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Study of CK-MB Levels in Asphyxiated Neonates Admitted in Neonatal Intensive Care Unit (NICU) at Tertiary Care Hospital

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ABSTRACT

Perinatal asphyxia is a lack of blood flow or gas exchange to or from the foetus in the period immediately before, during, or after the birth process. Perinatal asphyxia is an important cause of admission to neonatal intensive care units (NICU) with multi organ dysfunction. CK- MB is one of the three isoenzymes of creatine Kinase and is expressed in myocardial muscle and in very small amounts in skeletal muscle. There is evidence that CK-MB levels are significantly elevated in asphyxiated infants compared with controls. CK-MB may be helpful in identifying infants with neonatal hypoxic ischemia who have cardiovascular compromise but may be more useful as part of a predictive model for poor outcome following neonatal hypoxic ischemia. The study was conducted in Neonatal Intensive care unit of a tertiary care centre from February 2021 to August 2022. 203 Neonates who have been clinically diagnosed as perinatal asphyxia admitted to NICU over a period of one and half years were included in the study. Detailed demographic data with respect to maternal history birth events, Apgar score, sex of the baby and weight of the baby was recorded on the Pre-coded proforma. Data was entered from case record form in excel sheet. Care was taken to enter data accurately. Majority of neonates post-delivery, needed bag and mask resuscitation (80.30%), did not cry (81.7%), few had delayed cry (18.3%) with 60.1% in normal cry tone and 39.9% had poor cry tone activity. Majority of neonates needed oxygen supply (80.30%), anticonvulsants (47.4%), inotropes (40.4%) and few needed ventilatory support (19.70%). CK-MB can be very useful to differentiate HIE new-borns which will help in appropriate management and better outcome of these new-borns. Evaluation of CK- MB levels as a marker of severity of perinatal asphyxia shows promising results.

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Key Words
Neonates, asphyxia, CK-MB, NICU, hypoxia

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INTRODUCTION

Perinatal asphyxia is a condition characterized by an impairment of exchange of the respiratory gases (oxygen and carbon dioxide) resulting in hypoxemia and hypercapnia, accompanied by metabolic acidosis[1]. Perinatal asphyxia is a lack of blood flow or gas exchange to or from the fetus in the period immediately before, during, or after the birth process. It can result in profound systemic and neurologic sequelae due decreased blood flow and/or oxygen to a fetus or infant during the peri-partum period[2]. It is estimated that globally 2.5 million new-born deaths occur annually contributing to 47% of the under-5 child mortality[3]. Worldwide, perinatal asphyxia is encountered amongst 6-10 newborns per 1000 live full-term birth. Apparently, the numbers are higher for low and middle-income countries[4-6]. In India, it is found to be responsible for 28.7% deaths in hospital settings and 20% deaths in rural/tribal areas[7]. Perinatal asphyxia may occur in utero, during labour and delivery, or in the immediate postnatal period. There are numerous causes, including placental abruption, cord compression, transplacental anaesthetic or narcotic administration, intrauterine pneumonia, severe meconium aspiration, congenital cardiac or pulmonary anomalies, and birth trauma[8,9]. Postnatal asphyxia can be caused by an obstructed airway, maternal opiates which can cause respiratory depression or congenital sepsis[8]. When placental (prenatal) or pulmonary (immediate post-natal) gas exchange is compromised or ceases altogether, there is partial (hypoxia) or complete (anoxia) lack of oxygen to the vital organs[9]. This results in progressive hypoxemia and hypercapnia. If the hypoxemia is severe enough, the tissues and vital organs (muscle, liver, heart, and ultimately the brain) will develop an oxygen debt. Anaerobic glycolysis and lactic acidosis will result[10].

