, were included in the study: positive sepsis screen, positive blood culture, positive urine culture, positive Procalcitonin, or cerebrospinal fluid (CSF) positive for meningitis.
- Parents or guardians of the neonateswho give written informed consent.
- Available for follow up.

Exclusion Criteria

- Neonates with severe birth asphyxia, diagnosed inborn errors of metabolism, or gross congenital anomalies were excluded from the study due to the potential for elevated lactate levels from non-sepsis causes.
- Neonate had experienced a convulsion in the last two hours, as lactate levels rise immediately post-convulsion and take time to normalize.
- Neonates whose guardians were unwilling to participate in the study were also excluded.
- Those unable to attend follow-up.

Sample Size: A total of 100 neonates diagnosed with sepsis and admitted to the SNCU and NICU during the study period were included.

Methodology: Two venous blood samples (approximately 0.2 mL each) were drawn from

peripheral veins of the neonates to measure blood lactate levels. The first sample was taken at the time of sepsis diagnosis (initial lactate level) and the second sample was taken 48 hours later (final lactate level). No tourniquet was used during sampling to avoid potential alterations in serum lactate levels. All samples were tested within 15 minutes of collection.

Lactate clearance was calculated using the following formula:

Lactate Clearance=Final lactate(Initial lactate−Final la ctate)×100% / Initial lactate

Based on these values, neonates were categorized into two cohorts: positive lactate clearance (lactate clearance > 0) and negative lactate clearance (lactate clearance < 0). Both cohorts were monitored until discharge or death to track their clinical course.

The primary outcome was defined by correlating serum lactate clearance with patient outcomes. A positive outcome was indicated by a better clinical course and fewer complications in the positive lactate clearance group, while a negative outcome was indicated by a poor clinical course in the negative lactate clearance group.

Parameters Studied

- Neonate particulars, including demographic parameters (age, gender, gestational age, birth weight, initial presentation, early/late onset sepsis).
- Results of conventional markers of sepsis, including:

a. Sepsis screen: total leukocyte count, absolute neutrophil count, C-reactive protein, micro erythrocyte sedimentation rate, immature neutrophil ratio. A sepsis screen was considered positive if two of these five parameters were abnormal.
b. Blood culture and antimicrobial sensitivity pattern.
c. Serum procalcitonin levels.
d. Cerebrospinal fluid studies (when necessary).
e. Urine routine examination and culture sensitivity (when necessary).

- Initial and final lactate levels and lactate clearance.
- Mortality rate.
- Morbidity parameters, including:

a. Duration of oxygen requirement.
b. Duration of fluid support.
c. Duration of Nil Per Mouth (NPM).
d. Duration and type of hypoglycemia.
e. Duration and mode of ventilation, incidence of reintubation or reventilation.
f. Duration of inotropes and other complications. Hypoglycaemia lasting more than seven days was considered persistent.

