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RESEARCH ARTICLE

THE ROLE OF CREATINE KINASE-MB AS A MARKER TO IDENTIFY AND CORRELATE WITH THE SEVERITY OF BIRTH ASPHYXIA IN TERM NEONATES

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ABSTRACT

The study is an effort to identify correlation between the levels of creatine kinase-MB (CK-MB) with birth asphyxia in term babies and to ascertain whether this enzyme is helpful in determining the severity and prognosis of birth asphyxia. A serum CK-MB value of >92.6 IU/L at 8± 2 hour of life and > 39.2 IU/L at 72 ± 2 hour of life was taken as cut off level. The mean CK-MB level among the case group is 251.67 ± 251.15 and 164.27 ± 211.22 at 8± 2 hour of life and 72± 2 hour of life respectively and among the control group is 48.99 ± 19.51 and 33.9 ± 12.26 at 8± 2 hour of life and 72± 2 hour of life respectively. Estimation of CK-MB can help in distinguishing an asphyxiated from non-asphyxiated neonate helping in management of these babies.

INTRODUCTION

Perinatal asphyxia is a major contributor to neonatal morbidity and mortality. Globally, hypoxia of the newborn (birth asphyxia) or the fetus ("fresh stillbirth") is estimated to account for 23% of the 4 million neonatal deaths and 26% of the 3.2 million stillbirths each year (Lawn JE *et al*, 2005). Data from National Neonatal Perinatal database (NNPD) suggests that perinatal asphyxia contributes to almost 20% of neonatal deaths and in India between 250,000 to 350,000 infants die each year due to it, mostly within the first three days of life and in addition; ante-partum and intra-partum asphyxia contributes to as many as 300,000 to 400,000 stillbirths (NNF NNPD Network, 2005). In India, 8.4% of inborn babies have a one minute Apgar score less than 7 and 1.4% suffer from hypoxic ischemic encephalopathy (HIE) (NNF NNPD Network, 2005). The signs of asphyxial injury are nonspecific and overlap with other illnesses. In the absence of perinatal records, it is difficult to retrospectively diagnose perinatal asphyxia. A variety of markers have been examined to identify perinatal hypoxia including electronic fetal heart monitoring, low Apgar scores, cord pH, electroencephalograms, computed tomography (CT) and magnetic resonance imaging (MRI) scans and Doppler flow studies. In a term infant with perinatal asphyxia, renal, neurologic, along with cardiac and lung dysfunction occur in 50%, 28%, 25% and 23% cases respectively (Perlman J M *et al*, 1989). Transient myocardial ischemia with myocardial dysfunction may occur in any neonate with a history of perinatal asphyxia. An elevated serum creatine kinase MB fraction or cardiac troponin level may be helpful in determining the presence of myocardial damage. An elevation of serum creatine kinase myocardial bound (CK-MB) fraction of >5% to 10% may indicate myocardial injury (Addok L M *et al*, 2008). This work was undertaken to study the correlation between the levels of CK-MB with birth asphyxia in term baby and to ascertain that whether this enzyme is helpful in determining the severity and prognosis of birth asphyxia.

Aim of Study

To identify correlation between the levels of creatine kinase-MB (CK-MB) with birth asphyxia in term babies and to ascertain whether this enzyme is helpful in determining the severity and prognosis of birth asphyxia.

MATERIALS AND METHODS

This case control study was conducted on asphyxiated and non-asphyxiated term neonates recruited from special care neonatal unit, Tata main hospital, Jamshedpur.

Babies with Gestational age ≥ 37 weeks, Appropriate for gestational age and having experienced birth asphyxia were included. The neonates were identified to have experienced perinatal asphyxia when at least 3 of the following were present:

- Intra-partum signs of fetal distress, as indicated by late decelerations on fetal monitoring or by thick meconium staining of the amniotic fluid.
- Apgar score of <7 at one minute.

- Resuscitation with >1 minute of positive pressure ventilation before stable spontaneous respiration.
- Profound metabolic or mixed acidaemia (pH<7.00) in an umbilical artery blood sample, if obtained
- Mild, moderate or severe hypoxic ischemic encephalopathy (HIE), as defined by Sarnat & Sarnat, [1976].

Babies with congenital malformations, maternal drug addiction, neonates born to mothers who had received magnesium sulphate within 4 hours prior to delivery or opioids (pharmacological depression), congenital or acquired infections and hemolytic disease of the newborn were excluded.

