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ABG Lactate Levels As Predictor Of Neonatal Outcomes In Neonatal Intensive Care Unit

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Abstract

Background: Admission of neonates to Neonatal Intensive Care Unit (NICU) has increased over time. The adequate management of the neonates demands the serial monitoring of metabolic parameters like lactate level & acid base status.

Objectives: To determine the utility value of lactate levels, in predicting neonatal outcomes.

Study design: A prospective observational study (12 months) (from 1/7/19 to 31/6/20).

Participants: A total of 121 newborns who were admitted to the NICU.

Intervention: The arterial blood sample was taken to assess the lactate (in mmol/L), with ABL800 fully automated machine at 0,12,24 and 48 hours of admission.

Outcomes: The outcome measures included duration of hospital stay, requirement of respiratory support in the form of nasal oxygen (O_2) or high flow nasal cannula (HFNC) or continuous positive airway pressure (CPAP) or mechanical ventilation (MV) and mortality.

Results: In this study, 112 (92.56%) study subjects survived and 9 (7.44%) study subjects did not survive. Lactate levels were a significant predictor of mortality at 12hrs (cut off >3.9, P value of <0.0001), 24hrs (cut off >4, P value<0.0001) and 48 hrs (cut 0ff > 2.7, P value <0.0001). Lactate levels were a significant predictor of requirement of respiratory support at 24hrs (cut off >2.1, P value <0.0003), and 48 hrs (cut off >1.8, P value <0.0001). There was a significant correlation of lactate with hospital stay (correlation coefficient 0.189, P value 0.037).

Conclusion: It can be concluded that serial estimation of lactate helps in determining the outcome of neonates admitted in NICU. Serial lactate levels at different time intervals with cut offs have better utility value than a single lactate level.

Keywords: Lactate, neonate, mortality, respiratory support, hospital stay

Introduction

The neonatal period is the first 28 days of life. It is the most vulnerable time for a child's survival. Neonates face the highest risk of mortality in their first month of life at an average global rate of 17 deaths per 1,000 live births in 2020. According to latest UNICEF data 2.4 million infants died in the first month of life in 2020 globally. Approximately 6,500 neonatal deaths occur every day with about a third of all neonatal deaths occurring within the first day of life and close to three quarters occurring

within the first week of life. Hence prognostic factors are developed for early recognition and management of neonatal problems to decrease mortality.

Umbilical cord PH of 7.2 immediately after birth is an unfavourable prognostic factor for short term outcomes in newborns [1]. Acid–base disorders reflect the seriousness of the underlying disease and are also indicators for morbidity and mortality in sick neonates [2]. Literature review show that studies have mainly been done on Arterial Blood Gas analysis (ABG) and Base Excess (BE) to know their values as outcome predictor of neonates admitted in NICU [5-7]. The use of lactate as a clinical prognostic tool was first suggested in 1964 by Broder and Weil when they observed that a lactate level of > 4 mmol/L was associated with poor outcomes in patients with undifferentiated shock [3]. Measurement of plasma lactate level in neonates with HIE serves as a tool for predicting mortality in neonates [4]. Thus the following study focuses on the use of lactate levels as the predictor of neonatal outcomes in NICU.

Methods

We conducted a prospective observational study for a period of 12 months (from 01/07/2019 to 31/07/2020). Study included 121 neonates who were admitted to NICU. Informed consents from parents of every neonate were taken. Neonates with congenital malformations, chromosomal abnormalities, surgical emergencies, and neonates getting discharged from NICU before 48 hours were excluded from the study. Arterial blood samples were taken at 0, 12, 24, and 48 hours. The samples were processed with ABL800 fully automated machine. The Lactate levels were analysed.

Ethical clearance

Ethical approval from institutional ethics committee was taken.

Statistical Analysis

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Science (SPSS) version 21.0. The tests used were Independent t test / Mann-Whitney Test, Spearman rank correlation coefficient, Receiver operating characteristic curve (ROC) and Univariate linear regression. On comparison, a p value of < 0.05 was considered statistically significant.

