

A comparison study of blood lactate and lactate clearance with SNAP II score as predictors of outcome in sick neonates

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Abstract

Introduction: Necessity of longer stay in NICU reinforces the need for more sensible and specific parameter to evaluate the length of stay and outcome. In order to improve the clinical outcomes in sick neonates, it is crucial to obtain early recognition of those who are at risk of morbidity and mortality and to optimize the clinical decision making in a timely manner and to counsel the parents. **Aims & Objectives:** This study was designed to compare and obtain best predictor of outcome irrespective of diagnosis. **Materials and Methods:** The study was “prospective observational” study, conducted at NICU over 188 sick neonates of Pragna hospitals, Hyderabad in the period of October 2013 to September 2015. **Results:** Among 188 sick neonates 20 were non survivors, and 168 survived. There was significant correlation between high lactate at admission, low LAC₂₄ of less than 30% and high SNAP II score at admission with mortality among sick neonates. Neonates with LAC₂₄ of <30% had significantly higher requirement of oxygen (p-0.00*), fluid support (p-0.00*), ionotropes (p-0.0002**), ventilator support (p-0.0015**) and length of stay (p-0.004*) than with LAC₂₄> 60%. There were 23 neonates with initial lactate of more than 9mmol/dl. 6 out of 23 had LAC₂₄ of less than 30%. 4 out of 6 had LAC₄₈ of more than 30% yet, all 6 neonates had prolonged duration of stay with an average of 15.3 days. Neonates with high SNAP II score at admission of more than 60 had higher requirement ionotrope, and ventilator support. The area under curve (ROC) revealed poor correlation with overall morbidity. **Conclusion:** Lactate clearance value of less than 20.4% at 24 hours of admission could be useful to predict the adverse outcome with significant need for mechanical ventilation, higher oxygen, fluid and inotrope support and prolonged stay in sick neonates irrespective of diagnosis

Key words: Sick neonates, Lactate, Lactate clearance, Snap II score, Out come

Introduction

The primary goal for of hemodynamic monitoring is to ensure adequate tissue perfusion and oxygenation and assess the prognosis. Many Variables and popular scores like score for neonatal acute physiology (SNAP) measured in critically ill, have been used to estimate severity of disease, prognosticate morbidity and mortality, but they were influenced by various factors specially in neonates. In recent years two major neonatal severity measures, the score for neonatal acute physiology SNAP-II score [1] and CRIB [2] score focus on measuring and scoring physiological

derangements. They are compared with invasive laboratory studies like CRP and blood lactate to best predict the outcome and length of stay [3]. Increased blood lactate levels are commonly seen as a consequence of its accumulation from anaerobic metabolism in hypoxic neonates causing hypothermia and decreased survival in neonates. Hyperlactatemia is the sequel of asphyxia, severe lung injury, volume depletion, inefficient vasoregulation and sepsis.

Global tissue hypoxia resulting in systemic inflammatory response syndrome would result in endothelial activation, vasodilation, release of inflammatory mediators and altered coagulation

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ultimately leading to multiorgan dysfunction which is compensated by catecholamine surge and neural regulation [4]. This would result in normalization of vitals but at cellular compromise which is denoted by elevated lactate. Prognostic implications of lactate more than 2 mmol/dl were studied extensively in adults [5] and neonates pertaining to specific conditions. Recent studies showed low lactate clearance correlates with prolonged stay & mortality in PICU [6] & in neonates with sepsis and HIE who underwent brain cooling [7]. There were no studies in neonates to predict the outcome and length of stay irrespective of diagnosis. This study investigated which among initial lactate, lactate clearance and SNAP II score best predicted the outcome among sick neonates.

Aims and Objectives

Aims- To correlate initial blood lactate, lactate clearance, SNAP II score with outcome in sick neonates. To compare initial lactate, lactate clearance and SNAP II score in predicting the outcome in sick neonates.

