Utility of creatine kinase MB in the diagnosis of myocardial dysfunction in asphyxiated term newborns – Prospective study

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Abstract

Introduction: Perinatal Asphyxia is a multi-system disorder and its effects are not limited to central Nervous System. Cardiac impairment occurs in about 24-60% of neonates with asphyxia. Myocardial dysfunction secondary to severe birth asphyxia will lead to loss of cerebral auto-regulation with subsequent severe encephalopathy. This study was done to evaluate the usefulness of Creatine Kinase MB (CKMB) in diagnosing myocardial injury in perinatal asphyxia well as prognostic indicator of perinatal asphyxia.

Materials and Methods: A Hospital based Prospective Analytical Study performed in 100 asphyxiated term neonates. CKMB was evaluated for sensitivity and specificity in comparison with clinical diagnosis of myocardial injury and were correlated with results from ECG, ECHO, duration of inotrope, severity of shock and outcome.

Results: In our study among 100 term asphyxiated neonates, 79% neonates had clinical evidence of myocardial injury. We had large number of neonates (41%) with HIE grade 3 while 35% were stage 1 HIE and 24% were stage 2 HIE. The ROC curve for cardiac dysfunction showed that the value of CKMB for prediction of cardiac dysfunction was 42 IU/L (sensitivity of 79.5% and specificity of 93.3%). The cut off CKMB value for prediction of mortality in our study is 91.1 IU/L with sensitivity of 90.0% and specificity of 83.8% Also the value of CKMB had strong statistical significance with severity of HIE ($p<0.001$),severity of shock($p<0.001$) and duration of inotrope support ($p<0.0001$).

Conclusion: CKMB is valuable tool in resource limited settings for early detection of myocardial injury due to perinatal asphyxia. The early detection and prompt treatment of condition will help in improving prognosis of these asphyxiated newborns.

Keywords: Perinatal asphyxia, Creatine kinase – MB, Myocardial Injury.

Introduction

Perinatal asphyxia is associated with high mortality and morbidity. According to estimates, approximately 130 million births worldwide each year, four million infants will suffer from birth asphyxia, and of these, one million will die and a similar number will develop serious and long-term sequelae including neurodevelopmental disorders.[1,2]

Perinatal asphyxia is a major root cause for neonatal mortality and long term morbidity next to Sepsis.[3] Incidence is about 1.0 -1.5% of live births comprising 20% neonatal death in India.[3,4] In India, between 250,000 to 350,000 infants die each year due to birth asphyxia, mostly within the first three days of life.[5]

Perinatal asphyxia can cause multi-organ injury and dysfunction of heart, brain, lungs, kidney and bone marrow.[5] Cardiac dysfunction results from hypoxic ischemic damage to sub-endocardial tissue, papillary muscle and myocardium.[6] A neonate‘s heart muscle is extremely susceptible to such hypoxic events and myocardial damage could have a significant effect in neonatal circulation, leading to circulatory insufficiency.[7] 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.[7-9]

The incidence of clinical cardiac dysfunction in perinatal asphyxia varies from 24–60%.[10] Cardiac dysfunction forms a part of the clinical spectrum of multi-organ dysfunction in asphyxiated newborns. Some studies found that the more cardiac dysfunction the patients have, more severe encephalopathy they would experience. They also suggested that myocardial dysfunction secondary to severe birth asphyxia will lead to loss of cerebral auto-regulation with subsequent severe encephalopathy.[11] Therefore; early cardiovascular assessment in asphyxiated newborns will allow more rapid detection of cardiac dysfunction and allow early initiation of inotropic support along with neuro-protective measures. This may preserve cardiac function and decrease morbidity and mortality in these infants.[12]

An elevated serum creatine kinase MB fraction may be helpful in determining the presence of myocardial damage[13] and help doctors in resource limited settings as prognostic indicator of perinatal asphyxia.

Objectives of the study

1. To study the utility of CK –MB levels in the diagnosis of myocardial dysfunction in asphyxiated newborns.
2. To evaluate the utility of CKMB as prognostic indicator of perinatal asphyxia

Materials and Methods

This is hospital based prospective study done in 100 term asphyxiated neonates who fulfilled inclusion criteria and consented for the study. The ethical clearance was taken for Institutional Ethical Committee. The CTRI registration number is CTRI/2018/03/018812.