Results

Demographic results of 121 neonates showed, 72 (59.50%) males and 49 (40.50%) females. The mean birth weight of the study neonates was 2.52 ± 0.82 Kgs. (Table 1(a))

The outcome parameters showed, the respiratory support (Nasal O2/ HFNC/ CPAP/ Ventilator) was required in 101 (83.47%) subjects for a mean period of 2.68 ± 2.09 days. The total hospital stay was 12.37 ± 7.02 days and the NICU stay was 10.87 ± 6.63 days. 112 Neonates (92.56%) got discharged and 9 (7.44%) expired. (Table 1(b))

In our study the serial estimation of lactate concentrations at 0, 12, 24 and 48 hours showed significant associations with the outcomes. Among the outcome variables, the usage of respiratory support (in the form of Nasal O2/HFNC/ CPAP/ Ventilation) was seen in 101 out of 121 neonates. It was seen that lactate levels were significantly more for the neonates (n=101) who required the use of respiratory support (as compared to those who did not need the respiratory support, n=20) at 24 hours (2.2 vs 1.75; P=0.003) and at 48 hours (1.9 vs 1.55; P=0.0006) but not at the initial presentation (3.3 vs 3.7; P=0.869) or at the 12th hour (2.9 vs 2.6; P=0.065). This suggests that high lactate level at 24 and 48 hours suggest a higher degree of sickness and the continuing requirement of respiratory support. The ROC curve analysis showed that the requirement of respiratory support was significantly more when the lactate levels were >2.1mmol/L at 24 and >1.8mmol/L at 48 hours with p value of <0.05. (Figure 1(a) & Table 2(a)).

As far as hospital stay was concerned, on performing univariate linear regression there was a significant positive correlation of Lactate only at 12 hours (r=0.189, P=0.0377). However at 0 hours(r=0.006, p=0.9476); 24 hours (r=0.0377, p=0.3987) and at 48 hours (r=0.066, p=0.4733) the correlation was statistically not significant. Thus neonates with higher lactate levels in the serial evaluation at 12 hours had significantly higher hospital stay in the study. (Table 2(c)).

In the current study, 9 neonates did not survive and 112 were discharged. It was seen that lactate levels were significantly more for the neonates who expired (n=9) (as compared to those who were discharged,

Volume 6, Issue 2; March-April 2023; Page No 559-566

n=112) at 12 hours (6.3 vs 2.75; P=0.0003), at 24 hours (7.2 vs 2; P=0.0002) and at 48 hours (8.8 vs 1.8; P<.0001) but not at the initial presentation (4.8 vs 3.3; P=0.069). This suggests that there may be an association between the neonatal death and the higher lactate levels during the hospital stay of the neonate after 12th hour until 48th hour. The ROC curve analysis showed that lactate levels at 12, 24, 48 hours were significant predictors of neonatal mortality. It was seen that mortality was significantly more when the lactate levels were >3.9mmol/L at 12 hours, >4.0mmol/L at 24hours and >2.7mmol/L at 48 hours with a p value of <0.05. (Figure 1(b)& Table 2(b)).

Table 1a :- Distribution of baseline characteristics.

Baseline characteristics	Frequency	Percentage
Gender		
Female	49	40.50%
Male	72	59.50%
Birth weight (in kgs)		
Mean ± Stdev	2.52 ± 0.82	
Median(IQR)	2.6(1.95-3.2)	
Range	0.9-4.2	

Table 1b :- Distribution of outcome.

Outcome	Frequency	Percentage
Outcome		
Discharged	112	92.56%
Expired	9	7.44%
Respiratory support requirements		
Yes	101	83.47%
No	20	16.53%
Number of days of respiratory support		
Mean ± Stdev	2.68 ± 2.09	
Median(IQR)	3(2-3)	
Range	0-15	
Total days of hospital stay		
Mean ± Stdev	12.37 ± 7.02	
Median(IQR)	10(7-15)	
Range	2-45	
Number of days of ICU stay		
Mean ± Stdev	10.87 ± 6.63	

Volume 6, Issue 2; March-April 2023; Page No 559-566

Median(IQR)	10(6.5-15)
Range	2-45

Figure 1(a):-Association of trend of lactate (mmol/L) at different time intervals with respiratory support requirements.