Detailed maternal history, assessment of intrauterine fetal well-being by non-stress test, birth events, along with sex and weight of the baby were recorded. Gestational age was assessed by LMP, USG record if available and New Ballard scoring system. APGAR score at 1 min was taken on account of definition of birth asphyxia given by various agencies. The World Health Organization has defined birth asphyxia as "failure to initiate and sustain breathing at birth" (Agarwal R *et al*, 2008) and based on Apgar score as an Apgar score of < 7 at one minute of life. The ICD -10 definition of birth asphyxia is dependent on the Apgar score at 1 minute of life, an Apgar score at 1 min of 0-3 defines severe birth asphyxia and an Apgar score of 4-7 defines moderate asphyxia (Tooly, 2008). All of them have taken 1 min Apgar score, to define birth asphyxia and also to categorise the severity of birth asphyxia. So in our study we have taken only the 1 min Apgar score, similar to other study done by Boshra *et al* (2013) and Masaraddi Sanjay K *et al* (2014) that used 1 min Apgar score in the inclusion criteria**.** Thorough clinical and neurological examination was done in each baby. The asphyxiated neonates were monitored for seizures, hypotonia or HIE in the immediate neonatal period.

Blood sample were collected from the neonates and sent for:

1. Creatine Kinase Muscle-Brain fraction (CK-MB) levels at 8±2 hours and 72±2 hours of age respectively from both cases and control group were estimated by an auto-analyser to see whether there is persistent elevation, fall or rise in the level of CK MB and tried to find out the changes in the level of CK MB in asphyxiated and non-asphyxiated neonates with increasing age and correlate these changes with degree and severity of birth asphyxia.
2. Investigations to rule out the cause for hypotonia, seizure, lethargy, poor feeding other than birth asphyxia (complete blood counts, peripheral smear, CRP, blood culture, serum electrolytes, serum creatinine etc.)
3. Arterial blood gas analysis (ABG) sampling was done from the umbilical artery.

Observation

Table 1 Correlation between the cut-off levels of CK–MB (at8±2 hour) among the case and control group.

Birth asphyxia	CK - MB		Row Total
	>92.6 IU/L	≤ 92.6 IU/L	
Present	28	22	50
Absent	3	47	50
Column Total	31	69	100

Among the 50 neonates in the case group, 22 (44%) had CK-MB levels ≤ 92.6 IU/L and 28(56%) had CK-MB levels >92.6 U/L. Three (6%) of the neonates in control group had CK-MB levels >92.6 U/Land 47(94%) had CK-MB levels ≤ 92.6 IU/L. This has a sensitivity of 56%, specificity of 94%. This also has a positive predictive value at 90.32% and negative predictive value at 68.12% with an Odds ratio of 19.94. The observation of higher CK-MB values of newborns with birth asphyxia at 8±2 hours of birth was statistically significant with $p < 0.0001$.

Table 2 Correlation between the cut-off levels of CK–MB (at 72 ± 2 hour) with birth asphyxia

Birth asphyxia	CK - MB		Row Total
	>39.2 IU/L	≤39.2IU/L	
Present	23 (true +)	27 (false -)	50
Absent	8 (false +)	42 (true -)	50
Column Total	31	69	100

Among the 50 neonates in the case group, 27 (54%) had CK-MB levels <39.2IU/L and 23 (46%) had CK-MB levels >39.4 IU/L at 72±2 hour of life. 8 (16%) among the control group had CK-MB levels >39.4IU/L and 42(84%) had CK-MB levels <39.2IU/L.

This has a sensitivity of 46%, specificity of 84%. This also has a positive predictive value at 74.19% and negative predictive value at 60.87% with an Odd ratio of 4.47. The observation of higher CK-MB values of newborns with birth asphyxia at 72±2 hours of birth was statistically significant with $p < 0.0018$.

There were no statistically significant difference between two levels in HIE – I, but in HIE – II and HIE – III, we did not apply any statistical test because in both the categories CK-MB level were higher.

There were statistically significant difference between two levels in HIE – I, but in HIE – II and HIE – III , we did not apply statistical test of significance because in both the categories CK–MB level are higher .

There were statistically significant difference between the mean CK-MB value in cases and control groups.

DISCUSSION

Several studies have been conducted to evaluate markers that help to differentiate as phyxial and non-asphyxial aetiology in neonates. Primhak *et al* (1985), observed that the CK-MB in both normal (n=43) and asphyxiated (n=20) neonates, peaked at 8 hours and fell by 72 hours. Absolute and percentage CK-MB levels were higher in asphyxiated babies. Omokhodion SI *et al* (1991) studied the creatine kinase (CK) and CK-MB activities in 23 perinatally asphyxiated newborns and 12 healthy controls during the first 100 hour of life. The asphyxiated infants had significantly elevated mean CK and absolute CK-MB but no fractional CK-MB activities. The healthy controls, on the other hand, showed a steady decline in the activities of these enzymes from birth. Fonseca E *et al* (1995) found that antepartum fetal distress is associated with release of CK-BB, and particularly CK-MB; therefore, these biochemical markers may indicate either brain or myocardial damage. BarberiI *et al* (1999) reported that CK, CK-MB, CK-MB/CK ratio and LDH were all increased in an asphyxiated group, while in a group with respiratory distress; only CK-MB and the CK-MB/CK ratio were abnormal.