Inclusion Criteria

Term neonates with Perinatal Asphyxia with

1. APGAR score <5/10 at 5 min (or)
2. pH <7.2 (Metabolic Acidosis) (or)
3. Clinical evidence of hypoxic-ischemic encephalopathy (HIE) 24 hrs after birth

Exclusion criteria for cases

1. Preterm babies.
2. Neonates with Early onset Sepsis.
3. Neonates with congenital malformation.
4. Neonates with congenital myopathy.
5. Neonates with Inborn Error of metabolism.
6. Babies who died before evaluation.
7. Not consenting for the study.

Study Protocol

Institutional Ethical committee clearance was obtained to conduct the study in our Hospital. All neonates with more than 37 weeks of gestation who will be admitted in Neonatal Intensive Care Unit of HSK Hospital and Research Centre, S.Nijalingappa Medical College, Bagalkot with history suggestive of perinatal asphyxia who fulfill the inclusion criteria was included in the study. Baseline data and clinical findings of the cases were obtained based on inclusion criteria mentioned above. Prestructured preformed questionnaire was completed with complete physical, neurological and cardiovascular examination, which was done on admission and 48-72 hrs. A detail history was elicited for all recruited babies and was thoroughly examined.HIE staging of asphyxiated newborn were done using Sarnat and Sarnat classification. Details of the gestational age, mode of resuscitation, Apgar score, birth weight and maternal complications, duration of inotropic, and severity of shock if any were documented. Severity of shock was documented as fluid responsive, fluid resistant, inotropic responsive, catecholamine responsive, catecholamine resistant shock.[13] Clinical progression of the neonates was closely observed.

Arterial blood sample 2 ml was taken by aseptic precautions within 72 hrs after birth. Blood is tested for CK-MB. Blood culture was also sent and reports were traced. Those with Positive sepsis were not enrolled for study.

Case Definition of Myocardial Injury

The paradigm for cardiovascular impairment in perinatal hypoxia as proposed by Shah et al[32] was systemic hypotension requiring vasopressors (dopamine, dobutamine) to sustain mean arterial pressure of 45 -55mm Hg for more than 24 hours. Cardiac enzymes; CKMB was evaluated for sensitivity and specificity in comparison with clinical diagnosis of myocardial injury and was correlated with results from, requirement of inotrope, duration of inotrope, severity of shock, outcome.

Statistical Analysis

All the information and test results from the cases were collected and recorded in a master chart. Data analysis was done using statistical package for social sciences (SPSS) software, version 20. Chi-square test for qualitative data, and student t-test for quantitative data and other appropriate statistically tests were applied for data. P value <0.05 was considered as statistical significant

Results

During the study period from 1st January 2017 to 31st December 2017 babies who were delivered in S.Nijalingappa Medical College & Hanagal Shri Kumareshwara Hospital, Navanagar, Bagalkot & babies who were referred from outside who were fulfilling the inclusion criteria were included in the study.

Total 100 babies were included in the study, of which male were 57% and females were 43%In the study, babies born through vaginal delivery were 55%, followed by assisted vaginal delivery 24% and cesearean delivery 21%.HIE staging of asphyxiated term neonates was done by Sarnat and Sarnat staging. 35% of newborns were stage 1 HIE, 24% were stage 2, and 41% were stage 3 HIE.

Table 1: Distribution of CKMB values with stage of HIE

HIE stage	CKMB				
	N	Minimum	Maximum	Mean	SD
Stage 1	35	12.0	295.0	42.372	46.8233
Stage 2	24	8.0	172.0	76.698	44.0185
Stage 3	41	14.0	700.0	194.011	153.1734
F-value = 21.80 P-value <0.01					

The mean CKMB value in HIE Stage 1 is 42.372 IU/L while in HIE stage 2 it is 76.698 IU/L and in Stage 3 HIE it is 194.011 IU/L. As the HIE severity increased the mean value of CKMB raised. There is statistical significance p<0.01. For the convince of comparison of statistical data the CK-MB value were divided into <25IU/L, 25-100 IU/L and 100 IU/L. It was also noted that the values of CKMB had good statistical significance with that of Apgar scores. (p<0.01). (Table 2)

Table 2: Correlation of APGAR score @5 minutes and CKMB values

APGAR 5min	CKMB Values						Total	
	<25		25-100		>100			
	No. of babies	%	No. of babies	%	No. of babies	%	No. of babies	%
<3	0	0.0%	3	6.3%	8	24.2%	11	11.0%
3—5	3	15.8%	9	18.8%	19	57.6%	31	31.0%
>6	16	84.2%	36	75.0%	6	18.2%	58	58.0%
Total	19	100.0%	48	100.0%	33	100.0%	100	100.0%
Chi-square value = 35.04 Df = 6 P-value <0.01								

Correlation of stage of HIE and CKMB values

It was also noted that CKMB values also had very high statistical significance with that of severity of HIE ($p<0.01$). Thus it can observed that the grade of HIE increased, CKMB value also increased. Thus, we can imply that CKMB value within 72 hours of birth can predict the stage of HIE.