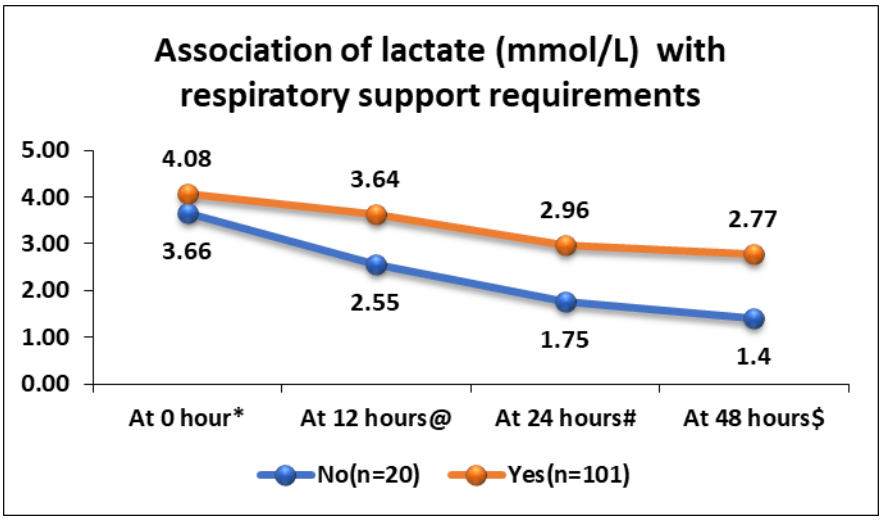
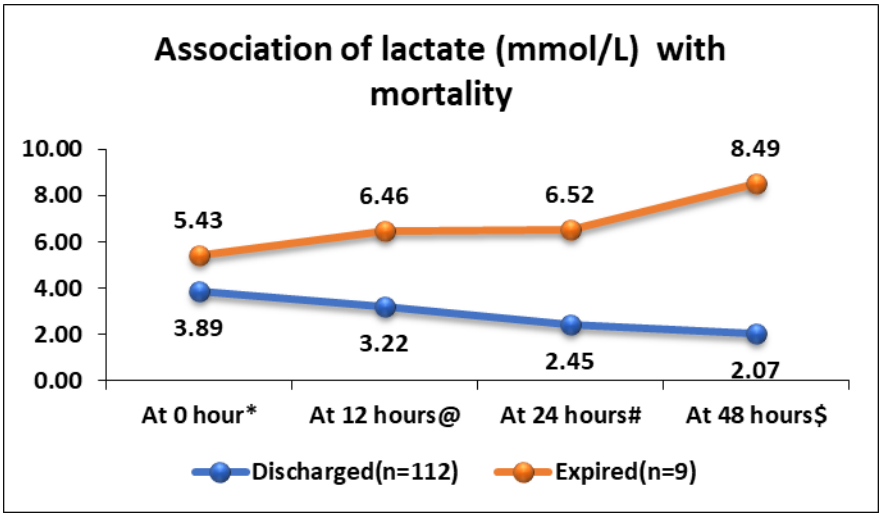


Figure 1(b):-Association of trend of lactate (mmol/L) at different time intervals with mortality.



*-0.869, @-0.065

#-0.003, $-0.0006

Table 2(a):-Receiver operating characteristic curve of lactate for predicting respiratory support requirements.

Respiratory support requirements	AUC	Cut off	Sensitivity(95 % CI)	Specificity(95 % CI)	PPV(95% CI)	NPV(95% CI)	P value

Volume 6, Issue 2; March-April 2023; Page No 559-566

At 0 hours							
Lactate	0.512	≤3.2	48.51%(38.4% - 58.7%)	75%(50.9%-91.3%)	90.7%(79.7%-96.9%)	22.4%(13.1%-34.2%)	0.8634
At 12 hours							
Lactate	0.631	>3.2	41.58%(31.9% - 51.8%)	95%(75.1%-99.9%)	97.7%(87.7%-99.9%)	24.4%(15.3%-35.4%)	0.0308
At 24 hours							
Lactate	0.707	>2.1	51.49%(41.3% - 61.6%)	80%(56.3%-94.3%)	92.9%(82.7%-98.0%)	24.6%(14.8%-36.9%)	0.0003
At 48 hours							
Lactate	0.743	>1.8	55.45%(45.2% - 65.3%)	95%(75.1%-99.9%)	98.2%(90.6%-100.0%)	29.7%(18.9%-42.4%)	<0.0001

Table 2(b):-Receiver operating characteristic curve of lactate for predicting mortality.