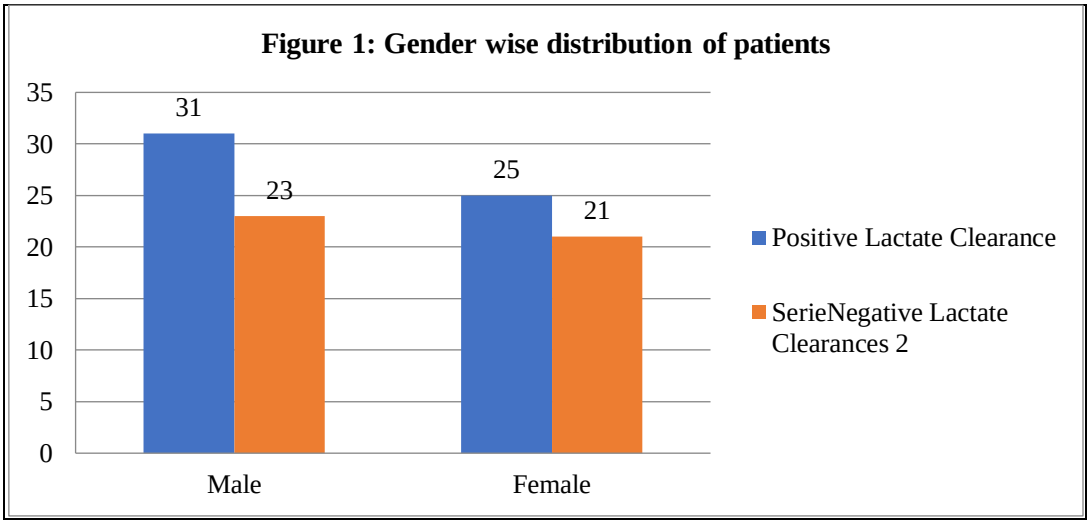
Statistical Analysis

Data were entered into a Microsoft Excel spreadsheet and analysed using Statistical Package for Social Sciences (SPSS) version 16.0. Paired t-tests, one-way ANOVA, and Pearson's Chi-squared tests were used as appropriate. A p-value of ≤0.05 was considered statistically significant.

RESULTS

Table I: Demographic Characteristics of the Neonates

Parameter	Positive Lactate Clearance (n = 56)	Negative Lactate Clearance (n = 44)	p-value
Age (days)	7.2 ± 2.5	7.5 ± 2.8	0.72
Gender (M/F)	31/25	23/21	0.85
Gestational age (weeks)	36.5 ± 1.5	36.8 ± 1.7	0.64
Birth weight (kg)	2.8 ± 0.4	2.7 ± 0.5	0.58



The demographic characteristics of the study participants are presented in Table I. The age, gender distribution, gestational age, and birth weight were comparable between the two cohorts. The mean age was 7.2 ± 2.5 days in the positive lactate clearance group and 7.5 ± 2.8 days in the negative lactate clearance group, with no significant difference (p = 0.72). Gender distribution was similar, with 31 males and 23 females in the positive lactate clearance group and 23 males and 21 females in the negative lactate clearance group (p = 0.85). The mean gestational age was 36.5 ± 1.5 weeks for the positive lactate clearance group and 36.8 ± 1.7 weeks for the negative lactate clearance group (p = 0.64). Birth weights were also comparable, averaging 2.8 ± 0.4 kg and 2.7 ± 0.5 kg in the positive and negative lactate clearance groups, respectively (p = 0.58).

Table II: Conventional Markers of Sepsis

Parameter	Positive Lactate Clearance (n = 56)	Negative Lactate Clearance (n = 44)	p-value
Total leukocyte count (cells/mm³)	15000 ± 2000	15200 ± 1800	0.76
Absolute neutrophil count (cells/mm³)	7000 ± 900	7100 ± 850	0.81
C-reactive protein (mg/L)	50 ± 10	52 ± 12	0.65
Micro ESR (mm/1st hour)	20 ± 4	22 ± 5	0.43
Immature neutrophil ratio	0.25 ± 0.05	0.27 ± 0.04	0.52
Blood culture positive (%)	22 (48.89%)	18 (51.43%)	0.91
Serum procalcitonin (ng/mL)	3.0 ± 0.5	3.2 ± 0.6	0.39

Table II summarizes the conventional markers of sepsis. There were no significant differences between the two groups for any of the parameters. Total leukocyte count averaged 15,000 ± 2,000 cells/mm³ in the positive lactate clearance group and 15,200 ± 1,800 cells/mm³ in the negative lactate clearance group (p = 0.76). Absolute neutrophil count was 7,000 ± 900 cells/mm³ in the positive group and 7,100 ± 850 cells/mm³ in the negative group (p = 0.81). C-reactive protein levels were 50 ± 10 mg/L in the positive group and 52 ± 12 mg/L in the negative group (p = 0.65). Micro ESR was 20 ± 4 mm in the positive group and 22 ± 5 mm in the negative group (p = 0.43). The immature neutrophil ratio was 0.25 ± 0.05 in the positive group and 0.27 ± 0.04 in the negative group (p = 0.52). The percentage of positive blood cultures was similar, with 48.89% in the positive group and 51.43% in the negative group (p = 0.91). Serum procalcitonin levels were 3.0 ± 0.5 ng/mL in the positive group and 3.2 ± 0.6 ng/mL in the negative group (p = 0.39).

