Original Research Article

A biochemical profile of cardiac involvement in perinatal asphyxia

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ABSTRACT

Background: Perinatal hypoxia is one of the leading causes of mortality and morbidity in developing countries like India, and even in developed countries. Perinatal hypoxia can result in Transient myocardial ischemia, tricuspid and mitral regurgitation, myocardial infarction, cardiac failure. The measurement of Creatine kinase -MB isoenzyme a cardiac specific enzyme helps in assessing the degree of myocardial involvement in asphyxiated infants.

Methods: A Prospective case-control study was done in a Tertiary care centre serving rural areas predominantly, to determine the cardiac involvement by measuring serum MB isoenzyme of creatine kinase in perinatally asphyxiated inborn term babies for a period of six months.

Results: There was a significant difference in the CK-MB values with regard to weight in both cases and controls. The mean CK-MB levels were higher in babies who had assisted delivery (forceps and breech) than those delivered by labour natural and LSCS. Mean CK-MB values of asphyxiated and controls were 133.8u/l and 27.12 u/l respectively with a p value of < 0.01. There was a significant difference between HIE1 and 3 with a p value of <0.02. Out of 60 cases 28 had abnormal ECG findings (46.6%). Statistically significant difference was found in the mean CK-MB between the normal and Grade4 ECG changes group. The overall predictive accuracy of CK-MB is high in Perinatal asphyxia (88%), Cardiac involvement (83%), Mortality (83%) and a moderate predictive accuracy for HIE (75%).

Conclusions: Cardiac abnormalities in asphyxiated neonates are often underdiagnosed and requires high index of suspicion. Cardiac specific enzyme CK-MB helps in early recognition of myocardial damage and better management of cases, would reduce the neonatal mortality and morbidity. An expectant eye can be kept for complications in babies with markedly elevated CK-MB enzyme.

Keywords: Cardiac involvement, CK-MB, Perinatal hypoxia

INTRODUCTION

Perinatal hypoxia is one of the leading causes of mortality and morbidity in developing countries like India, and even in developed countries. Asphyxia is an important cause of static developmental and neurologic handicaps both in Term and Preterm infants. The way an asphyxiated baby is managed, determines the mortality and quality of life among survivors. The survivors have increased risk of epilepsy, mental retardation, neonatal

encephalopathy, deafness, visual impairment and disorders of learning and behaviour in later childhood.¹ A Canadian data from cerebral palsy registry, suspected birth asphyxia was observed in 41% of cases of neonatal encephalopathy with cerebral palsy only. Perinatal asphyxia can result in Transient myocardial ischemia, tricuspid and mitral regurgitation, myocardial infarction, cardiac failure.

The cardiovascular system of the foetus differs from that of the adult in its response to hypoxia. The cardiac output

increases in adult to maintain oxygen delivery to the vital organ systems. In contrast the cardiac output of the foetus which is already high, remains constant under such conditions. The foetus compensates by increasing the blood flow to vital organs such as heart, brain and adrenals at the expense of less vital organs such as lungs, abdominal viscera, muscles and bones. Normally fetal heart and brain receive 7% of cardiac output, whereas during hypoxia these organs require up to 26% of cardiac output to maintain adequate tissue oxygenation.^{2,3} Brain has one of the highest oxygen requirements and is vulnerable to hypoxia. Prolonged hypoxia can produce significant brain damage depending on the severity and duration of hypoxia.

Cardiac output is maintained early in asphyxia, associated with selective regional vasoconstriction which reduces blood flow to the less vital organs. As asphyxia progresses to the severe stage, oxygen delivery to the brain and heart suffers. The myocardium then uses its stored glycogen reserve for energy.

Eventually, the glycogen reserve is consumed, and the myocardium is exposed to progressively lower PO₂ and pH. The combined effects of hypoxia and acidosis lead to depressed myocardial function and decreased blood flow to vital organs.³⁻⁵

Cardiac abnormalities in perinatal asphyxia were recognised as an entity when Richard Rowe and his colleagues described ischemic changes in their landmark papers as early as in 70's.⁶ Broadly there are two entities namely,

1. Transient myocardial ischemia (TMI) of the newborn
2. Persistent pulmonary hypertension of the newborn (PPHN)

These can be diagnosed by

- Enzyme analysis
- Electrocardiography
- Echocardiography

Enzymatic changes

Creatine kinase and its isoenzymes increase because of ischemia induced leakage of enzymes from injured tissues. Therefore, marked elevation of CK-MB may be a sensitive indicator of myocardial damage.

