Original Article

STYLING PERINATAL ASPHYXIA AND THE IMPACT OF LDH AND CKMB – ENZYME MARKERS

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Abstract

The neonatal mortality rate (NMR) decreased from 52 per 1000 live births in 1990 to 28 per 1000 live births in 2013[1]. "The slower decline has led to increasing contribution of neonatal mortality to infant and under-five mortality. Among neonatal deaths, the rate of decline in early neonatal mortality rate (ENMR) is much lower than that of late NMR. Similarly, the perinatal mortality is also still fairly high. The rate of decline in NMR, and to an extent ENMR, has accelerated with the introduction of National Rural Health Mission in mid- 2005. Almost all states have witnessed this phenomenon, but there is still a huge disparity in NMR between and even within the states. The disparity is further compounded by rural–urban, poor–rich and gender differentials. There is an interplay of different demographic, educational, socioeconomic, biological and care-seeking factors, which are responsible for the differentials and the high burden of neonatal mortality. Addressing inequity in India is an important cross-cutting action that will reduce newborn mortality."

Introduction

"The neonatal period—the first 28 days of life—carries the highest risk of mortality per day than any other period during the childhood. The daily risk of mortality in the first 4 weeks of life is ~30-fold higher than the post-neonatal period, that is, from 1 month to 59 months of age. Still, newborn health did not receive the commensurate attention it deserved until during the past decade. This has resulted in a slow decline in neonatal mortality rate (NMR) in most countries including India, and has hampered their achieving the Millennium Development Goal-4 (MDG 4) by year 2015."

"India contributes to one-fifth of global live births and more than a quarter of neonatal deaths. Given the early NMR of 22 per 1000 live births, deaths in the first week alone account for ~45% of total under-five deaths. Obviously, the 'Committing to Child Survival: A Promise Renewed' goal of reducing under- five mortality to 20 or less per 1000 live births by 2035[2] will not be attained without specific efforts to reduce newborn mortality."

"A systematic analysis of global, regional and national causes of child mortality in 2013 identified preterm birth complications and infections to be the two major causes of neonatal deaths in India The review, which included the data from the Million Death Study from India, found perinatal asphyxia and malformations to be the other two significant causes of neonatal mortality."

Review of Literature

In 2005, **Boo NY et al**[17]showed that "at birth, asphyxiated infants had significantly higher concentrations of cTnT and CK-MB than controls. Unlike CK- MB, serum cTnT concentrations were significantly higher in asphyxiated infants who died or developed cardiac dysfunction."

In 2008 **Reddy S et al**[18]concluded that "raised LDH had 100% sensitivity, while CK-MB had 100% specificity for asphyxia. They found that LDH at 72 hoursof life is the most accurate at differentiating asphyxiated from non- asphyxiated symptomatic neonates and that LDH could be used at 3 days of age to diagnose asphyxia retrospectively."

In a study by **Rajakumar PS et al** [19]in 2008, " the cardiac enzymes, cTnT and CK-MB were significantly elevated in cases when compared with controls. The mean CK-MB levels among cases and controls were 121±77.4 IU/L and 28.8±20.2 IU/L respectively. The specificity and sensitivity of CK-MB were 56.5% and 75.7% respectively."

Karlsson M et al [20]in their "clinical and experimental study done in 2008 on evaluation of organ damage in perinatal asphyxia concluded thatin asphyxiated infants with differing degree of HIE and in infants where there had been signs of fetal distress during birth a cut off level of 1049 U/L for LDH was the most suitable predictor of mild, moderate, and severe HIE with a sensitivity of 100% and specificity of 97%."