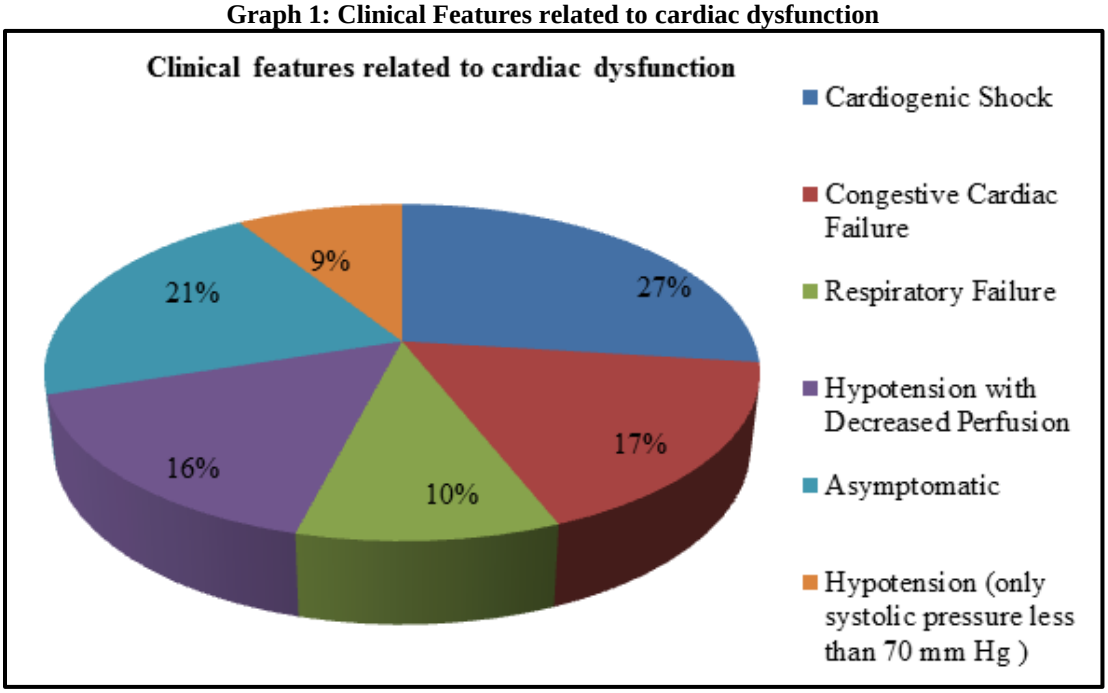
Table 3: Correlation of stage of HIE and CKMB values

CKMB	Stage of HIE						Total	
	Stage 1		Stage 2		Stage 3			
	No. of babies	%	No. of babies	%	No. of babies	%	No. of babies	%
<25	13	37.1%	3	12.5%	3	7.3%	19	19.0%
25-100	21	60.0%	15	62.5%	12	29.3%	48	48.0%
>100	1	2.9%	6	25.0%	26	63.4%	33	33.0%
Total	35	100.0%	24	100.0%	41	100.0%	100	100.0%
Chi-square value = 36.24 Df = 4 P-value <0.01								

Clinical features related to cardiac dysfunction.

Clinical features related to Cardiac dysfunction were noted in term asphyxiated neonates. Cardiogenic Shock was seen in 27%, Congestive cardiac failure in 17%, Respiratory Failure in 10% cases, hypotension with decreased perfusion was seen in 16% cases while 9% newborns only had hypotension while 21 neonates had no cardiac dysfunction. Thus, cardiac involvement in term asphyxiated neonates in our study was noted to be 79%.

