

Original Research Article

Association of creatine kinase and its isoenzymes (CK-MB, CK-BB) activity with high risk pregnancy

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ABSTRACT

Background: Creatine kinase (CK) is a key enzyme of energy metabolism, especially in muscle tissue. CK has two polypeptide chains of M and B, and three isomers, CK-BB, CK-MB and CK-MM. In some conditions like acute myocardial infarction and neuromuscular disorders, increased CK activity is used as a part of diagnosis. CK can also be elevated in absence of neuromuscular diseases or cardiac injury, such as strenuous exercise, intramuscular injections etc. Several reports indicate elevated activity of serum CK in the maternal blood during child birth. This study aimed to correlate total CK and its isoenzymes activity in the cord blood with high risk pregnancies.

Methods: This was a Prospective observational study conducted in the Obstetrics and Biochemistry Department of Era's Lucknow Medical College and Hospital, Lucknow, Uttar Pradesh, India. Cord blood of 100 full term newborns was collected and serum was analyzed for total CK and its isoenzymes activity by modified IFCC method. SPSS software was used in data analysis.

Results: CK-total and its isoenzymes (CK-MB, CK-BB) activities were observed higher in cases with risk as compared to those without risk. Total CK activity was observed independent while CK-MB and CK-BB were found dependent on different risk factors like pregnancy induced hypertension and fetal distress etc.

Conclusions: Present study revealed that high risk pregnancies are associated with increased total CK, CK-MB as well as CK-BB activity.

Keywords: CK-Isoenzymes, CK-total, High risk pregnancy

INTRODUCTION

Creatine kinase (CK) is a key enzyme of energy metabolism, especially in muscle tissue. It helps in reversible transfer of phosphoryl group from phosphocreatine to adenosine diphosphate (ADP), and generation of adenosine triphosphate (ATP).¹ CK has three isomers of CK-BB (CK-1), CK-MB (CK-2) and CK-MM (CK-3) with 2 polypeptide chains M and B. M chain is specific for muscle tissue and B chain is specific for brain tissue. Although small activity of CK is present

in the blood, its highest activity is noted in cells with high energy requirements such as skeletal, cardiac and smooth muscles. It is also found in kidneys, brain, neuronal tissues, retinal photoreceptor cells, spermatozoa and sensory hair cells of the inner ear.²⁻⁴ CK is predominantly used to diagnose myocardial infarction, acute skeletal muscle atrophy, muscular dystrophy etc. Some other disorders like burns, epilepsy, surgical procedures, streptococcus postpartum infection, Streptococcal toxic shock syndrome also result in an increase in CK activity. Apart from these disorders physiologic rise in CK activity

has also been reported with enhanced muscle activity and exercise.⁵⁻⁷ Pharmacological agents such as cocaine, ethanol and halothane are other factors responsible for increased CK activity.^{8,9} Creatine kinase and its isoenzyme activity show a great variation during pregnancy and labour.^{10,11} Fetal distress, brain damage, low birth weight, preterm deliveries and skeletal muscle injury during delivery could be related to higher CK activity in cord blood.^{12,13} Persistent high activity may implicate some conditions such as rhabdomyolysis and significant brain injuries.¹⁴⁻¹⁶

Since cord blood activity of Creatine kinase and its isoenzymes are found associated with different prenatal events, it might be of interest to measure CK and its isoenzymes activity in the cord blood and then analyzing them with various high risk factors associated with pregnancy.

Objective

Present study aimed to correlate total CK and its isoenzymes (CK-MB, CK-BB) activity with high risk pregnancy.

METHODS

The Study was conducted in the department of Obstetrics and Gynecology, and Biochemistry, Era's Lucknow Medical College and Hospital, Lucknow, Uttar Pradesh, India. Cord blood of 100 full term newborns was collected and serum was analyzed for total CK, CK-MB and CK-BB activity by modified IFCC method.

Study sample: Cord blood.

Sampling frame

The sampling frame was bound with the following inclusion and exclusion criteria:

- Singleton deliveries with normal birth weight babies born at gestational age 37-42 weeks were included in the study and all multiple gestations, pre- and post-term deliveries, low birth weight babies and newborns with any congenital malformation were excluded from the study.
- After obtaining history of mother and previous offsprings, the informed consent was taken from parents and 3ml cord blood samples of study participants were collected in a plain vial. Serum was used to estimate the total CK, CK-MB and CK-BB activity. Data about any association with high risk pregnancy factors were also recorded.

Estimation of total CK, CK-MB and CK-BB activity

Total CK, CK-MB and CK-BB activities were measured by modified IFCC method on semi-auto analyzer by

immune-inhibition method. Technical bulletin supplied along with the kit was followed.

Ethical issues

Ethical clearance and permission was obtained from the Institutional Ethical Committee, Era's Lucknow Medical College, Lucknow, Uttar Pradesh, India. Informed consent was obtained from the parent/guardians of the newborns. Confidentiality regarding sample collection and newborn's information was maintained.