In a study by **Shylaja et al**[21] in 2014, "on 50 asphyxiated neonates comprisingthe cases and 50 non-asphyxiated neonates comprising the controls, serum CK-MB at 8 hours and 24 hours and serum LDH were performed. A serum CK-MB value >92.6U/L at 8 hours, >60 U/L at 24 hours and LDH value >580 U/L at 72 hours was taken as the cut-off level. The sensitivity, specificity, Positive predictive value (PPV), Negative predictive value (NPV) was calculated for both CK-MB and LDH. It was found that he cut-off CK-MB value of >92.6 U/L at 8 hours had 82% sensitivity with a specificity of 80%. CK-MB had a positive predictive value of 80.34% with a negative predictive value of 81.63%.The cut-off CK-MB value of >60 U/L at 24 hours had 58.33% sensitivity with a specificity of 95.83%. CK-MB had a positive predictive value of 93.33% with a negative predictive value of 69.70%.The cut-off LDH value of >580 U/L at 72 hours had 100% sensitivity with a specificity of 88%. LDH hada positive predictive value of 89.29% with a negative predictive value of 100%. It concluded that estimation of CK-MB at 8 hours and 24 hours of life and LDH at 72 hours of life can help distinguish an asphyxiated from a non- asphyxiated neonate in correlation with history and clinical features in the neonate. The diagnostic performance of LDH is better than CK-MB."

In a 2015 study by **Vargas et al**[23], "they concluded that perinatal asphyxia may be diagnosed in any hospital if the neonatologist or the neurologist apply the easy clinical score of Sarnat and Sarnat, the iso-enzyme CKMB and the serial ultrasonography. In this study the worse alteration was with 72 hours of life, however they noted that they must be careful because in one neonate the alteration was present only with 28 days of life."

In a 2017 study by **Jones et al**[29], "infants qualifying for therapeutic hypothermia (TH) based on aEEG abnormalities were considered to have HIE (*n* = 13; 16.5%), whereas babies with normal aEEG were classified as ―non-HIE‖ (*n* = 66; 83.5%). The highest AUC measure was associated with the five- minute APGAR score (0.89 (0.79–0.99)). Troponin T (0.81 (0.64–0.98)) and ALT (0.78 (0.60–96)) also showed high values.They concluded that the APGAR score, troponin T and ALT were found to be strong and useful predictors of HIE."

In a 2018 study by **Graham et al**[31] they concluded that "although new single biomarker studies continue to emerge, utilizing metabolic profiling to more comprehensively understand the effects of injury and treatment on entirepathways following neonatal brain injury may identify new therapeutic targets in neonatal brain injury. A number of biomarkers used to identify other conditions are now being used to identify neonatal neurologic injury." "Markers of cardiac injury are increasingly useful in this respect. Cytokine biomarkers in a relevant preclinical model of HIE identify a proinflammatory surge during the rewarming period following therapeutic hypothermia. If confirmed, these studies may reveal an additional therapeutic target in neonatal HIE. Until recently, very few biomarker studies in neonatal brain injury included post hospital outcomes. Future studies will need to include these data to provide maximal information about their utility."

"Newer terms include ‗birth depression', which is a descriptive term to indicate a newborn with poor APGAR but without passing judgement on etiology. The use of word ‗perinatal' rather than ‗birth' supports the pathological processes that may begin many hours before birth and continue for many hours afterwards. There are numerous causes, and the clinical manifestations vary. Infants who experience mild asphyxia may show no neurological injury. However, severe asphyxia may be fatal in utero, or immediately after birth, with survivors showing extensive neurological sequelae, with or without cognitive deficits."

Incidence

"The frequency of perinatal asphyxia is approximately 1% to 1.5% of live births in the Western Hemisphere and is inversely related to gestational age andbirth weight[42]. It occurs in 0.5% of live born infants >36 weeks gestation and accounts for 20% of perinatal deaths (50% if stillborns are included) . A higher incidence is noted in term infants of diabetic or toxemic mothers, infants with intrauterine growth restriction, breech presentation, and postdated infants ..In India, 8.4% of inborn babies have a one minute APGAR score less than 7and 1.4% suffer from HIE"[43] .

Etiology.