Perinatal asphyxia is an important cause of admission to neonatal intensive care units (NICU) with multi organ dysfunction. When an asphyxic event occurs, it leads to a series of physiological mechanisms in order to preserve the function of vital organs (brain and heart), whereas other organs such as the kidneys, gastrointestinal tract and skin are affected to a varying degree based on the duration of the episode.[11] However, in spite of compensatory mechanisms, it may progress to hypoxic-ischemic encephalopathy (HIE) involving the brain and heart[12]. Neonatal hypoxic-ischemic encephalopathy refers specifically to the neurologic sequelae of perinatal asphyxia[13]. The incidence of cardiac dysfunction in perinatal asphyxia varies from 24-60%[14]. Apart from the clinical presentation, electrocardiography (ECG), echocardiogram and determination of cardiac enzymes are useful tools to detect myocardial involvement. Many assessments tools are available to predict fetal well-being during labour and following delivery. These include electronic fetal heart rate monitoring via a cardio-tocograph, APGAR score and the assessment of fetal acid-base balance[11]. Transient myocardial ischemia (TMI) with myocardial dysfunction occurs in neonate with a history of perinatal asphyxia. In contrast to adults, recognition of myocardial ischemia is far more difficult in neonates[15]. Myocardial dysfunction may occur in any neonate with a history of perinatal asphyxia and injured cells leak intracellular enzymes like lactate dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase muscle-brain fraction (CK-MB) which signals multi- organ dysfunction, so evaluation of these enzymes (LDH and CK-MB) may be used as potential predictors to grade hypoxic ischemic injury in newborns with perinatal asphyxia[16]. CK-MB is one of the three isoenzymes of creatine Kinase and is expressed in myocardial muscle and in very small amounts in skeletal muscle. There is some evidence that CK-MB levels are significantly elevated in asphyxiated infants compared with controls[17]. Therefore, CK-MB may be helpful in identifying infants with neonatal hypoxic ischemia who have cardiovascular compromise but may be more useful as part of a predictive model for poor outcome following neonatal hypoxic ischemia[18]. Therefore, the above study was conducted to estimate the CK-MB levels in asphyxiated neonates admitted in neonatal intensive care unit (NICU) at tertiary care hospital.

MATERIALS AND METHODS

Study place: The study was conducted in Neonatal Intensive care unit of a tertiary care centre from February 2021 to August 2022.

Study design: Observational cross-sectional study.

Inclusion criteria: Neonates with gestational age ≥37 weeks, who were identified to have experienced Perinatal asphyxia, whose parents were ready to give consent.

Exclusion criteria: Preterm neonates gestational age < 37weeks, Neonates with major congenital anomalies, syndromic appearance, born at other hospital, having birth weight of less than 2000 grams and those whose parents refused to give consent.

Sample size: Two Hundred three neonates admitted to NICU.

Data analysis: Data was entered from case record form in excel sheet. Care was taken to enter data accurately.

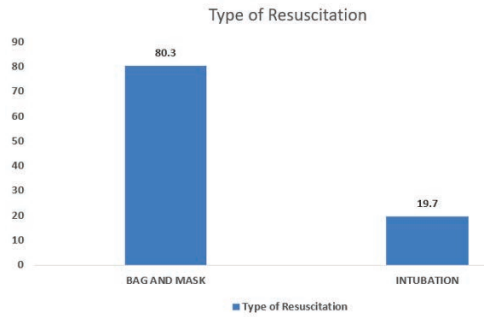

Fig. 1: Majority of patients in our study population observed types of resuscitation

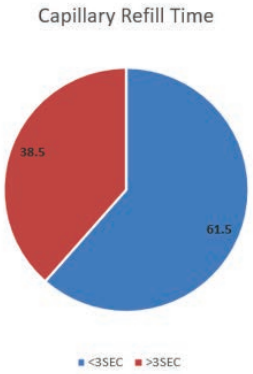

Fig. 2: Majority of patients in our study population observed types of resuscitation

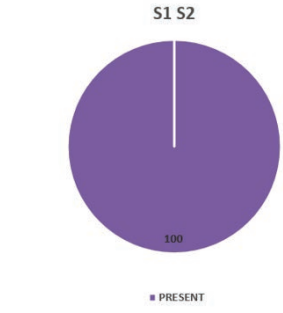

Fig. 3: Majority of patients in our study population observed types of resuscitation

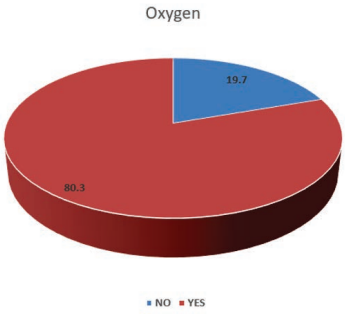

Fig. 4: Majority of patients in our study population observed types of resuscitation

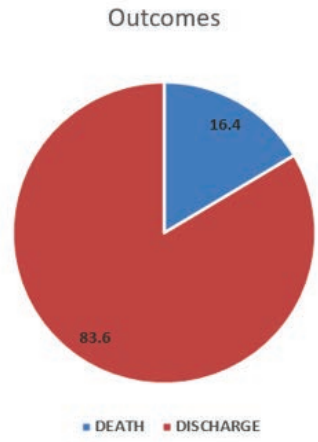

Fig. 5: Majority of patients in our study population observed types of resuscitation

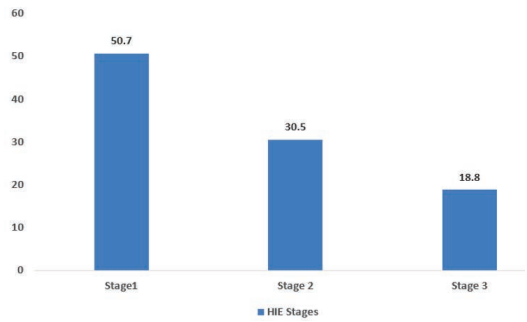

Fig. 6: Majority of patients in our study population observed types of resuscitation

Data was saved every week. Backup for data was maintained. Confidentiality was maintained. Data validation was done periodically by guide and subject experts.