Objectives- Obtaining best cut-off for timely lactate clearance percentage for predicting negative outcome and length of stay in sick neonates irrespective of diagnosis.

Materials and Methods

Centre for study- The study was conducted as a single centre study at Pragna hospitals, Punjagutta,

Results

In 188 neonates the mean gestational age of included babies was 37 weeks. About 100 were male babies and 88 were female babies.

Table-1: Demographic variables

Parameter	Number and range
Mean age	1.4 days [0.8 to 3.6 days]
Average weight	2.63kgs [1.4 to 3.8 kgs]
Average gestational age	37 weeks [32 to 40 weeks]
Total no. of survivors	168
Total no. of non survivors	20
Total no. female neonates	88
Total no. of male neonates	100
Average duration of stay in survivors	11.2 days
Average duration stay in non survivors	4.06 days.

Demographic characteristics of study population at admission into NICU (Table-1)

Weight of the enrolled babies at admission had a range of 1.4kgs to 3.8kgs with an average age of 2.63 kgs.

Andhra Pradesh, India, which is a tertiary care hospital and has got comprehensive paediatric department with neonatal intensive care unit.

Centre for period- October 2013 to September 2015

Type of study- A “prospective observational” study conducted on data collected during above mentioned period from neonatal intensive care unit.

Study sample- 188. The study is approved by hospital ethics and scientific committee.

Inclusion criteria- Sick neonates with respiratory distress, signs of sepsis, acute life threatening event, seizures, renal failure, hypotension and shock with initial blood lactate > 2mmol.

Exclusion criteria- Neonates with congenital abnormalities, Less than 30 week gestation, Post surgical cases, Less than 1 kg weight

Statistical Analysis- Data is entered in an excel sheet and is analyzed. Continuous variables are assessed with Mann Whitney tests and correlation curves (ROC) were plotted.

ANOVA was used to elaborate significance. SPSS version 20 and WINDOSTAT are used for statistical analysis. P value of less than 0.05 is considered as significant and is indicated by (*).

Among 168 survivors in 20 (10.6%) survivors, mean lactate value at admission was 13.6 mmol/dl, mean lactate clearance at 24 hours of admission was – 4.08, and average SNAP II score at admission was 74. Initial lactate and SNAP II score were very high in the non survivors compared to survivors (figure-1).

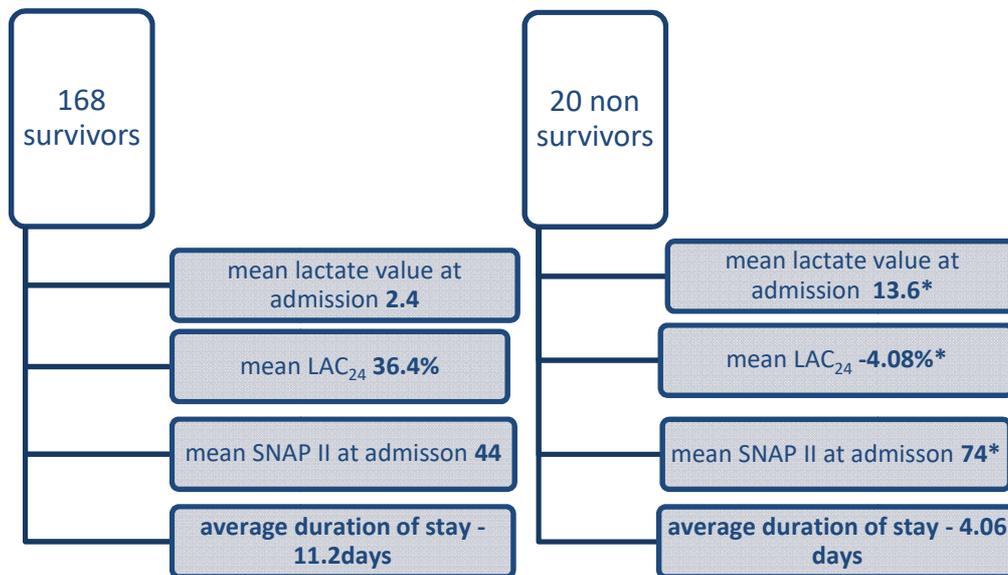


Figure-1: Comparison of lactate variables and SNAP II score between survivors and Nonsurvivors

Table-2: survivor population with lactate level at admission and their outcome.