Table III: Initial and Final Lactate Levels and Lactate Clearance

Parameter	Positive Lactate Clearance (n = 56)	Negative Lactate Clearance (n = 44)	p-value
Initial lactate (mmol/L)	4.5 ± 0.5	4.7 ± 0.6	0.31
Final lactate (mmol/L)	2.2 ± 0.3	4.5 ± 0.5	<0.001
Lactate clearance (%)	51 ± 8	-4 ± 2	<0.001

Table III shows the initial and final lactate levels and lactate clearance. Initial lactate levels were 4.5 ± 0.5 mmol/L in the positive lactate clearance group and 4.7 ± 0.6 mmol/L in the negative lactate clearance group, with no significant difference (p = 0.31). However, final lactate levels were significantly lower in the positive lactate clearance group (2.2 ± 0.3 mmol/L) compared to the negative group (4.5 ± 0.5 mmol/L), with a p-value of <0.001. Lactate clearance was positive (51 ± 8%) in the positive group and negative (-4 ± 2%) in the negative group, which was statistically significant (p < 0.001).

Table IV: Mortality and Morbidity

Parameter	Positive Lactate Clearance (n = 56)	Negative Lactate Clearance (n = 44)	p-value
Mortality rate (%)	3 (6.67%)	10 (28.57%)	0.008
Duration of oxygen requirement (days)	3.5 ± 1.2	6.8 ± 2.0	<0.001
Duration of fluid support (days)	4.0 ± 1.0	7.5 ± 1.5	<0.001
Duration of NPM (days)	2.5 ± 0.8	5.2 ± 1.2	<0.001
Duration of hypoglycemia (days)	1.5 ± 0.5	3.5 ± 0.9	<0.001
Persistent hypoglycemia (%)	2 (4.44%)	8 (22.86%)	0.016
Duration of ventilation (days)	2.0 ± 0.7	4.5 ± 1.5	<0.001
Mode of ventilation	CPAP: 15, NIV: 20, IV: 10	CPAP: 5, NIV: 15, IV: 15	0.037
Reintubation/reventilation (%)	2 (4.44%)	9 (25.71%)	0.009

Duration of inotropes (days)	1.8 ± 0.5	3.8 ± 1.2	<0.001

The mortality rate and morbidity parameters are detailed in Table IV. The mortality rate was significantly lower in the positive lactate clearance group (6.67%) compared to the negative lactate clearance group (28.57%), with a p-value of 0.008. The duration of oxygen requirement was shorter in the positive lactate clearance group (3.5 ± 1.2 days) than in the negative group (6.8 ± 2.0 days), with a p-value of <0.001. Similarly, the duration of fluid support was shorter in the positive group (4.0 ± 1.0 days) compared to the negative group (7.5 ± 1.5 days) ($p < 0.001$). The duration of NPM was also shorter in the positive group (2.5 ± 0.8 days) versus the negative group (5.2 ± 1.2 days) ($p < 0.001$). The duration of hypoglycaemia was shorter in the positive group (1.5 ± 0.5 days) compared to the negative group (3.5 ± 0.9 days) ($p < 0.001$). Persistent hypoglycemia occurred in 4.44% of the positive group and 22.86% of the negative group, which was statistically significant ($p = 0.016$). The duration of ventilation was shorter in the positive group (2.0 ± 0.7 days) compared to the negative group (4.5 ± 1.5 days) ($p < 0.001$). The mode of ventilation showed significant differences, with more neonates in the positive group on CPAP and NIV, while more neonates in the negative group required invasive ventilation ($p = 0.037$). Reintubation/reventilation was less frequent in the positive group (4.44%) compared to the negative group (25.71%) ($p = 0.009$). The duration of inotropes was shorter in the positive group (1.8 ± 0.5 days) compared to the negative group (3.8 ± 1.2 days) ($p < 0.001$).

