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Original Article

Paediatrics Section

# Lactate Dehydrogenase as a Prognosticating Tool in Predicting NICU Stay and Oxygen Dependence in Meconium Stained Amniotic Fluid Neonates

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## ABSTRACT

**Introduction:** Lactate Dehydrogenase (LDH) is elevated in blood during hypoxia/ tissue damage. The LDH values are elevated in newborns born to Meconium Stained Amniotic Fluid (MSAF); the degree of elevation correlates with the amount of hypoxia. Hence, LDH values can be used to quantify the outcome in MSAF newborns.

**Aim:** To assess the LDH level and relation of duration of Neonatal Intensive Care Unit (NICU) stay. To predict the duration of oxygen dependence in newborns born to MSAF using LDH level at birth.

**Materials and Methods:** A prospective cross-sectional study was conducted between January 2018 to June 2018. Cord blood LDH in all MSAF newborns (118) was measured. The newborns were observed for prolonged NICU stay and duration of oxygen dependence. Re was assessed between high LDH level and prolonged NICU stay and duration of oxygen dependence.

**Results:** The study showed a relation between higher level of cord blood LDH and prolonged NICU stay (p=0.08). It also depicted that as the cord blood LDH level increases, there is an increase in duration of oxygen supplementation to the newborns (p=0.8), however on further increase in LDH level the duration of oxygen given decreased.

**Conclusion:** LDH levels can be used as a prognosticating tool in predicting NICU stay and oxygen dependence. However, larger studies are needed in the Indian population to conclude the same.


**Keywords:** LDH significance, MSAF morbidity, MSAF prognosis, NICU financial planning

## INTRODUCTION

Neonatal death is still the leading cause of under-five mortality. As per UNICEF 2018 data, India stands 12th amongst 52 lower middle class income countries for its high mortality rate of having Neonatal Mortality Rate (NMR) of 25.4 deaths per 1,000 live births [1].

Meconium Aspiration Syndrome (MAS) is among the most common causes of hypoxemic respiratory failure in term neonates who require intensive care [2]. Approximately, 5% of neonates born with Meconium Stained Amniotic Fluid (MSAF) develop MAS. Despite recent reports of significantly reduced MAS fatality rate, approximately 1/3rd of neonates with MAS require intubation, mechanical ventilation and other new therapies such as high frequency ventilation, inhaled Nitric Oxide (iNO) and surfactant administration [3].

Lactic acid is a terminal product of the anaerobic metabolism of glucose, and it is obtained by a reduction of pyruvic acid in a reaction catalysed by the lactic dehydrogenase enzyme where Nicotinamide Adenine Dinucleotide (NAD) coenzyme goes from its reduced form to its oxidised form. An early mechanism in the cascade of events leading to cell damage or death is leakage of certain intracellular components such as LDH through the cell membrane into the plasma [4].

Lactic acid is catalysed by enzyme LDH [4-8]. Under normal conditions, serum LDH levels in newborn are less than 580 [9]. However, its value gets increased in situations of hypoxia-ischemia and its level have a higher correlation with higher morbidity and mortality [4,8,10-17].

The newborns who are born to MSAF need an early recognition and the plan for management towards the duration of NICU need to be done. This can also help in bringing down the mortality due to MAS.

Early suspicion of upcoming problems in a neonate and prompt referral for adequate workup and treatment would reduce permanent damage and mortality and consequently, improve the overall outcome. However, signs of serious disease in newborn are often seen early and are difficult to interpret for the non-specialist. Clinical algorithms for identifying seriously ill neonates have been developed but experience for its use during the first week, which happens to be the period of highest morbidity and mortality, is limited.

There have been various studies conducted in adults and children which showed higher levels of lactic acid at the time of admission had poorer prognosis and risk of death [10-14]. But there has been no study so far in Indian population with respect to LDH as prognosticating tool.

We hypothesise that LDH is an early biomarker of cellular compromise. Also, measurement of the same can be done in any laboratory and it is highly cost effective. In the present study, we have investigated to see if LDH can be used as a potential prognostic factor in determining NICU stay and Oxygen dependence in MSAF babies.

## MATERIALS AND METHODS

A prospective observational study was conducted between January 2018 and June 2018 at Adichunchanagiri Institute of Medical Sciences. Ethical Committee approval was obtained.

All the babies born with MSAF, inborn or outborn, were enrolled in the study irrespective of gestational age. The study samples included all the newborns with Meconium stained amniotic fluid those were born in the study period, which consisted of 118 newborns.

### Methods

MAS were clinically defined as a respiratory dysfunction in neonates born with MSAF and which experienced symptoms in the first four to six hours of life that could not be explained otherwise. Those neonates who had other causes of respiratory distress like pneumonia, Respiratory distress syndrome, Transient tachypnea of Newborn, Congenital malformation of Lung, cardiac illness were excluded.

Data was recorded with regard to gender, modes of delivery, gestational age by dates, maternal evidence of fetal distress, any history to cause acute intrapartum hypoxia, if weight was appropriate for gestational age, Apgar scores at first and five minutes, oxygen dependency by hood/Continuous Positive Airway Pressure (CPAP), mechanical ventilation, duration of oxygen given, sepsis, Acute Kidney Injury (AKI), Persistent Pulmonary Hypertension (PPHN), blood LDH level and their outcome.