The MB isoenzyme of CK has the advantage over total CK that it is not present in significant concentration in extra cardiac tissues and is therefore considerably more specific. It has been found by various studies, that there is elevation of creatine kinase and its isoenzymes in asphyxiated infants as compared to the normal. It has also been found out that newborns with acidosis and abnormal fetal heart rates had higher levels of CK and its isoenzymes.^{3,4,6}

Electrocardiographic changes

ECG is one of the diagnostic tools to diagnose myocardial damage and changes during perinatal asphyxia had been described by Rowe and colleagues.⁶⁻⁸ Following are the ECG changes and their grading.

- Grade 1: Equivocal-Flat or inverted T wave in one lead only.
- Grade 2: Suggestive-Flat or inverted T in several leads with abnormal Q wave in any lead.
- Grade 3: Moderate-Flat or inverted T in several leads or Bundle branch block with abnormal Q plus abnormal ST segments.
- Grade 4: Severe- Classical segmental infarction pattern with abnormal Q waves with markedly elevated ST segments.

Aims and objectives of present study were to determine the correlation between CK-MB and Sex, Birth weight, Mode of delivery, to find out the correlation between CK-MB and Asphyxia, Hypoxic-ischemic-encephalopathy (HIE), Grades of HIE, ECG changes and cardiac involvement, associated cardiopulmonary symptoms and to determine the predictive accuracy of CK-MB in Perinatal asphyxia, HIE, Cardiac involvement and mortality.

METHODS

It was a prospective case control study conducted at Tertiary care setting in Chengalpattu Medical College. Study was conducted for the period of six months (2011 December-May 2012).

Term baby with birth asphyxia were selected for the present study

Birth asphyxia

Definition I (for extramural babies)

- Moderate birth asphyxia: Slow gasping breathing at 1-minute of age.
- Severe birth asphyxia: No breathing at 1-minute of age.

Definition II (for intramural babies)

- Birth asphyxia: Apgar score of less than 7 at 1 minute of age
- Moderate birth asphyxia: Apgar score between 4 to 6 at 1-minute of age
- Severe birth asphyxia: Apgar score of 3 or less at 1-minute of age.

Controls definition

Term babies without any perinatal complications and who's APGAR is normal.

Sixty babies who satisfied the above-mentioned criteria were registered as cases and twenty-five babies with normal antenatal and perinatal events born during the same period were taken up as controls.

Exclusion criteria

Cases with congenital anomalies, congenital heart disease and very low birthweight were excluded, as these cases may have false positive results.

Subjects and methods

After recruitment in to the study a thorough history about maternal complications like anemia, maternal diabetes, hypertension, premature rupture of membranes, abruptio placenta, placenta previa, fetal distress, meconium staining of amniotic fluid, cord around the neck, abnormal CTG tracings, duration of labour, second stage of labour, mode of delivery and resuscitation measures required as per NRP protocol with APGAR score at 1 and 5 minutes were recorded.

Details like sex, birth weight, respiratory status, cardiovascular status, neurological status were recorded and treated as per unit protocol.

The asphyxiated babies were classified using SARNAT and SARNAT as Grade I, II, III. Two millilitres of peripheral venous blood were obtained by venepuncture from each infant between 6 and 24 hours.

Care was taken to see that samples were not hemolysed. CK-MB estimation was done at the Department of Biochemistry using CK-MB kits from sigma diagnostics.

The quantitative determination of enzymes was done using Transasia ERBA-chem 5plus semianalyser. A 12 lead ECG was done for all babies using paediatric electrodes and the ECG changes were graded as per Rowe's grading.

RESULTS

Age

CK-MB enzyme rise was appreciated within 6 hours in asphyxiated babies and remained high till 24 hours.

Table 1: Sex incidence of cases and controls.

Sex	No. of babies	Mean CK-MB in u/l
Cases		
Male	34 (57%)	131±98.93
Female	26 (43%)	137.5±134.6
Controls		
Male	14 (56%)	27.07±12.5
Female	11 (44%)	27.18±9.45

Sex

In both the asphyxiated and the control groups there were no significant differences in the CK-MB values with regard to sex (Table 1).

Weight

In the asphyxiated group, the mean CK-MB value of babies who had IUGR (40%), was 125.5u/l, whereas babies who were appropriate for gestational age (AGA 48.3%) was 147.3u/l. In the control group 20% were in IUGR group whose mean CK-MB value was 30.2u/l and in the AGA group (72%) was 25.38u/l (Table 2).