Ethical consideration: The study protocol was approved by the Institutional Ethics Committee (IEC). Patients admitted to NICU of a tertiary care teaching institute were screened by the clinician. Those found meeting the inclusion criteria, the parents or guardians of neonates were briefed about the trial. Screening were carried out and the eligible neonates were included in the study. After initial screening the data regarding maternal history, birth events, Apgar score (at 1 min), sex of the baby and weight of the baby was recorded on the Pre-coded proforma. Gestational age was assessed by New Ballard scoring system or by antenatal USG. Thorough clinical and neurological examination was done between 12 hrs to 24 hrs for all the neonates included in the study. The asphyxiated neonates were monitored for seizures, hypotonia and

HIE in the immediate neonatal period in the NICU. Blood sample was collected from the neonates between 12 hrs to 24 hrs of life and sent for Creatine Kinase Muscle Brain fraction (CK MB) levels.

RESULTS

Majority of patients in our study population observed types of resuscitation are bag and mask are 80.30% and intubation are 19.70%. Majority of patients in our study population observed that capillary refill time are <3 sec that is 61.5% followed with >3 sec that is 38.5%. Majority of patients in our study population observed that is S1 S2 all are present that is 100%.

Majority of patients in our study population observed that RD is absent in majority cases that 58.2% followed with 41.8% are present. Majority of patients in our study population observed that Oxygen by Nasal prongs was sufficient in majority patients that is 80.30% and only 19.70% Needed Mechanical Ventilation support. Majority of patients in our study population observed that in final outcome patients are discharge that is 83.6% and death observed are 16.4%. Majority of patients in our study population observed that in HIE patients found in Stage 1 that is 50.7% followed with stage 2 that is 30.5% and the minimum are in stage 3 that is 18.8%.

This shows a significant difference between HIE and Outcome. Association was assessed between HIE and outcome using the Chi-square test. This shows a significant Correlation between HIE and CPKMB. Correlation was assessed between HIE and CPKMB using the Pearson's correlation and spearman correlation.

Table 1: Distribution of patients according to type of resuscitation (N = 213)

Type of resuscitation	Frequency	Percentage
Bag and mask	171	80.30
Intubation	42	19.70
Total	213	100.0

Table 2: Distribution of patients according to capillary refill time (N = 213)

Capillary refill time	Frequency	Percentage
<3SEC	131	61.5
>3SEC	82	38.5
Total	213	100.0

Table 3: Distribution of Patients according to S1 S2 (N=213)

S1 S2	Frequency	Percentage
Presentage	213	100.0

Table 4: Distribution of Patients according to Respiratory Distress (RD) (N=213)

	Frequency	Percentage
Respiratory distress present /absent absent	124	58.2
Presentage	89	41.8
Total	213	100.0

Table 5: Distribution of patients according to oxygen (N = 213)

Oxygen	Frequency	Percentage
NO	42	19.70
YES	171	80.30
Total	213	100.0

Table 6: Distribution of patients according to outcomes (N = 213)

Outcomes	Frequency	Percentage
Death	35	16.4
Discharge	178	83.6
Total	213	100.0

Table 7: Distribution of patients according to HIE stages (N = 213)

HIE	Frequency	Percentage
Stage1	108	50.7
Stage 2	65	30.5
Stage 3	40	18.8
Total	213	100.0

Table 8: Association between HIE and Outcomes

	Outcomes		
	Death	Discharge	p-value
HIE			
Stage1	0	108	0.001**
Stage 2	2	63	
Stage 3	33	7	
Total	35	178	213

Note: p-value considered significant difference at 95% CI (p<0.05) p-value considered significant difference at 99% CI (p<0.01)

Table 9: Correlation between HIE and CPKMB

Correlation between HIE and CPKMB	Value	p-value
Interval by Interval Pearson's R	0.663	0.0001*
Ordinal by Ordinal Spearman Correlation	0.605	0.0001*

Note: * P- value considered significant difference at 95% CI (p<0.05)
** P-value considered significant difference at 99% CI (p<0.01)