Neonates were defined as Oxygen dependant when they had clinical distress (tachypnea, chest retraction, cyanosis), poor oxygen saturation (<91%) or abnormal blood gas (Po2 <60 mmHg). Mild cases were given oxygen by hood, moderate by CPAP and severe by mechanical ventilation. Downe's scoring [18] was used as clinical assessment of hypoxemia for categorising the neonates into Mild, Moderate and Severe.

Sepsis was defined as per National Neonatology Forum (NNF) criteria- if any one of the sepsis screening investigations (leucopenia <5000, CRP >10 mg/dL, abnormal peripheral smear with band cells and I:T >0.2 or blood culture with microbial growth) were abnormal. Perinatal asphyxia was defined as umbilical artery pH <7.0, Acute Kidney Injury (AKI) was defined as plasma creatinine >1.5 mg/dL for 24 hours, if mothers renal functioning is normal. PPHN was considered in those newborns with gradient of 10% or more between preductal and postductal ABG.

All neonates who required intensive care were immediately admitted in the NICU and clinically stable babies were shifted to mother's side. Discharge criteria from NICU were followed as per institutional guidelines, i.e., baby is clinically stable (no tachypnea/tachycardia/hypotension/temperature instability), not requiring oxygen and taking direct breast feeding well. All the newborns admitted at our institute are usually discharged between five to seven days unless child is not clinically/haemodynamically stable and hence newborns staying at NICU for more than seven days were considered to have prolonged NICU stay.

## Sample Collection

A 2 mL of cord blood was collected in a plain tube from each MSAF neonate and thus no extra prick was made to the neonate. The above sample was immediately sent to the central laboratory and results were obtained. LDH levels were measured from lactate/LDH scout analyser.

## Data Analysis

Descriptive and inferential statistical analysis has been carried out. The results in our study which are on continuous measurements are presented on Mean and SD and results on categorical measurements are presented in percentage (%). Level of significance was taken as 5%.

The Chi-square/Fisher-Exact test has been used to find the significance of study parameters on categorical scale between two or more groups in our study, non-parametric setting for Qualitative data analysis. We used Fisher-Exact test when cell samples were very small.

# RESULTS

In the cohort of 118, males were 61 (51.78%), females were 57 (48.3%). Term neonates were 111 (94.1%) and preterm 7 (5.9%); this shows that MSAF is more common in term neonates compared to preterm. Further, maximum number of neonates were in the gestational age group of 38-40 weeks (85.6%), it was so because MSAF is more common as the pregnancy advances. However, there was lesser number of cases beyond 40 weeks, the reason being that our institution considers all post-dated pregnancies as an indication for induction of delivery [Table/Fig-1].

In the overall oxygen support given, 2 (1.7%) of the 118 were mechanically ventilated, 36 (30.5%) of them were given CPAP and 40 (33.9%) were given by hood. Most neonates were given oxygen by more than one modality during the stay.

The complications other than that of MAS during NICU stay was mainly sepsis, birth asphyxia, AKI, PPHN, hypoglycaemia, polycythemia etc. The distribution of morbidity was MAS 37 (31.4%), sepsis 23 (19.5%), birth asphyxia 17 (14.4%) AKI 4 (3.4%), PPHN 1(0.8%). In our cohort, we observed that around 30% of the babies with MSAF developed MAS.

| Parameters | Number of patients | Percentage distribution |
|---|---|---|
| ***Gender** | | |
| Female | 57 | 48.3 |
| Male | 61 | 51.7 |
| ***Period of Gestation (weeks)** | | |
| Term | 111 | 94.1 |
| Preterm | 7 | 5.9 |
| 34-37 | 13 | 11 |
| 38-40 | 101 | 85.6 |
| >41 | 4 | 3.4 |
| ***LDH(U/L)** | | |
| 160-450 | 5 | 4.2 |
| 450-1000 | 40 | 33.9 |
| 1000-2000 | 53 | 44.9 |
| >2000 | 20 | 16.9 |
| ***Oxygen support** | | |
| Mechanical ventilation | 2 | 1.7 |
| CPAP | 36 | 30.5 |
| Hood | 40 | 33.9 |
| ***Morbidity** | | |
| MAS | 37 | 31.4 |
| Sepsis | 23 | 19.5 |
| Birth Asphyxia | 17 | 14.4 |
| AKI | 4 | 3.4 |
| PPHN | 1 | 0.8 |

**[Table/Fig-1]:** Demographical characteristics of the cohort.
LDH: Lactate dehydrogenase; CPAP: Continuous positive airway pressure; MAS: Meconium aspiration syndrome; AKI: Acute kidney injury; PPHN: Persistent pulmonary hypertension of newborn