Table 2: Birth weight and CK-MB correlation.

Birth weight	No. of babies	Mean CK-MB u/l
Cases		
<2 Kg	2 (3.3%)	73
2-2.5Kg	24 (40%)	125.5
2.6-3 Kg	29 (48.3%)	147.3
>3Kg	5 (8.3%)	119.8
Controls		
<2kg	0	
2-2.5Kg	5 (20%)	30.2
2.6-3 Kg	18 (72%)	25.38
>3Kg	2 (8%)	35

There was a significant difference in the CK-MB values with regard to weight in both cases and controls (Table 2).

Mode of delivery

The mean CK-MB levels were higher in babies with assisted delivery (forceps and breech extraction) the value being 182.4 u/l compared to those delivered by labour natural and LSCS whose value was 119 u/l (Table 3).

Table 3: Mode of delivery and CK-MB correlation.

	No. of babies	HIE	No. HIE	Mean CK-MBu/l
Cases				
Breech	2 (3.3%)	2	0	173
Natural	27 (45%)	16	11	119.18
LSCS	14 (23.3%)	7	7	111
Forceps	17 (28.3%)	12	5	182.4
Controls				
Breech	0	--	-	-
Natural	15 (60%)	-	--	27.6
LSCS	7 (28%)	-	-	22.57
Forceps	3 (12%)	-	-	35

Asphyxia and grades of HIE

Mean CK-MB values of asphyxiated and controls were 133.8u/l and 27.12 u/l respectively with a p value of

<0.01. Those babies who developed HIE, were further assessed as per sarnat and sarnat staging. There was no gross difference in the mean enzyme levels between HIE1 and 2, whereas there was a significant difference between HIE1 and 3 with a p value of <0.02 (Table 4).

Table 4: Grading of HIE among asphyxiated infants.

Grade	No. of Babies (%)	Mean CK-MB U/L
HIE 1	41 (68.3%)	104
HIE 2	9 (15%)	168
HIE 3	10 (16.6%)	319

Cardiopulmonary symptoms

In present study, it was observed that there was significant enzyme elevation in those who had cardiopulmonary symptoms and signs (viz., congestive cardiac failure, pulmonary hypertension) than those who did not with a mean CK-MB values of 230.4 u/l and 81.8 with a p value of <0.05 (Table 5).

Table 5: Cardiopulmonary symptoms and CK-MB correlation.

Symptoms	No. of Babies (%)	Mean CK-MB U/L
Present	21 (35%)	230.4
Absent	39 (65%)	81.84

Electrocardiographic changes

ECG was done for all cases. Out of 60 cases 28 had abnormal ECG findings (46.6%). They were graded as per Rowe classification.

Grade1 changes were observed in 10 babies who had a mean CK-MB of 130.2u/l, Grade 2 changes in 10 babies with a mean of 218.1u/l, 6 babies had Grade 3 changes with a mean of 288.3u/l, and 2 babies had Grade 4 changes with a mean of 288.45u/l.

ECG was normal 32 babies with a mean of 70.31u/l. Statistically significant difference was found in the mean CK-MB between the normal and Grade 4 group, but there was no difference between Grade 3 and Grade 4 groups. All the controls had normal ECG.

Outcome

Out of the total 60 cases, two went against medical advice. Out of the remaining 58 cases (93.1%) ,4 died (6.9%) and Their mean enzyme values were 128.07 and 257.5 with statistical significance (Table 6).

Table 6: Outcome.

Cases	Number	Mean CK-MB u/l
Alive	54	128.07
Dead	4	257.5

Total cases = 60; AMA = 2; Remaining cases = 58

Efficacy analysis of CK-MB with various parameters

In this study the relevance of CK-MB in predicting asphyxia, HIE, cardiopulmonary symptoms, mortality was tried by analysing the sensitivity, specificity, positive and negative predictive values with certain CK-MB cut off values.

- A cut-off value of 45u/l for predicting asphyxia has a sensitivity of 85%, specificity 96%, positive and negative predictive values of 98% and 73% respectively and an overall accuracy of 88%. High values were associated with asphyxia whereas the lower values do not exclude asphyxia.
- A cut off value of 100u/l for predicting HIE has 71% sensitivity, 78% specificity, 79% positive predictive value, 70% negative predictive value with an overall accuracy of 75%
- Relevance of CK-MB with cardiopulmonary symptoms has high sensitivity, specificity, negative predictive value. i.e, in an infant with no cardiopulmonary symptoms, CK-MB was mostly negative.
- For predicting mortality, a cut-off value of 250u/l was kept which has high specificity and negative predictive value and low positive predictive value which implies that if the level is below 250u/l, the survival is almost certain. If the level is above 250u/l, the baby still can survive.