Study design

Prospective observational study.

Statistical tool

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 18.0 statistical Analysis Software. The values are represented in Number (%) and Mean \pm SD. Significance was considered at 'p' value less than 0.001.

RESULTS

The present study was carried out with an aim to study total creatine kinase and its isoenzymes activity in cord blood of full term newborns in association with high risk pregnancy factors. Total of 100 full-term newborns falling in the sampling frame were included in the study. Maternal age ranged from 20 to 40 years. Maximum number of mothers were aged between 21 to 25 years (47%), followed by those aged 26-30 years (39%), 31-35 years (7%), < 20 years (5%) and 36-40 years (2%). Mean age of mothers was 26.14 \pm 3.97 years.

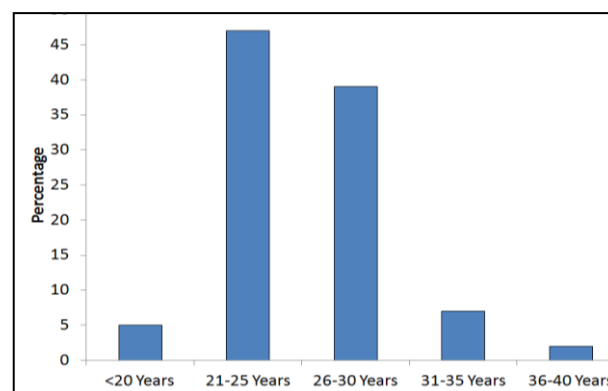


Figure 1: Percentage distribution of cases according to maternal age.

History of risk was positive in 51% cases. Fetal distress (21%) was the most common risk factor followed by meconium stained liquor (MSL)/leaking per vaginum (PV) (11%), non-progression of labour (NPOL) (7%), pregnancy induced hypertension (PIH) (3%), breech presentation (2%), arrest in second stage (2%),

cephalopelvic disproportion (2%) and others (3%). Other risks included oligohydramnios, placenta previa and placental insufficiency in one case each.

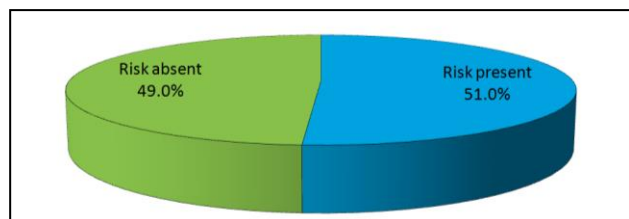


Figure 2: Percentage distribution of cases according to history of risk factors.

Table 1: Distribution of cases according to history of risk.

Risk category	No. and %
No risk	49
Risk	51
Fetal distress	21
MSL/Leaking PV	11
NPOL	7
PIH	3
Breech presentation	2
Arrest in second stage of labour	2
CPD	2
Others	3

Cord blood total creatine kinase activity ranged from 65.59 to 327.00 U/L with a mean of 146.20 and standard deviation of 45.79. Cord blood creatine kinase-MB activity ranged from 20.00 to 189.33 U/L with a mean of 57.21 and a standard deviation of 27.82. Cord blood creatine kinase-BB activity ranged from 10.00 to 94.67 U/L with a mean of 28.61 and a standard deviation of 13.91.

Table 2: Assessment of CK-Total, CK-MB and CK-BB activity (U/L) in cord blood.

	Activity (U/L)
CK-total	146.20±45.79
CK-MB	57.21±27.82
CK-BB	28.61±13.91

Values are expressed as Mean±SD.

Mean total CK activity was maximum in age group <20 years and minimum in age group 36-40 years yet the association of total CK activity with maternal age was not significant (p=0.982). Mean CK-MB activity was minimum in age group 31-35 years and maximum in age group 36-40 years, however, the association of age with CK-MB activity was not significant statistically (p=0.299). Mean CK-BB activity was minimum in age group 31-35 years and maximum in age group 36-40 years. However, the association of age with CK-BB activity was not significant statistically (p=0.299).

Table 3: Association of Total CK, CK-MB and CK-BB activity (U/L) with maternal age.

Maternal Age	Number	Total CK	CK-MB	CK-BB
		Mean±SD	Mean±SD	Mean±SD
<20 Years	5	149.27±43.03	56.69±24.54	28.35±12.27
21-25 Years	47	144.70±44.27	57.42±22.43	28.71±11.22
26-30 Years	39	149.07±50.35	56.37±33.30	28.19±16.65
31-35 Years	7	141.02±36.06	49.21±29.24	24.61±14.62
36-40 Years	2	135.91±70.85	98.00±2.82	49.00±1.41
'p'		0.982	0.299	0.299

Table 4: Association of Total CK, CK-MB and CK-BB activity (U/L) with risk during pregnancy.