We can infer from [Table/Fig-2,3] that there has been a direct relation with the LDH value and prolonging of NICU stay and Oxygen dependence. [Table/Fig-3] shows that after categorising the new borns, maximum of the oxygen dependency were seen in those with LDH range 1000-2000 U/L. There were 53 (44.9%) cases in this group of which 36 (42.4%) received oxygen for less than six hours, 2 (66.7%) cases who received oxygen for 25-48 hours, 6 (60%) cases who received oxygen for 49-72 hours. There were 4 (40%) cases who received oxygen for 73-120 hours, 5 (50%) cases who received oxygen for more than 121 hours. The p-value was found to be 0.8. Maximum number of babies having prolonged NICU stay are seen to have LDH values between 1000-2000 U/L and similarly, highest number of oxygen dependent newborns were present in the group of babies having LDH values between 1000-2000 U/L. Considering this data, babies having LDH >2000 should have had a worse prognosis, but on looking into reasons for this contradiction, having LDH above 2000 U/L, was not only the morbidity but also ABO incompatibility and Rh incompatibility which has led to early haemolysis and release of LDH into blood.

| LDH (U/L) | Number of cases with prolonged NICU stay | Number of cases without prolonged NICU stay | Total | p-value |
|---|---|---|---|---|
| 160-600 | 2 (2.6%) | 3 (7.3%) | 5 (4.2%) | |
| 600-1000 | 29 (37.7%) | 11 (26.8%) | 40 (33.9%) | |
| **1000-2000** | **37 (48.1%)** | **16 (39%)** | **53 (44.9%)** | 0.084 |
| >2000 | 9 (11.7%) | 11 (26.8%) | 20 (16.9%) | |
| Total | 77 (100%) | 41 (100%) | 118 (100%) | |

**[Table/Fig-2]:** LDH values and frequency distribution of the same with prolonged NICU stay.

| LDH (U/L) | Duration of oxygen given | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <6 hours | 6-24 hours | 25-48 hours | 49-72 hours | 73-120 hours | >121 hours | Total | p-value |
| 160-600 | 5 (5.9%) | 0 (0%) | 0 (0%) | 1 (10%) | 1 (10%) | 0 (0%) | 7 (5.9%) | 0.898 |
| 600-1000 | 30 (35.3%) | 1 (100%) | 1 (33.3%) | 2 (20%) | 2 (20%) | 2 (22.2%) | 38 (32.2%) | |
| **1000-2000** | **36 (42.4%)** | **0 (0%)** | **2 (66.7%)** | **6 (60%)** | **4 (40%)** | **5 (55.5%)** | **53 (44.9%)** | |
| >2000 | 14 (16.5%) | 0 (0%) | 0 (0%) | 1 (10%) | 3 (30%) | 2 (22.2%) | 20 (16.9%) | |
| Total | 85 (100%) | 1 (100%) | 3 (100%) | 10 (100%) | 10 (100%) | 9 (100%) | 118 (100%) | |

**[Table/Fig-3]:** LDH values and its relation with oxygen dependence.

## DISCUSSION

The study which we conducted showed that all the newborns born to MSAF showed a higher incidence of prolongation of hospital stay and greater oxygen dependence although the p-values have not been statistically significant. Hence we have been able to infer that LDH is helpful in predicting the outcome of MSAF newborn.

In a study done by Karlsson M et al., at Sweden to look for LDH as an indicator of severe illness in NICU showed strong relationship between bad clinical condition of infants during first week of life and elevated plasma LDH. But the population of the study was different and hence could not be implemented to ours unless there is a study to prove the same. Similarly our study has also demonstrated a relation with LDH values and outcome of the newborns [19].

In a study done by Karabayir N et al., in Turkey on blood lactate levels and MAS, it was shown that there was correlation between blood lactate levels, blood pH value and hospitalisation duration. But the study lacked the LDH demonstration; LDH assessment is less expensive than S. Lactate level measurement. Hence our study adopted LDH as a marker and like the above study there was a relation to the duration of NICU stay to the marker [3].

In a study done by Rodriguez B et al., in Mexico on risk factors and relation of lactic acid to neonatal mortality in first week of life, it showed that high lactate levels had good positive prediction towards the morbidity. Our study was also of the same opinion [20].

Although there are only few studies which have been conducted in our country [21,22] to demonstrate the relation between LDH and morbidities, in our study we have successfully demonstrated a positive relation in our objective. It is advantageous for the treating doctor to have a prognosticating tool. In a rural set up like ours NICU stay can be a financial burden on the parents and hence, early prediction of the same can help in financial planning for the parents.

Competence in assessing the status of the new born baby is often low in places of limited resources. Hence, it is important to have an easy and economical tool for patient counselling. Also, by early detection of 'at risk' babies, prompt intervention can be made which can help in reducing neonatal mortality rate.

## LIMITATION

The study group was small which has led to the probable reason for being statistically not significant. Hence larger size is required to be tested to apply the same results. The group of babies with increased LDH level but no abnormality/oxygen dependency was found to have elevated LDH due to haemolysis either because of Rh incompatibility or ABO incompatibility. Hence Rh and ABO incompatibility should have been an exclusion criterion in our study in order to have precision of the results.

## CONCLUSION

LDH levels can be used as a prognosticating tool in predicting NICU stay and oxygen dependence. If adopted in MSAF born babies, can be used as a cost effective and simple predictive measure.

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