Lactate at admission	Total No. of Neonates	Mean lactate value	Mean oxygen requirement in hours	Mean fluid support in hours	Mean hours of ionotrope support	Mean days of ventilation support	Average length of stay
2 – 5mmol/dl	70	3.72	76.24	96.6	36.6	4.45	7.98
5-9mmol/dl	75	6.48	68.5	101.95	48.5	3	9.7
>9mmol/dl	23	11.85	83.3	160	102	7.6	13.2

Average requirement of oxygen, fluid, ionotrope, mechanical ventilation and length of stay with respect to lactate at admission (Table-2)

Requirement of oxygen, fluid, ionotrope support, mechanical ventilation and length of stay in 70 neonates where lactate level at admission was 2-5mmol/dl were 76.24,96.6,36.6,3,7.98.

Table 3: Survived neonates with lactate clearance value at 24 hours and their outcome.

LAC ₂₄	Total No. of neonates	Mean value	Mean oxygen requirement in hours	Mean fluid support in hours	Mean hours of ionotrope support	Mean days of ventilator support	Average length of stay
> 60%	33	66.7%	30.9	65	17.9	0	6
30 – 60%	66	47%	58	110	49	4	10.1
< 30%	69	9.81%	85	132	72.5	6.95	11.18

Requirement of oxygen, fluid, ionotrope support, mechanical ventilation and length of stay in 33 neonates where lactate level at 24 hours was > 60% were 30.9,65,17.9,0,6.

Table 4: Neonates according to initial SNAP II score at admission and their outcome.

SNAP II at admission	Total No. of Neonates	Mean SNAP II score	Mean oxygen requirement in hours	Mean fluid support in hours	Mean hours of ionotrope support	Mean days of ventilator support	Average length of stay
<30	30	13.8	12.4	46.4	6.5	0	5.06
30 – 60	126	45.9	69.8	116.91	54.07	4.7	10
>60	21	70	101.9	165	112	12	11.9

Requirement of oxygen, fluid, ionotrope support, mechanical ventilation and length of stay in 30 neonates where SNAP II at admission was <30 were 12.4,46.4,6.5,0,5.06.

Table 5: Comparison between lactate variables and snap ii score in relation with morbidity determinants.

Parameter	Oxygen requirement (p value)	Fluid requirement (p value)	Ionotrope requirement	Ventilator requirement (p value)	Average duration of stay (p value)
Initial lactate of > 9mmol/dl	83.3 hours (0.3)	160 hours (0.33)	102 hours (0.08)	7.6 hours (0.058)	13.2 days (0.055)
LAC ₂₄ < 30%	85 hours (0.000 ^{***})	132 hours (0.00 ^{**})	72.5hours (0.0002 ^{***})	6.95hours (0.0015 ^{**})	11.18 days (0.004 ^{**})
SNAP II > 60	101.9 hours (0.09)	165 hours (0.4)	112hours (0.0009 ^{***})	12 hours (0.00089 ^{***})	11.9 days (0.052)

Requirement of oxygen in various parameters was 83.3 hours in Initial lactate of > 9mmol/dl, 85 hours in LAC₂₄< 30%, 101.9hours in SNAP II > 60.

Relation between initial lactate, lactate clearance and outcome- There were 23 neonates with more than 9mmol/dl of lactate at admission. 6 neonates had clearance value of less than 30% at 24 hours. All 6 babies had prolonged stay of more than 15 days and their outcome was negative. The duration of stay in 21 neonates with SNAP II score was shown in figure-2.