"In term infants, 90% of asphyxial events occur in the antepartumor intrapartum period as a result of impaired gas exchange across the placenta that leads to the inadequate provision of oxygen (O_2) and removal of carbon dioxide (CO_2) and H^+ from the fetus. The remainder of these events occurs in the postpartum period and is usually secondary to pulmonary, cardiovascular, or neurologic abnormalities" [44].

A. Factors that increase the risk of perinatal asphyxia include the following:

1. "Impairment of maternal oxygenation."
2. "Decreased blood flow from mother to placenta."
3. "Decreased blood flow from placenta to fetus."
4. "Impaired gas exchange across the placenta or at the fetal tissue level."
5. "Increased fetal O_2 requirement."

B. Etiologies of perinatal hypoxia-ischemia include the following:

1. "Maternal factors: hypertension (acute or chronic), infection, diabetes, hypotension, vascular disease, drug use, and hypoxia due to pulmonary, cardiac, or neurologic disease."
2. "Placental factors: infarction, fibrosis, abruption, or hydrops."
3. "Uterine rupture."
4. "Umbilical cord accidents: prolapse, entanglement, true knot, compression."
5. "Abnormalities of umbilical vessels."
6. "Fetal factors: anemia, infection, cardiomyopathy, hydrops, severe cardiac/ circulatory insufficiency."
7. "Neonatal factors: severe neonatal hypoxia due to cyanotic congenital heart disease, persistent pulmonary hypertension of the newborn, cardiomyopathy,other forms of neonatal cardiogenic and/or septic shock."

"The 1-minute APGAR score reflects the need for immediate resuscitation. The 5-minute score, and particularly the change in score between 1 and 5 minutes, is a useful index of the effectiveness of resuscitative efforts. The 5- minute APGAR score also has prognostic significance for neonatal survival, because survival is related closely to the condition of the infant in the delivery room" [50].

"The APGAR score was not designed to predict neurologic outcome. Indeed, the score is normal in most patients in whom cerebral palsy subsequently develops, and the incidence of cerebral palsy is low in infants with APGAR scores of 0-3 at 5 min (but higher than in infants with APGAR scores of 7-10). The APGAR score and umbilical artery blood pH both predict neonatal death. An APGAR score of 0-3 at 5 min is uncommon but is a better predictor of neonatal death (in both term and preterm infants) than an umbilical artery pHof 7.0 or less; the presence of both variables increases the relative risk of neonatal mortality in term and preterm infants."

"In an analysis of more than 150,000 infants delivered at Parkland Hospital, Casey and associates assessed the contemporaneous significance of the 5-minute score for predicting survival during the first 28 days of life. They found that in term infants the risk of neonatal death was approximately 1 in 5000 for those with APGAR scores of 7 to 10, as compared with approximately 1 in 4 for those with scores of 3 or less . Low 5-minute scores were comparably predictive of neonatal death in preterm infants. They concluded that the APGAR scoring system is as relevant for the prediction of neonatal survival today as it was almost 50 years ago" [51].

"Despite the methodological challenges, erroneous definitions of asphyxia by many groups were established solely based upon low APGAR scores. The promulgation of such definitions prompted the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics to issue a joint statement in 1986 on the use and misuse of the APGAR score that was reaffirmed in 1996" [52].

Material and Methods

Setting:

New born infants admitted to the NICU, department of Pediatrics, KrishnaHospital, Karad during the study period of December 2017 to May 2019

Type - Prospective Observational Study

Study Period:

1 December 2017 to 30 September 2019

Method of Collection of Data (including sampling procedure if any):

Cases were the new born infants admitted to the NICU, Krishna Hospital, Karad.They were studied from 1 December 2017 - 31 May 2019.

Sample Size: n= [4 * (SD)squared] / (x * ε)squaredSD-standard deviation

x- mean

ε- precision

Using above formula, sample size calculated was 55 cases at precision ε= 0.4based on the study by Shylaja et al in 2014.