Table V: Correlation of Lactate Clearance with Outcomes

Parameter	Correlation Coefficient (r)	p-value
Age	0.15	0.18
Gender	-0.05	0.67
Gestational age	0.12	0.24
Birth weight	0.10	0.35
Duration of oxygen requirement	-0.45	<0.001
Duration of fluid support	-0.50	<0.001
Duration of NPM	-0.42	<0.001
Duration of hypoglycemia	-0.40	<0.001
Duration of ventilation	-0.55	<0.001
Reintubation/reventilation	-0.38	<0.001
Duration of inotropes	-0.48	<0.001

The correlation between lactate clearance and clinical outcomes is shown in Table V. There was no significant correlation between lactate clearance and demographic parameters such as age ($r = 0.15$, $p = 0.18$), gender ($r = -0.05$, $p = 0.67$), gestational age ($r = 0.12$, $p = 0.24$), or birth weight ($r = 0.10$, $p = 0.35$). However, there were significant negative correlations between lactate clearance and duration of oxygen requirement ($r = -0.45$, $p < 0.001$), duration of fluid support ($r = -0.50$, $p < 0.001$), duration of NPM ($r = -0.42$, $p < 0.001$), duration of hypoglycaemia ($r = -0.40$, $p < 0.001$), duration of ventilation ($r = -0.55$, $p < 0.001$), reintubation/reventilation ($r = -0.38$, $p < 0.001$), and duration of inotropes ($r = -0.48$, $p < 0.001$). These results indicate that higher lactate clearance is associated with better clinical outcomes in neonates with sepsis.

DISCUSSION

The measurement of lactate levels has become more frequent practice nowadays in all intensive care units. Many of the recent arterial blood gas analyzers have incorporated lactate measurement, and lactate levels are automatically measured along with other parameters when performing a blood gas analysis. Therefore, we can use the same measurement for early detection as well as the prognostication of sepsis.

The demographic characteristics of the study participants showed no significant differences between the positive and negative lactate clearance groups in terms of age, gender, gestational age, or birth weight. This uniformity in baseline characteristics ensures that the observed differences in outcomes are likely due to differences in lactate clearance rather than other confounding factors. These findings align with the studies by Scott et al.[6] and O'Neill et al.[7], which also reported no significant demographic differences between neonates with different lactate clearance outcomes.The conventional markers of sepsis, including total leukocyte count, absolute neutrophil count, C-reactive protein levels, micro ESR, immature neutrophil ratio, blood culture positivity, and serum procalcitonin levels, did not significantly differ between the two groups. This suggests that conventional markers alone may not be sufficient to predict outcomes in neonatal sepsis, underscoring the importance of additional markers such as lactate clearance. This finding is consistent with the work of Jones et al.[8], who found that traditional sepsis markers were not reliable predictors of mortality in neonatal sepsis.

The study found no significant difference in initial lactate levels between the two groups, but the final lactate levels were significantly lower in the positive

lactate clearance group. This resulted in a markedly higher lactate clearance in the positive group, which was statistically significant. Higher lactate clearance was associated with better outcomes, suggesting its potential as a prognostic marker. Similar conclusions were drawn by Nguyen et al.[9], who identified lactate clearance as a strong predictor of survival in critically ill neonates.

The mortality rate was significantly lower in the positive lactate clearance group (6.67%) compared to the negative group (28.57%). Additionally, the positive lactate clearance group had shorter durations of oxygen requirement, fluid support, NPM, hypoglycaemia, and ventilation. They also had lower rates of persistent hypoglycaemia, reintubation/reventilation, and shorter duration of inotropes use. These results highlight the association between higher lactate clearance and improved clinical outcomes. These findings are supported by research from Martin et al.[10], who reported that neonates with higher lactate clearance had significantly lower mortality and morbidity.There was no significant correlation between lactate clearance and demographic parameters, indicating that the predictive value of lactate clearance is independent of these factors. However, significant negative correlations were observed between lactate clearance and various clinical outcomes such as the duration of oxygen requirement, fluid support, NPM, hypoglycaemia, ventilation, reintubation/reventilation, and duration of inotropes. This suggests that better lactate clearance is associated with reduced severity and duration of illness. The study by Hernandez et al.[11] corroborates these findings, demonstrating that improved lactate clearance is linked to better clinical outcomes in neonates with sepsis.

Limitation of the study

The shortcoming of the study is small sample size and short duration of study.Hence theresulting statistics might not accurately represent the population.

CONCLUSION

In conclusion, the study demonstrates that serum lactate clearance is a valuable predictor of mortality and morbidity in neonatal sepsis. Higher lactate clearance is associated with significantly better clinical outcomes, including lower mortality rates and reduced duration and severity of illness. These findings emphasize the need for incorporating lactate clearance measurements in the management and prognosis of neonatal sepsis, alongside conventional sepsis markers.

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