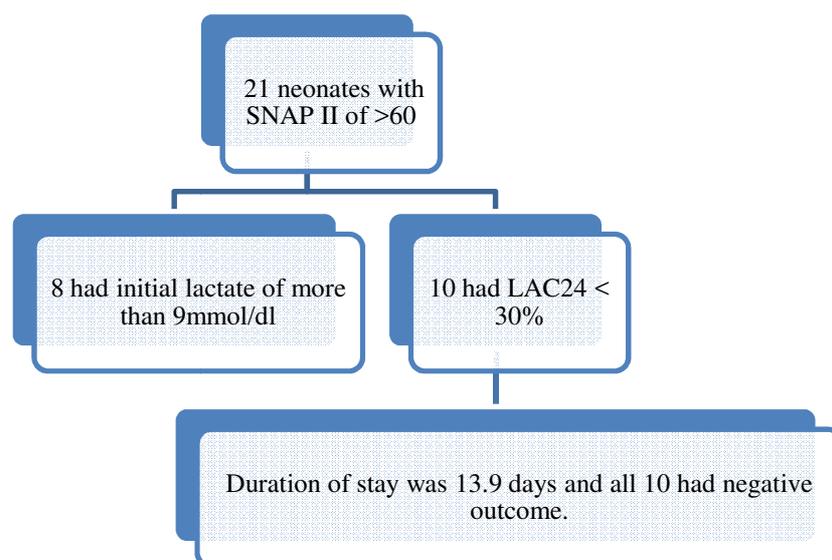


Figure 2: Relation between SNAP II score, lactate variables and outcome
Comparison between SNAP II Score AND Lactate Clearance at 24 hours [LAC₂₄]

Table 6: Comparison between SNAP II Score AND LAC₂₄

Parameter	LAC ₂₄ <30%	SNAP II > 60
Total no. of neonates	69	21
P value:		
oxygen	0.00**	0.09
Fluid	0.001**	0.4
Inotrope	0.0002***	0.0009***
Mechanical ventilation	0.0015***	0.0089***
Length of stay	0.004*	0.052
Area under ROC curve	0.84	0.224
Mortality	0.002***	0.038**

In 21 neonates SNAP II score was more than 60 at admission but, lactate clearance were less than 30% in 69 neonates (41%). LAC₂₄ and SNAP II score had significant correlation with mortality as depicted in table-6.

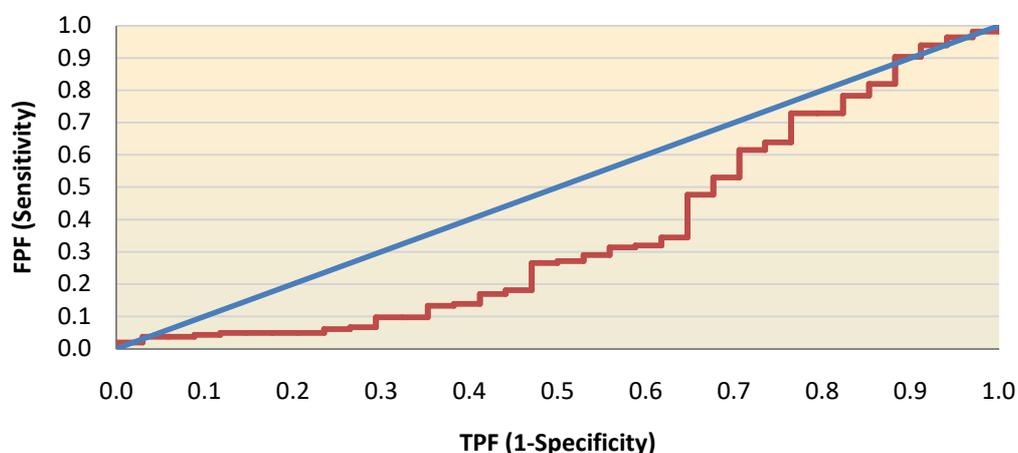
The study attempted to establish differences in outcome when SNAP II score and lactate clearance at 24 hours were combined in the small group of 10 neonates and outcome was assessed and compared with clearance and score individually (table-7).