Mortality	AUC	Cut off	Sensitivity(95% CI)	Specificity(95% CI)	PPV(95% CI)	NPV(95% CI)	P value
At 0 hours							
Lactate	0.682	>6.5	44.44%(13.7%-78.8%)	92.86%(86.4%-96.9%)	33.3%(9.9%-65.1%)	95.4%(89.6%-98.5%)	0.081
At 12 hours							
Lactate	0.862	>3.9	88.89%(51.8%-99.7%)	79.46%(70.8%-86.5%)	25.8%(11.9%-44.6%)	98.9%(94.0%-100.0%)	<0.0001
At 24 hours							
Lactate	0.873	>4	88.89%(51.8%-99.7%)	89.29%(82.0%-94.3%)	40%(19.1%-63.9%)	99%(94.6%-100.0%)	<0.0001
At 48 hours							
Lactate	0.974	>2.7	100%(66.4%-100.0%)	84.82%(76.8%-90.9%)	34.6%(17.2%-55.7%)	100%(96.2%-100.0%)	<0.0001

Table 2(c):-Correlation of lactate with hospital stay on performing univariate linear regression

Correlation with hospital stay		Lactate (mmol/L)
At 0 hour	**Correlation Coefficient**	0.006
	P value	0.9476

Volume 6, Issue 2; March-April 2023; Page No 559-566

At 12 hours	**Correlation Coefficient**	0.189
	P value	0.0377
At 24 hours	**Correlation Coefficient**	0.077
	P value	0.3987
At 48 hours	**Correlation Coefficient**	0.066
	P value	0.4733

Test: Spearman rank correlation coefficient

Discussion

The measurement of blood lactate concentrations is one of the important tools in neonatal management and prognostication. The serial measurements of lactate levels are more valuable than a single measurement, not only in providing a more precise assessment of prognosis, but also in evaluating response to treatment [8]. Previous studies have shown that increased lactate concentrations have been associated with sepsis, ECMO support, need for blood transfusions and increased mortality [9-12].

The current study results enhance the importance of the lactate in determining the neonatal outcomes during NICU admission. As lactate is the end product of the anaerobic metabolism of glucose, its increase is obvious during sick conditions [13]. Normally most of the lactate is efficiently eliminated from the body by the liver and is utilized in gluconeogenesis or in the production of energy. However, when considerable amount of lactate is produced during the period of illnesses, with a reduction in lactate to pyruvate conversion, metabolic acidosis occurs, which leads to increased morbidity and mortality [13]. Thus the management approach should aim to decrease the lactate levels by serial monitoring during the NICU stay of the neonate.

Study by Kruse JA et al on blood lactate concentrations in the umbilical arterial blood of healthy term and preterm infants showed that lactate values are less than 2.5 mmol/l beyond the first six hours after birth [14, 15]. And any increase in the blood lactate concentration above 2.5 mmol/l leads to increased neonatal mortality [16]. Thus, some studies take this cut off criteria to define hyperlactatemia in neonates and manage the neonatal lactate below this level for a better outcome [9]. Thus, we determined our own cut-offs for lactate for various outcomes based on the ROC curves. It was seen that the cut-offs derived were separate for the outcomes at various time intervals.

In our study AUC curves and ROC analysis results showed that Lactate level cut-offs (mmol/l) that could significantly predict mortality at 12, 24 and 48 hours were >3.9mmol/L, >4.0mmol/L and >2.7mmol/L respectively. But the lactate level cut off determined at admission (0 hour >6.5mmol/L) was not a significant predictor of mortality. In the study by Natesan RS et al, high arterial cord lactate of 6.0mmol/L was a significant predictor of admission to Neonatal intensive care unit (NICU) which adversely affected the neonatal outcomes as well [17]. A study by Rodríguez-Balderrama I et al. determined Lactate cut-offs during the first week of life and found that lactate levels of > 1.5 mmol/l at 72 h and lactate levels > 2.5 mmol/l at 7th day had the best prediction for mortality among the neonates [13] .In another of the recent observational study by Herminia Couto Fernandez et al, the best cut off point of the plasma lactate concentration as determined by the ROC curve for death during the first 3 days of life was 4.2 mmol/L [10].