DISCUSSIONS

In the above study, with regards to capillary refill time, maximum neonates had timing of less than 3 sec (61.5%) followed by timing more than 3 sec. While, RD was valued to be absent in majority neonates (58.2%) and present in few (41.8%). CTA was normal in majority neonates (60.1%), followed by poor CTA status (39.9%) which is observed between 12- 24 hrs of life. Lakshmanan *et al.*, appraised overall incidence of increased capillary refill time as 39.24% in their study. Rajakumar *et al.*[19-20] reported overall incidence of prolonged capillary refill time in 16.7% of overall cases. These incidences were slightly higher than tour study data. Systolic murmurs were present in 9.4% of the patients in a study by Issa *et al*.[21] This is close to 10.0% reported by other workers.[22] In contrast, it is considerably lower than 20.0% reported by Rajakumar *et al*.[20] Respiratory distress was seen in 64.7% of asphyxiated neonates by Issa *et al*.[21] This is within the range of 47.5-66.7% reported by Rajakumar *et al.*[20] Overall incidence of respiratory depression was 67.08% as per Lakshmanan *et al*.[19] Goel *et al.*[23] reported respiratory distress only in 70% of severe grade and 25% of moderate asphyxia.

All the recruited neonates were transfused with IV fluids and antibiotics (100%). Majority of patients in our study population were managed by oxygen by nasal prongs that is 80.30% and only 19.70% needed mechanical ventilation support. It was a good finding that majority neonates did not need mechanical

ventilation (80.3%), while few needed ventilatory support (19.7%). Singh *et al.*[24] estimated that found that 32% asphyxiated newborns required inotropic support on day 1 of life, however, on 2nd day, only 21% of asphyxiated cases required inotropic support. The number of newborns requiring inotropes decreased over next few days and only 4% of newborns required inotropes by 5 7 days of life. These findings were in accordance with our study data. A number of studies looking at the effect of prophylactic anticonvulsants in reducing the development of perinatal asphyxia with seizures.

In present study, we distributed cases with regard to death and discharge as final outcomes. We valued that maximum neonates got discharged (83.6%) and few were dead (16.4%). In a study by Gebregziabher *et al.*, when we see the outcome of asphyxiated neonates, 56.25% (28) discharged improved, while 37.5% newborns died, resulting in a case fatality rate of 37.5%. According to Singh *et al.*[25] 42% neonates died with cardiovascular dysfunction.[24] In the study by Shah *et al.*[26] death or adverse outcomes were seen in 64% of those with cardiovascular involvement. In present study, we divided HIE stages as stage 1, stage 2 and stage 3. Majority cases pertained to Stage 1 (50.7%) followed by stage 2 (30.5%) and stage 3 that (18.8%). We established statistical significant association between all stages of HIE and outcomes as well as CPK-MB levels in asphyxiated neonates and outcomes. (p-value = 0.001, 99% CI and p-value = 0.001, 95% CI). There was a linear relation between the severity of asphyxia as assessed by HIE grading and the CK-MB values in a study by Kumar *et al.*[27] The Percentage of babies in this study with grade three HIE was similar to Rajkumar *et al.*[20] Karnik *et al.*[28] whereas HIE grade 3 was higher in Agrawal *et al.*[29] In Kumar *et al.*[27] study, there was no significant difference in CK-MB values between HIE 1 and 2, whereas between HIE 1 and 3 the rise was statistically significant showing that evaluation of enzymes can be a good tool to assess the severity of HIE. In a study conducted by Merchant *et al.*[30] also there was a significant difference between HIE1 and 3. In asphyxia tissue perfusion and oxygen supply to the fetal vital organs is highly impaired. This leads to the production of lactic acid from pyruvate by the enzyme lactate dehydrogenase due to lack of oxygen for TCA to proceed. Hypoxia is mainly responsible for myocardial ischemia and myocardial damage in asphyxiated neonates. If there is severe hypoxia, the peripheral tissues develop oxygen deficiency which leads to lactic acidosis, due to anaerobic glycolysis. This leads to depression of cardiovascular functions resulting in ischemia. With progress in ischemia, Creatine phosphate reserves are utilized, ATP levels falls down and myocardium gets more acidic due to accumulation of lactate and other acidic intermediates of glycolysis. Raised levels of CK-MB was significant in neonates with moderate and severe HIE ($p<0.001$) according to Waddankeri *et al.*[27]

CONCLUSION

Hence, CK-MB can be very useful to differentiate HIE newborns which will help in appropriate management and better outcome of these newborns. Evaluation of CK- MB levels as a marker of severity of perinatal asphyxia shows promising results. Further studies with larger sample size will help establish the association. Results of this study show the need for the better maternal care, creating awareness about contributing factors of birth asphyxia to the maternity health professionals, careful monitoring of labour, identifying and taking proper measure could help in decreasing the occurrence of birth asphyxia.

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