Table 7: Comparison between LAC₂₄, SNAP II, and SNAP II score and LAC₂₄ combined.

Parameter	SNAP II > 60 combined with LAC ₂₄ less than 30%	LAC ₂₄ < 30%	SNAP II > 60
Average no. of hours with oxygen	110.4	85	101.9
No. of hours with fluid	176.19	132	165
No. of hours with inotropes	123.4	72.5	112
No. of days with ventilator	13.7	6.95	12
Average duration of stay.	12	11.18	11.9

The area under ROC curve for LAC₂₄ of less than 30% in predicting the negative outcome is 0.8475, with standard error of 0.05 and confidence interval of 0.95 and probability of 0.002**.(figure-3,4,5)

ROC Curve for lactate at admission

**Figure-3: ROC curve of lactate at admission in predicting outcome(r = 0.346)**

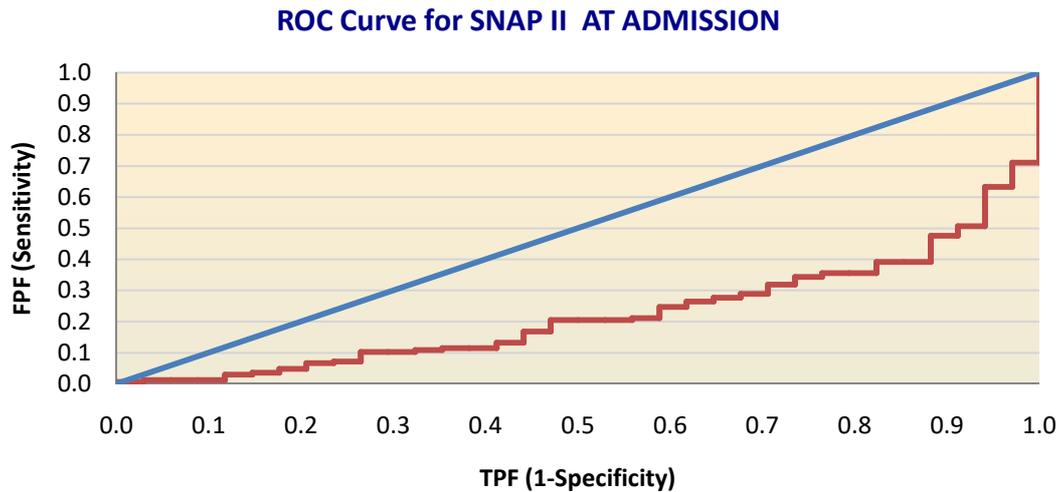


Figure-4: ROC curve of SNAP II score in predicting outcome ($r = 0.22$)