Graph 1: Clinical Features related to cardiac dysfunction



Roc curve based on clinical features and ckmb value

Graph 2: Roc curve based on clinical features and CKMB value

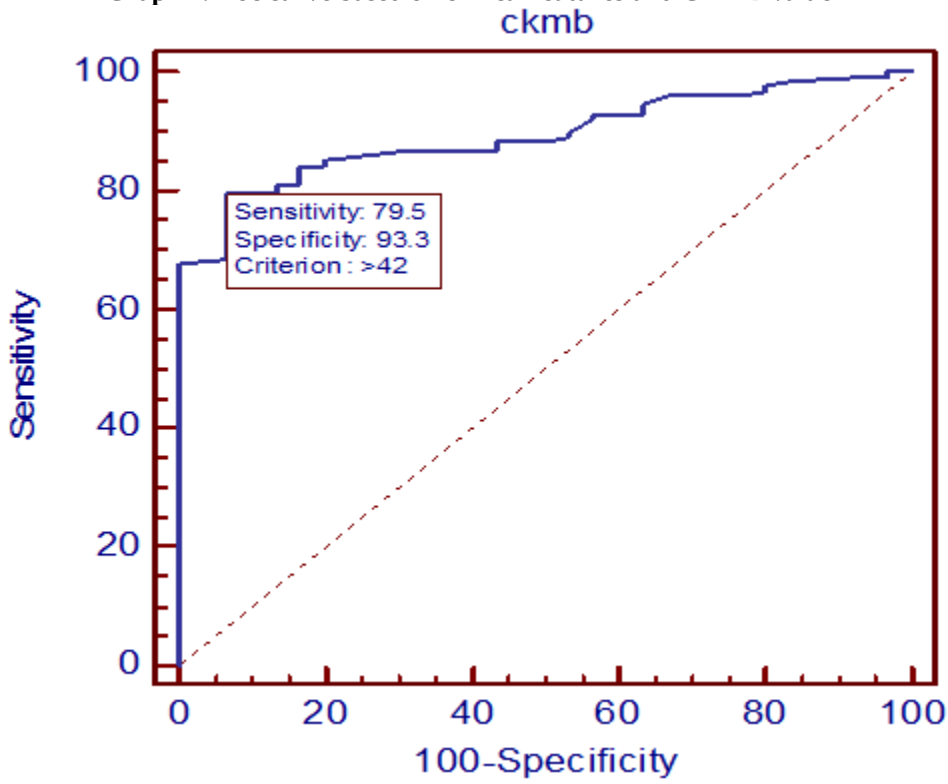


Table 4: Roc curve based on clinical features and CKMB value

Area under the ROC curve (AUC)	0.893
z statistic	15.607
Significance level P (Area=0.5)	<0.0001

Based on ROC curves for CKMB and cardiac dysfunction, it was noted that the asphyxiated baby with the value of CKMB 42 IU/L had sensitivity of 79.5% and specificity of 93.5% chances of having cardiac dysfunction.

Correlation of severity of shock with CKMB value

Table 5: Correlation of severity of shock with CKMB value.

CKMB values	Severity of Shock										Total	
	Fluid responsive		Fluid refractory dopamine±dobutamine responsive		catecholamine responsive		catecholamine resistant		No shock			
	No. of babies	%	No. of babies	%	No. of babies	%	No. of babies	%	No. of babies	%	No. of babies	%
<25	3	21.4%	6	15.0%	1	9.1%	0	0.0%	9	47.4%	19	19.0%
25-100	11	78.6%	24	60.0%	3	27.3%	2	12.5%	8	42.1%	48	48.0%
>100	0	0.0%	10	25.0%	7	63.6%	14	87.5%	2	10.5%	33	33.0%
Total	14	100.0%	40	100.0%	11	100.0%	16	100.0%	19	100.0%	100	100.0%
Chi-square value = 47.12 Df = 8 P-value <0.01												

It is observed that as the CKMB value increased the severity of shock in the form of fluid boluses, requirement of inotrope and catecholamine was also increased. This has high statistical significance ($p<0.01$). Thus, CKMB value can predict the severity of shock.

Correlation of duration of inotropes with CKMB values.

Table 6: Correlation of duration of inotropes with CKMB values

Duration of Inotrope	CK MB Values						Total	
	<25		25-100		>100			
	No. of babies	%	No. of babies	%	No. of babies	%	No. of babies	%
<24	1	5.3%	11	22.9%	4	12.1%	16	16.0%
24-48	5	26.3%	9	18.8%	3	9.1%	17	17.0%
48-72	1	5.3%	11	22.9%	9	27.3%	21	21.0%
>72	1	5.3%	3	6.3%	16	48.5%	20	20.0%
No Inotropes	11	57.9%	14	29.2%	1	3.0%	26	26.0%
Total	19	100.0%	48	100.0%	33	100.0%	100	100.0%
Chi-square value = 44.09 Df = 10 P-value <0.01								

It can be observed that as the value of CKMB increased the duration of inotropic support also increased. This has high statistical significance (p<0.01). Thus the value of CKMB can help the clinician in judging the duration the baby might require the inotropic support

Outcome of the study subjects

It was observed that the total non-survivors in the study were 28%. One case went discharged against medical advice due to financial constraints.