Inclusion Criteria:

Study group: New born infants with signs of birth asphyxia with

1. APGAR score <=7 at 5 min

2. In case of outborn patients,when APGAR score was not known - clinical evidence of multiorgan system dysfunction like oligo-anuria, congestive heart failure not related to structural defects, shock, ventilatory dependence or requirement of increased oxygen for more than 24 hours, elevated transaminases, DIC, Necrotising enterocolitis etc.

3. All term neonates (≥37 weeks of gestation) having birth weight (≥1.5kg)

Exclusion criteria:

Patients with -

1. Gestational age of <37 completed weeks

2. Very Low birth weight babies (<1.5 kg)

3. Major congenital malformations

4. Chromosomal abnormalities

5. Metabolic disorders

6. Congenital infection

7. Birth trauma

8. Septic shock

9. Full-term newborns with severe jaundice, severe septicemia, congenital anomalies of the hepatobiliary system

10. Babies undergoing potentially hepatotoxic drug therapy

Method of examination:

- Project was approved by institutional ethical committee before conduction. Written informed consent was obtained from parents/guardians prior to enrolment of subjects in study.

- At birth, all the babies fulfilling inclusion criteria were admitted to NICU where detailed examination was done by same assessor for all the patients. All relevant history and clinical findings as per proforma were noted.

- Babies were grouped according to Sarnat and Sarnat stages of HIE as Stage I, II, and III.

- The biochemical analysis for the parameters, that is LDH, CK-MB, was be done using reagent kits and Auto Analyzers– like TOSOH AIA-360 in the biochemistry laboratory of the institute.

- 1 ml venous blood was collected under aseptic precautions in a plain bulb for testing levels of CKMB at 8 hours, 24 hours and LDH at 72 hours after birth. The levels were compared against normal reference values mentioned in standard published literature.(upper limit of 4.5 ng/ml for CKMB at 8 and 24 hours and upper limit of 580 U/L for LDH at 72 hours).

After examining for APGAR score at 1 min, all patients had APGAR score lessthan 7. 48 patients had score between 0-3 indicating severe birth asphyxia. 7 neonates had APGAR score 0-3.

At 5 min,13 neonates had APGAR score 7 ,38 neonates had score between4 - 6,4 had score between 0-3.

Out of 55 neonates a total of 50 patients were discharged of which 48 (87.27%) patients were without neurodeficit and 2 (3.64%) patients were with neurodeficit. 5 (9%) patients died during treatment.

A study by Laryea CC et al in 2018 in Africa found that the mean out-of- pocket expenditure for perinatal asphyxia was 132.3 $.This amount assumes higher significance in our country where this will amount to a major portion of the average income of a caregiver.

In a large number of caregivers , basic needs of living are barely met withtheir incomes and bearing the costs of treatment in neonatal period followedby greatly added cost of providing for child with neurological sequelae of birth asphyxia is a matter that requires serious consideration. Withdrawing treatment is a big decision that the caregivers make in such situations and any test that can predict the outcome in such patients will greatly aid in decision making for caregiver as well as healthcare provider.

Various results of our study can be compared with existing studies as follows:Some basic parameters that were studied were-

Gender distribution:

In our study, maximum number of cases, 39 out of 55 (71%) were male.

This finding is similar to that obtained in studies by Reddy et al and HM Sanjay et al[110].

Birth order:

In our study there was apparently not much difference in frequency of birth asphyxia among mothers who were primigravida(45%) and multigravida (55%)

This was similar to findings in studies by Reddy et al and HM Sanjay et al but contradictory to study by Aslam et al[111] where birth asphyxia was found in higher frequency among primi gravida mothers.

Mode of delivery:

In this study among patients with birth asphyxia frequency of delivery by caesarean section (71%) was higher than delivery per vaginum (25%) or assisted vaginal delivery(4%). This is similar to findings in studies by Reddyet al and HM Sanjay et al but study by Aslam et al didn‘t find any significant increase in frequency of asphyxia in babies delivered by caesarean section.

NST:

In this study, frequency of patients with reassuring NST (73%) was higher than those with non reassuring NST (27%) compared to non reassuring NST being present in 78% cases in study by HM Sanjay et al and 92% in study by Reddy et al.