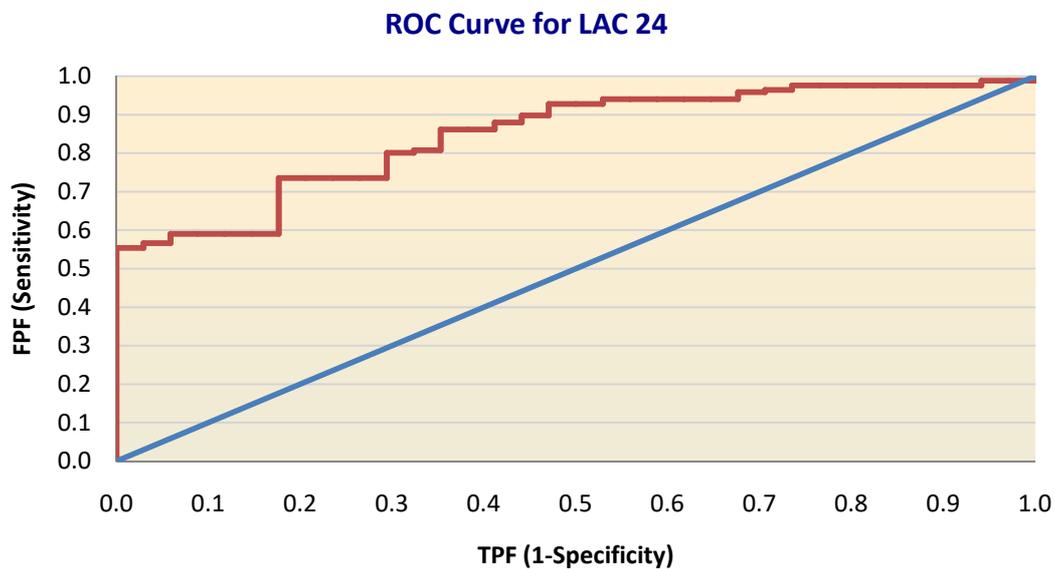


Figure 5: Correlation between LAC₂₄ <30% and Negative Outcome

Timely cut off of lactate clearance value at 24 hours in predicting the outcome

Lactate clearance value of **20.408%** at 24 hours of admission (LAC₂₄) was obtained as cut off value using logistic regression in predicting negative outcome with positive predictive value of 95.3% and negative predictive value of 38.8%. 44 neonates had clearance at 24 hours of admission (LAC₂₄) less than 20.4%. Average duration of oxygen requirement in them was for 85 hours, fluid support for 140 hours, inotrope requirement for 72 hours and required 7.6 days of mechanical ventilation. All neonates with LAC₂₄ less than 20.4% had an average duration of stay for 13.6 days.

Discussion

Blood lactate and mortality- The study of lactate levels in relation with in risk stratification and mortality rate helped in assessing the prognosis of the critically ill. Various studies used a ROC curve

to define the lactate level cutoff point with a better sensitivity and specificity to predict early death but there is currently no consensus for cut off value for blood lactate value in newborns. In contrast, for

adult patients, the reference values of blood lactate have already been established, and levels up to 2 mmol/L are considered normal. Initial lactate values of more than 5 mmol /dl [8] was significantly associated with negative outcome in pediatric patients with septic shock.

High lactate value of more than 9mmol/dl was associated with significant mortality in the study. However, the fact that the half-life of lactate is not known, might explain the reason why a single measurement of lactate performed during the first hours of life does not reflect the events that occur after 24 to 48 hours of hospitalization [9].

Lactate clearance and mortality- Lactate clearance has shown more promise in predicting mortality. Two studies in adult patients with shock showed lactate clearance of < 10% was related to mortality [10]. Our findings suggest that lactate clearance in the first 24 hour period of disease presentation, is an independent and superior variable associated with mortality.

Out of 188, 20 were non survivors, and 168 survived. Mean lactate at admission, lactate clearance at 24 hours, and SNAP II scores were compared between survivors and non survivors. Blood lactate levels in non-survivors were elevated and persistently high, while blood lactate levels in survivors decreased and normalize within 24 h which supports the importance of the time course of lactate levels in predicting the outcome among the survivors.

There was significant correlation between high lactate at admission, low LAC₂₄ of less than 30% and high SNAP II score at admission with mortality among sick neonates.

Lactate and morbidity- Neonates with initial lactate of more than 9 mmol/dl had significantly higher requirement of fluids and inotrope compared to those with lactate value of less than 9mmol/dl. There was no correlation with other morbidity determinants. The predictive value is less and the area under ROC shows poor correlation.

Lactate clearance and morbidity- There was significant correlation between lactate clearance, outcome and prognosis. Hence, clearance directed therapy with respect to time is being investigated

extensively among adults and pediatric population. There is no such studies in general neonatal ICU population to predict the outcome irrespective of type of illness. In septic patients, a lactate clearance directed therapy in the first 6 hours appeared as efficient as ScvO₂ [11]. In general adult ICU population an 8 hr therapy adaptation to lactate clearance reduced mortality rate in patients with hyperlactatemia compared with standard therapy [12].