Table 3 Correlation between the severity of HIE with CK–MB (at 8 ± 2 hour) in case group

HIE	CK – MB Level (Case)		Result		
(n= 32)	Normal (≤ 92.6 IU/L) Mean± S.D	Abnormal (>92.6 IU/L) Mean± S.D	$\|t\|_{cal}$	D.F	p-value
I	70.62 ± 13.37 IU/L (n = 4)	393.93 ±258.14 IU/L (n= 11)	1.464	13	0.1670
II	---	486.64 ± 113.17 IU/L (n=7)	Test not applied		
III	---	606.31 ± 225.65 IU/L (n=10)	Test not applied		

Table 4 Correlation between the severity of HIE with CK-MB (at 72 ± 2 hour) only of case group

HIE	CK – MB Level (Case)		Result		
(n= 32)	Normal (≤ 39.2 IU/L) Mean± S.D	Abnormal (>39.2IU/L) Mean± S.D	$\|t\|_{cal}$	D.F	p-value
I	35.88 ± 2.57 IU/L (n = 9)	72.4 ± 30.27 IU/L (n= 6)	3.670	13	0.0028
II	---	325.16 ± 111.50 IU/L (n=7)	Test not applied		
III	---	455.07 ± 253.78 IU/L (n=10)	Test not applied		

Table 5 Comparison between mean CK-MB value in cases and control groups

CK–MB Level	Case (n = 50)	Control(n = 50)	Result		
			$\|t\|_{cal}$	D.F	p-value
Mean± S.D at 8 hour	251.67 ± 251.15 IU/L	48.99 ± 19.51 IU/L	5.689	98	P<0.0001
Mean± S.Dat 72 hour	164.27 ± 211.22 IU/L	33.9 ± 12.26 IU/L	4.357	98	P<0.0001

The study by Karunatilaka DH *et al* (2000) also concluded that both the CK and LDH values are raised in birth asphyxia. LDH had 100% sensitivity, while CK-MB had 100%specificity for asphyxia in a study by Reddy S *et al* (2008). Rajakumar PS *et al* (2008) observed that the cardiac enzymes, cTnT (Cardiac troponin) and CK-MB were significantly elevated in cases when compared with controls.

The number of neonates with CK MB value >92.6 IU/L at 8±2 hour of life is significantly more in cases when compared to controls. Fifty six per cent of newborns in the cases group had CK- MB value>92.6 IU/L at 8±2 hour of life, which is comparable to Reddy S*et al* (2008).

The number of neonates with CK-MB value >39.2IU/L is significantly more in cases when compared to controls. Forty six per cent of the cases in present study had CK-MB value>39.2 IU/L at 72±2 hour of life. Mean level of CK-MB is significantly higher in cases, 251.67 ± 251.15IU/L at 8±2 hour of life and 164.27 ± 211.22at72±2 hour of life when compared to controls 48.99 ± 19.51 at 8±2 hour of life and 33.9 ± 12.26IU/L at 72±2 hour of life with p value<0.0001. This agree with Reddy S*et al* (2008) and Chauhan A *et al* (2013)who reported mean CK-MB value as high as 176.1IU/L& 200.84IU/L in cases respectively. We found that mean CK-MB is significantly higher in asphyxiated infants than in the control group.

In the control group, 3 babies had elevated level of CK MB at 8±2 hour of life and 8 babies at 72±2 hour of life, considered as false positive in our study. Proper follow up of those babies were not done in our study. Very few literatures are available which explain the cause of this rise in the level of CK-MB. In Washington university case conference Glenn F pierce (1986) enumerated the possible causes as inflammatory and non-inflammatory myopathy, hypothermia, hyperthermia, intramuscular injection, hypothyroidism and hyperthyroidism.
No other study has used CK-MB level at 72 ±2 hour of life; hence the data obtained at 72 ±2 hour of life could not be compared. However with the sensitivity, specificity, positive predictive value and negative predictive value of cut-off level of CK-MB at 72±2 hour of life of 46%, 84%,74.19%, 60.87% respectively, it can be helpful in distinguishing an asphyxiated from non-asphyxiated neonate with a reasonable degree of accuracy whose birth details are not well recorded.

The mean CK-MB level varies according to the extent of the hypoxic damage to the newborns. Mean CK-MB level in stages I, II and III are 393.93±258.14 (n=11), 486.64±113.17 (n=7) and 606.31 ± 225.65 (n=10) respectively at 8±2 hour of life and 72.4 ± 30.27 (n= 6), 325.16±111.50 (n=7), 455.07 ± 253.78 (n=10) respectively at 72 ±2 hour of life. These show greater myocardial involvement in severely asphyxiated infants and comparable to previous study of Chauhan A *et al* (2013).

CONCLUSION

Estimation of CK-MB in association with history and clinical features in the neonates can help in distinguishing an asphyxiated from non-asphyxiated neonate with a reasonable degree of accuracy whose birth details are not well recorded and help in subsequent management.

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