DISCUSSION

Most of the studies assessing the effects of perinatal asphyxia, mainly assess the neurological involvement and only few studies assess the role of cardiac involvement and its usefulness in grading the severity of hypoxic and ischemic damage. Hence this study was done to assess the role of cardiac dysfunction by evaluating CK-MB enzymes and ECG in perinatal asphyxia. Creatine kinase is an enzyme released during muscular trauma, myopathies and in myocardial damage. The total creatine kinase activity rises immediately after delivery and declines to normal values by 2-3days 9, whereas there is no significant elevation of CK-MB fraction in healthy infants during the initial 2-3 days of life.

Mode of delivery

In present study CK-MB elevated in breech and forceps delivery compared to LSCS and labor natural. This may be explained by the fact that forceps and breech delivered babies are likely to have more muscular trauma compared to other modes. This relation between mode of delivery and CK-MB levels have not been assessed in other studies.

Asphyxia and HIE

In present study the mean CK-MB values of asphyxiated and controls were 133.8±114.7 u/l and 27.12±11.05u/l

respectively, which is similar to Rajkumar PS et al, where the CK-MB values of cases and controls were 121 ± 77.4 u/l and 28.2 ± 20.2 respectively (Table 7).¹⁰

Table 7: CK-MB measurement among different studies.

CK-MB in U/L	Rajkumar PS et al	Sanath et al	Present study
Cases	121±77.4	176.1±243	133.8±114.7
Controls	28.8±20.2	49.6±36	27.12±11.05

In the study by Sanath et al, the mean CK-MB values were higher for cases as against the controls, but the enzymes were measured twice at 8 hours and 24 hours and a mean was taken.¹¹ There was a linear relation between the severity of asphyxia as assessed by HIE grading and the CK-MB values. The Percentage of babies with grade three HIE was similar to Rajkumar PS et al, Karnik E et al whereas HIE grade 3 was higher in Jyoti et al.^{10,12,13} In present 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 S et al also there was a significant difference between HIE1 and 3 (Table 8).¹⁴

Table 8: Association of cardiopulmonary symptoms.

Cardiopulmonary symptoms	Rajkumar PS et al	Present study
Present	33%	35%
Absent	67%	65%

Cardiopulmonary symptoms

The association of cardiopulmonary symptoms and severity of cardiac dysfunction as measured by CK-MB values, in our study was consistent with Rajkumar PS et al, (Table 9).¹⁰

Table 9: Grades of HIE among different studies.

HIE grade	Rajkumar PS et al	Jyoti et al	Present study
Grade 1	8 (26.6%)	13 (21.7%)	13 (21.6%)
Grade 2	18 (60%)	27 (45%)	9 (15%)
Grade 3	4 (13.33%)	20 (33.3%)	10 (16.6%)

ECG Changes

In the Present study 28 out of 60 babies (47%) had abnormal ECG findings, which is similar to Karnik E (38.2%), whereas more babies had abnormal ECG changes in Jyoti et al, (76.7%) and Rajkumar PS et al, (73%) 10 (Table 10).^{10,12,13} This may be due to great variation in T wave changes in normal babies in the first week of life. The ECG changes observed in asphyxiated babies is similar to those observed in Rajkumar PS et al,

except that in their study, Grade 2 changes were more.¹⁰ As per Rowe classification Grade 1 and 2 changes are equivocal or suggestive, which is less significant. In Jyoti et al, the ECG changes were classified based on Jedikien classification and Grade 1 changes which are non-specific.^{13,15}

Table 10: ECG changes among different studies.

ECG changes	Rajkumar PS et al	Jyoti et al	Present study
Grade1	6 (20%)	19 (41.3%)	10 (16.6%)
Grade2	12 (40%)	13 (28.2%)	10 (16.6%)
Grade3	4 (13.3%)	13 (28.2%)	6 (10%)
Grade4	0	1 (2.1%)	2 (3.3%)

CONCLUSION

Evaluation of CK-MB levels and ECG as a marker of severity of perinatal asphyxia shows promising results. Further studies with larger sample size will help establish the association. Troponin –I in addition to enzymes and ECG will improve the sensitivity and specificity of cardiac evaluation as tool for assessing the severity of perinatal asphyxia.

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