Correaltion of CKMB value with outcome

Table 7: Correlation of CKMB Value with Outcome

Parameters		CKMB				
		N	Minimum	Maximum	Mean	SD
Out come	Survival	71	8.00	295.00	62.90	49.47
	Not Survived	28	14.00	700.00	237.32	166.40
	DAMA	1	167.60	167.60	167.60	-
	F-value = 32.40 P-value <0.01					

It was observed that the neonates who were in non survivors group had very high CKMB values, there is very high statistical significance noted (p<0.01). Thus the CKMB can predict outcome and thus ROC curves were constructed.

Roc curve based on outcome and CKMB values

Graph 4: Roc curve based on outcome and CKMB values

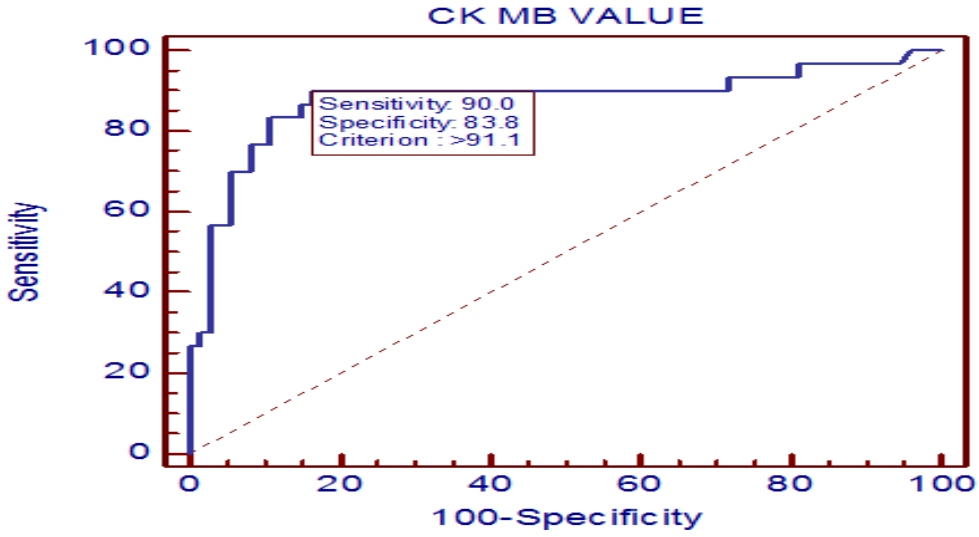


Table 8: Roc curve based on outcome and CKMB values

Area under the ROC curve (AUC)	0.88
z statistic	8.05
Significance level P (Area=0.5)	<0.0001

From the ROC curves, it is observed that at the CKMB value of more than 91.1 IU/L the chances of mortality was more with sensitivity of 90.0% and specificity of 83.8%.

Discussion

Cardiovascular dysfunction is one of the commonest complications in infants with perinatal birth asphyxia. The sequelae following birth asphyxia pertaining to cardio-vascular system ranges from transient myocardial ischemia, valvular insufficiency, decreased left ventricular contractility and output to pulmonary hypertension and systemic hypotension.

This study was done to determine these cardio-vascular changes resulting from asphyxia and to evaluate the utility of CKMB in early diagnosis of myocardial injury, thereby facilitating early and better management and subsequent reduction in morbidity and mortality in these asphyxiated infants in limited resource settings. The role of cardiac enzymes in detection of ischemic damage to heart is well established in adults. But recently, their role in detection of ischemia in new-borns due to perinatal birth asphyxia has been under debate.

Many comparative studies were done to investigate CK-MB for diagnostic significance in asphyxiated newborns. Rajakumar et al[9] and Boo et al[14] reproduced the results for troponin-T and CK-MB in myocardial dysfunction in new-borns with perinatal asphyxia.

Based on these researches of late, we are conducting this study in the region where there are insufficient reports and most of pregnant women report late to tertiary hospital. Many of these deliveries lack adequate time in planning the deliveries and end up poor outcome in form of birth asphyxia.

We need to provide a platform for paediatricians working in remote area where they lack expertise for pediatric ECHO and ECG, in taking early decision regarding the management of babies with birth asphyxia. We also need to recognise the cardiac dysfunction early and plan the proper line of management in reduction of morbidity and mortality in these infants.