MSAF:

In this study, frequency of patients with MSAF (29%) was lower than those with clear amniotic fluid(71%) compared to MSAF being present in 64% casesin study by HM Sanjay et al and 8% in study by Reddy et al.

In the current study the distribution of HIE was 73% with mild asphyxia, 18% with moderate asphyxia and 9 % with severe asphyxia. Thus, majority hadmild HIE unlike in the study by Rajakumar et al where although 100% patients developed HIE, majority (60%) had moderate asphyxia.

In the study by HM Sanjay et al,38% had HIE out of which maximum(24%) had moderate HIE.

Respiratory distress was present in 27% of cases in this study compared to 76% and 67% respectively in studies by HM Sanjay et al and Reddy et al respectively.

Shock developed in 11.5 % of the patients in this study ,with similar number in studies by HM Sanjay et al (12%), Reddy et al(16%) and Rajakumar et al(17%).

Congestive cardiac failure occurred in 1.8% of the patients in our study, similar to findings of Sanjay et al (2%) but much lesser than that observed in study by Rajakumar et al (37%).

Hypotonia was seen in 73 % of the cases in this study similar to that in studiesby Rajakumar et al (73%),Reddy et al(68%) but lesser than that in study by Sanjay et al (38%). Death occurred in 9.1 % patients of our study similar to proportion in the studyby Sanjay et al (10%). Differences observed in our study may be attributed to different inclusion criteria used in different studies, different grading systems used, differences in resuscitative measures used, post asphyxia monitoring, etc.

Table 6: Comparative study of CKMB level above cut off in cases at 24 hours

Study	**Above cutoff**	**Below Cutoff**
Current study	**100%**	**-**
Reddy et al	**36%**	**64%**
Shylajaet al	**40%**	**60%**

Table 7: Comparative study of LDH above cutoff in cases at 72 hours

Study	**Above cutoff**	**Below Cutoff**
Current study	**100%**	**-**
Reddy et al	**100%**	**-**
Shylaja et al	**96%**	**4%**

Among patients showing above cutoff values of CKMB, significantly higher proportion belonged to case group than the control group in studies by Reddy et al ,Shylaja et al.

In our study 98% cases had CKMB at 8 hours above cutoff and 100% had CKMB at 24 hours and LDH at 72 hours above cutoff. When compared to CKMB at 8 hours in this study ,other studies didn‘t show a higher frequency of above cutoff values among cases such as Reddy et al showing 36%,Shylaja et al showing 40% above cutoff. However in a study by Chawla et al, 100% of the patients with CKMB above cutoff belonged to the case group,i.e. had birth asphyxia. The differences may be due to the fact that our study is an observationalstudy and included only cases unlike the other studies which were casecontrol studies. In addition, all the cases in our study had more severe sequelae of birth asphyxia than these studies which may be the reason for higher enzyme levels in our study.

Table 8: Comparative study of mean CKMB level at 8 hours, CKMB at 24hours, LDH at 72 hours

Study	**Mean CKMB 8hours**	**Mean CKMB 24 hours**	**Mean LDH 72hours**
Current study	25.69+/-36.13 ng/ml	32.96+/-27.67 ng/ml	1474.15+/- 586.58 U/L
Reddy et al	176.1+/- 243 U/L	49.6+/-36 U/L	1109.5+/- 520.6U/L
Sanjay et al	83.98+/-19.6 U/L	-	555.65+/- 105.95U/L
Sadoh et al	2.3+/-2.5 ng/ml		
Vargas et al		36.7 ng /ml	546IU/L

Mean CKMB at 8 hours in this study was well above the cutoff similar to study by Reddy et al but unlike the study by Sanjay et al and Sadoh[112] et al. Difference may be due to greater severity of complications in cases of our study as described.

Mean CKMB at 24 hours was well above cutoff level similar to studies by Vargas et al. Mean LDH was well above cutoff similar to studies by Reddy et al.