We found that Lactate level cut-offs were significant predictors ($p<0.05$) for the respiratory support at cut off levels of >3.2mmol/L at 12 hours, >2.1mmol/L at 24 hours and >1.8mmol/L at 48 hours but at 0 hours lactate cut offs were not a significant predictor of use of respiratory support (cut off of ≤3.2 mmol/l, P=0.8634). The determination of the cut-offs for the use of respiratory assistance may be of some help in the future in the management of neonate. Among other previous studies, Deshpande SA et al. studied serial arterial acid- base status and blood lactate concentrations in 75 consecutive sick, ventilated neonates with indwelling arterial lines and did not determine any such cut off [9]. In another study by Ahmadpour-Kacho M et al, an umbilical cord PH less

Volume 6, Issue 2; March-April 2023; Page No 559-566

than 7.2 immediately after birth was established to be a useful prognostic factor for unfavourable short term outcome in newborns [18]. In a study by Patil, Suman Shivanagouda, et al Umbilical cord blood lactate is more specific than umbilical artery pH in predicting adverse neonatal outcome (19). A study by Chen D et al found that lactate levels at different postnatal time points and the lactate clearance rate are important for predicting neonatal mortality and mechanical ventilation. The lactate cut-off value for predicting adverse outcomes ranges from 3.2 to 10.0 mmol/L. And the cut-off point for predicting death at the initial lactate level was 7.7 mmol/L. The study also showed that a 6-hour lactate clearance rate of 6.09% was the most significant predictor of mortality, with the highest sensitivity and specificity (20). Nadeem et al. considered that a lactate level >5.6 mmol/L was an independent risk factor for adverse prognosis in premature infants with a gestational age <32 weeks (21). The differences in cut-off points between different studies are not only related to differences in analysis and the study population, but also to how prognosis was determined in the study.

Limitations of the study

First 6 hours of birth is crucial.We measured the ABG lactate at 0 and 12 hrs, 24 hrs, and 48 hrs of admission.The first sample in our study was not necessarily done in the first 6 hours of life as all neonates in our NICU are out born and might not have been referred before 6 hours to us.

The non inclusion of all mother baby pairs, whether they were preterm, term, vaginal or caesarean deliveries, was in itself a limitation of the study results. The reason being the ABG lactate values and the outcomes may show variation depending upon the mode of delivery, maturity of the baby, disease/condition affecting the neonate and birth weight of the neonate. Thus future studies are recommended on the specific groups of neonates to have a better significance value in the study.

Conclusion

The serial estimation of lactate levels among the neonates admitted to the NICU at 12, 24 and 48 hours proved to be useful in determining the cut off levels for significantly predicting mortality, need for respiratory support and the hospital stay. Finally we would like to suggest that aggressive treatment measures needs to be undertaken to reduce lactate level to <3.9mmol/L at 12 hours, <4.0mmol/L at 24 hours, and <2.47mmol/L at 48 hours, to improve survival of neonates and reduce mortality. Also reducing lactate to <2.1mmol/L at 24hours, and <1.8mmol/L at 48 hours will reduce requirement of respiratory support. Reducing lactate by 12 hours to <1.75mmol/L will also reduce hospital stay. Finally we would like to conclude that absolute reduction in lactate to < 1.8mmol/L by 48 hours by undertaking appropriate treatment modalities would improve neonatal outcomes in all the above three parameters.

What is already known?

Lactate is a good predictor of neonatal outcomes

What the study adds?

The cut offs of serial lactate levels at different time intervals of NICU admission and have better utility than a single cut off value to determine neonatal outcomes.

Conflicts of interest

There are no conflicts of interest

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Volume 6, Issue 2; March-April 2023; Page No 559-566

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Volume 6, Issue 2; March-April 2023; Page No 559-566