The ROC curve based on cardiac dysfunction was constructed in our study(Graph 2).The value of CKMB for prediction of cardiac dysfunction was 42 IU/L with sensitivity of 79.5% and specificity of 93.3%. This was comparable with Mishra et al [15] study where cut-off value of CKMB with birth asphyxia was 39.2IU/l

Grade of HIE

All the term asphyxiated neonates in the study were graded using Sarnat and Sarnat staging of HIE. In our study we had larger number of neonates (41%) with HIE grade 3 compared to other studies like Agrawal et al[15] study (33%), Rajkumar et al [9] (13%), and Shashtri et al (31%).[16] This high incidence was explained by the pregnant women reporting late with obstetrical complications.

It was noted that CKMB had very high statistical significance ($p<0.001$) with that of severity of HIE. Studies have shown that CKMB concentrations are significantly elevated in perinatal asphyxia.[14,15,16] Our present study confirms that for CKMB, early serum concentrations are significantly higher with increasing clinical severity of HIE. Our data show that CKMB level is possible but unusual in significant (grade 3) HIE. In neonates admitted with suspected severe HIE who have a normal or undetectable CKMB level, it is therefore reasonable to consider the possibility of an alternative diagnosis. For example, one neonate admitted to our neonatal unit with early seizures was treated with whole-body hypothermia for initially suspected moderately severe HIE. The infant's day 1CKMB was 25 IU/L, indicating no myocardial damage, and early neuroimaging led to a revised diagnosis of extensive middle cerebral artery infarction. In contrast, a very high day 1 cTnI value is an early poor prognostic indicator in HIE.

Severity of shock

Ours is the first study to categorise shock based on requirement of fluid boluses, inotrope and catecholamines. This helps in easy categorisation of shock in resource limited settings. It is observed that as the CKMB value increased the severity of shock in the form of fluid boluses, requirement of inotrope and catecholamine was also increased. This has high statistical significance ($p<0.001$) Based on the value of CKMB the requirement of inotrope can be assessed, and appropriate measures can be taken. Thus, CKMB concentrations may provide a useful proxy marker for the anticipated severity of myocardial dysfunction. Early detection can help in better management and survival of these neonates.

Duration of inotropic support

It was observed that as the value of CKMB increased the duration of inotropic support also increased. There was high statistical significance. ($p<0.0001$) Thus the value of CKMB can help the clinician in judging the duration the baby might require the inotropic support. Similarly, in Shastri et al[16] study the relationship between cTnI concentration and duration of inotropic support was examined and was showed that cTnI correlates strongly with duration of inotropic support. But the concentration of CKMB with duration of inotrope was not done in any of the studies.

Outcome

It was observed that the neonates who were in non-survivors group had very high CKMB. There is very high statistical significance noted ($p<0.01$)(table 7). The cut off CKMB value for prediction of mortality in our study is 91.1 IU/Lwith sensitivity of 90.0% and specificity of 83.8%.Unlike in other studies like Boo et al,[14] it was found that levels of CKMB were not statistically significant discriminators of death occurrence among asphyxiated neonates. However, in Primal et al[17] study, the value of CKMB were very high in asphyxiated neonates. But the status as statistical significant discriminator was not studied in these studies.

Assay of Cardiac enzymes like CKMB are not expensive, readily available and, in neonates admitted with asphyxia, provides a result within hours that correlates well with the degree of myocardial dysfunction as reflected ECG and ECHO findings. CKMB concentrations measured within 72 hours of birth correlate strongly with the clinical severity of HIE and with the duration of inotropic support and severity of shock. Early CKMB concentrations may provide a useful proxy marker of the anticipated severity of myocardial dysfunction in asphyxiated term neonates.

Limitations of the Study

1. There was no control group included in the study.
2. Comparison with other cardiac bio-markers like BNP, LDH, and troponin-T was not done.
3. Autopsy was not done in the non-survivors.

Conclusion

In resource limited setting where the accessibility to 12 lead ECG, ECHO and aid of cardiologist are not available, CKMB assay will serve a valuable handy screening tool which is readily available, and provides result within hours that correlates well with the degree of myocardial dysfunction as reflected by the duration of inotrope support, severity of shock and outcome. The early detection and prompt treatment of condition will help in improving prognosis of these asphyxiated newborns. Further large trials are needed in the future to validate it as a standard diagnostic tool in managing asphyxiated NICU neonates.

Conflict of Interest: None.

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