- Correlation between CKMB at 8 hours and severity of HIE

Our study found that there was a significant rise in CKMB at 8 hours withincrease in severity of HIE.

Similar findings were obtained in studies by Rabindran et al,Saha[113]etal,Beken S et al,Ashraf [114]et al.

- Correlation between CKMB at 24 hours and severity of HIE

Our study found that there was a significant rise in CKMB at 24 hours withincrease in severity of HIE.

Similar findings were obtained in studies by Rabindran et al,Saha et al,BekenS et al,Chawla et al.

- Correlation between LDH at 72 hours and severity of HIE

Our study found that there was a significant rise in LDH at 72 hours withincrease in severity of HIE.

Similar findings were obtained in studies by Rabindran et al,Patra et al,Muniraman et al, Beken S et al.

- Correlation between CKMB at 8 hours and outcome of HIE

Our study found that there was a significant rise in CKMB at 8 hours withworse outcome of HIE.

Similar findings were obtained in studies by Rabindran et al, Nakajima et al.

Summary

- In our prospective observational study we studied 55 neonates withperinatal asphyxia who fulfilled the inclusion criteria.

- Detailed history was noted and clinical examination was done as perproforma.

- Venous samples were assessed for CKMB at 8 hours and 24 hours, and LDH at 72 hours. Neonates were followed up until discharge and any relevant observations during course of stay and outcome were noted. These neonates were classified into 3 groups based on the stage of HIE they developed.

- Statistical analysis was done to find any correlation between increasein enzyme levels and severity of HIE, outcome of patient and the requirement for intensive procedures. We found that

➢ CKMB and LDH levels are elevated in patients of birth asphyxia

➢ There is a correlation between increased enzyme levels and

- Severity of HIE

- Outcome of these patients

- Need for intensive procedures

- Thus we found that enzyme levels of CKMB and LDH can be used to diagnose perinatal asphyxia and differentiate between asphyxiated andnon- asphyxiated babies.

- Mainly, the elevated enzyme levels can be utilised to predict the outcome and prognosis of birth asphyxia patients. This will help us to give guarded prognosis to caregivers of children whose enzyme values are markedly raised.

- Enzyme estimation has greater significance in developing countries like ours, where adequate birth history may not be available regarding resuscitation methods used at delivery, especially in the periphery.

- Tests to detect raised enzyme levels are economical and do not require sophisticated equipment or advanced technical expertise unlikesome other tests used to predict the outcome in perinatal asphyxia patients like -MRI scan, newer protein markers ,etc.

- Neuroprotective measures like therapeutic hypothermia (TH) can be initiated for asphyxiated neonates with raised enzyme levels. Although our study assessed first enzyme levels at 8 hours after birth and TH should ideally be started within 6 hours of birth, studies[106] have shown that even late TH within the first 24 hours may offer a modest protective benefit against severe neurodevelopmental disability.

Limitations of this study-

-Sample size was fairly small and it was an observational study. Large Multi centre case control studies and trials will be required to more definitively establish the role of enzyme markers as predictors of the presence of asphyxia, It‘s severity and outcome or prognosis. The cases of this study were followed only until discharge and longer follow up would give a better idea about long term neurodevelopmental disabilities.

Conclusion

- CKMB levels at 8 hours, 24 hours and LDH levels at 72 hours afterbirth are elevated in patients of perinatal asphyxia.

- There is a correlation between increased enzyme levels and

- Severity of HIE

- Outcome of these patients

- Need for intensive procedures

- Thus, enzyme levels of CKMB and LDH can be used to diagnose perinatal asphyxia, especially in cases where proper birth history is not available.

- Mainly, the elevated enzyme levels can be utilised to predict the outcome and prognosis of perinatal asphyxia patients. This will help us to give guarded prognosis to caregivers of children whose enzyme values are markedly raised.

- Neuroprotective measures like therapeutic hypothermia can be initiated in neonates having raised enzyme levels.

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