Absence of lactate clearance to less than 20% after 8 hours of resuscitation lead to therapy intensification even in those who reach standard hemodynamically target [13]. Less than 30 % clearance among pediatric population within first 24 hours of admission correlated significantly with mortality [14]. The nonsurvivor group of the present study also had lactate clearance of less than 30% at 24 hours which was significantly different from mean value among survivors.

The morbidity was high among the survived neonates with lactate clearance of less than 30% at 24 hours with significantly greater need of oxygen, fluid, inotrope, and mechanical ventilation.

Length of stay- There were 23 neonates with initial lactate of more than 9mmol/dl. out of which, 17 babies had lactate clearance of more than 30% after receiving treatment for 24 hours and only 6 had LAC₂₄ of less than 30%. All 6 neonates had negative outcome and prolonged duration of stay with an average of 15.3 days.

SNAP II score and morbidity- SNAP II score at admission was more than 60 in 21 neonates. They only had significant difference in terms of inotrope support and mechanical ventilation. The area under curve (ROC) of logistic regression was low with poor correlation with outcome among sick neonates.

These results of the study are comparable with recent studies on SNAP II score, that the score alone is poor predictor of morbidity [15]. The reason may be the fact that the components of score like, pH, urine output, presence of seizures etc. contribute to the morbidity individually with respect to diagnosis. Hence, SNAP II alone might have a role in assessing the severity of the illness but not in assessing the outcome.

SNAP II combined with LAC₂₄. Among 21 neonates who had SNAP score of more than 60, 10 neonates also had lactate clearance less than 30% hours of at 24 hours of admission.

The average duration of oxygen, fluid, inotrope, mechanical ventilator support were higher than in neonates with LAC₂₄ of less than 30%. However due to variable sample in each group correlation could not be established.

Timely cut off- This is the first study to obtain best cut off value of lactate clearance to predict outcome and length of stay among group 3 neonates with lactate clearance of less than 30% at 24 hours using logistic regression.

Neonates with lactate clearance of 20.4% at 24 hours of admission had negative outcome with an average of 74 hours of mechanical ventilation and prolonged stay. The area under ROC curve was significant (0.84) with respect to lactate clearance and negative outcome. In our study PPV, NPV and ROC curve analysis for morbidity prediction of lactate clearance are comparable to Hatheril et al findings at 24 hours in pediatric ICU [16].

Though low lactate clearance is correlated with mortality and morbidity in various studies, this is the first study to quantify the value in relation with time and outcome among critically ill neonates irrespective of diagnosis.

High lactate clearance in the early hospital course may indicate a resolution of hypoxia at cellular level. So clinicians should interpret clearance less than 30% at 24 hrs with normalized vitals or SNAP II score or as a warning, that the neonates actually did not clinically improve or even deteriorate. Our data suggest that lactate clearance at 24 hours is more sensible and specific to predict negative outcome with significant correlation than initial lactate, lactate clearance at 48 hours, SNAP II score and represents a useful and clinically obtainable surrogate marker of tissue hypoxia and disease severity, independent of high initial lactate and high SNAP II score.

Lactate clearance is the most proximal presentation in sick neonates. Hence, this study adds the importance of its inclusion in addition to SNAP II score and other scores in assessing sick neonates.

Conclusions

Initial lactate value of more than 9mmol/dl had poor correlation with outcome. SNAP II score of more than 60 is not well correlated with outcome. Neonates with low lactate clearance of less than 30% had significantly greater need of oxygen, fluid, inotrope, ventilator support and prolonged stay for more than 13 days irrespective of diagnosis. Lactate clearance of 20.4 % at 24 hours of admission can be used as cut off marker of negative outcome with good correlation in sick neonates irrespective of diagnosis.

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