Risk	Number	Total CK	CK-MB	CK-BB
		Mean±SD	Mean±SD	Mean±SD
Present	51	166.28±49.43	68.09±32.31	34.04±16.15
Absent	49	126.90±32.11	46.76±17.43	23.38±8.71
'p'		<0.001	<0.001	<0.001

Total CK, CK-MB as well as CK-BB activity were higher in cases with risk as compared to those in whom risk was absent (Table 3). Among different risk conditions, mean activity of total CK were of higher order in PIH and fetal distress, of middle order in leaking PV/MSL and NPOL

and of lower order in arrest in second stage of labour and breech presentation. However, the difference among different risk categories was not significant statistically (p=0.312). CK-MB activity was maximum in PIH cases followed by NPOL and arrest in second stage of labour and minimum in breech presentation. The association of

CK-MB activity with different risk factors was significant (p=0.001). For CK-BB activity too, mean values were minimum for breech presentation followed

by others and maximum for PIH. Statistically, there was a significant difference in mean value of CK-BB activity for different risk factors.

Table 5: Association of Total CK, CK-MB and CK-BB activity (U/L) with type of risk during pregnancy.

Risk	No.	Total CK	CK-MB	CK-BB
		Mean±SD	Mean±SD	Mean±SD
Arrest in second stage of labour	2	122.34±24.24	71.81±37.50	35.91±18.75
Breech presentation	2	127.20±13.19	34.62±2.77	17.31±1.39
Fetal distress	21	173.62±41.07	62.44±28.31	31.23±14.15
Leaking PV/MSL	11	163.73±36.76	60.29±21.33	30.15±10.66
NPOL	7	144.66±36.54	75.68±18.85	37.84±9.43
PIH	3	208.91±73.56	139.10±52.29	69.55±26.15
Others	5	171.20±92.91	60.09±20.97	30.05±10.48
'p'		0.312	0.001	0.001

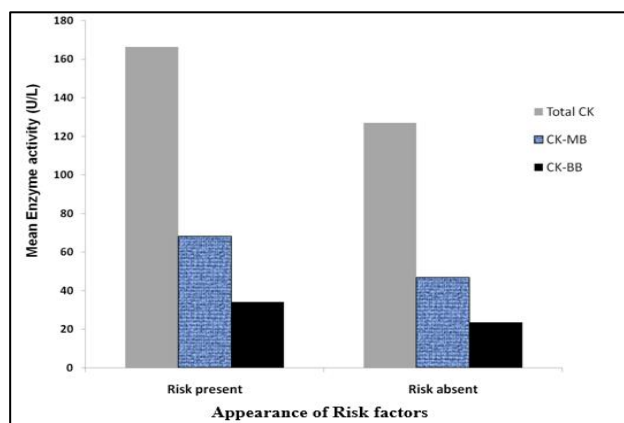


Figure 3: Association of enzyme activity with risk factors.

DISCUSSION

Increased muscular activity occurs during the birth process, as a result the creatine kinase activity is expected to be dependent on the level of strenuous activity.^{17,18} However, not all births follow same events—some births are associated with more stressful situation following fetal distress and end up in cesarean section while some other births do not witness such stress and are culminated into a successful delivery without any adverse event.^{19,20} It is of interest to understand the impact of these differences in circumstances through which a fetus undergoes during transition from fetus life to an ex-utero life, on the creatine kinase activity. Cord blood is considered to be immediate assessment of transition from fetal to an ex-utero life, can be easily and conveniently sampled and accessed and has been studied to have association with perinatal events.²¹⁻²³ Pregnancy events are affected by a host of factors that ultimately determine the level of risk for a fetus and/or mother. Maternal age is

one of them. Both delayed pregnancies (after 30 years or above) and teenage pregnancies have been considered to be accompanied with risk.^{24,25} The maternal age is stated to be related with adverse pregnancy events such as preterm delivery, stillbirth, preeclampsia, cesarean birth and a host of other complications.^{26,33} Thus in turn specifying that physiological changes specific to age lead to an increased risk for complications and in turn affecting materno-fetal physiology. In present study, we found the maternal age of 5 neonates to be in teenage range (<20 years) and 9 to be in advancing age (>30 years) and thus maternal age as a surrogate risk factor was noticed in these 14 cases.

As far as other antenatal and perinatal risk factors were concerned, we recognized the presence of these risk factors in as many as 51 neonates. Apart from the 14 neonates in whom maternal age was identified as a probable risk, a total of 51 neonates were also identified for presence of other risk factors such as fetal distress (n=21), MSL/leaking PV (n=11), NPOL (n=7), PIH (n=3), breech presentation (n=2), arrest in second stage (n=2), Cephalopelvic disproportion (n=2) others (n=3). Other risks included oligohydramnios, placenta previa and placental insufficiency in one case each. It is not so that there were no neonates with presence of more than one risk factors but for the purpose of classifying presence of risk as a categorical factor, we assessed the most dominating and immediate perinatal event/complication as a complication. As such presence of these complications in itself affects the physiological changes in pregnancy and can be perceived to have an effect on the neonatal cord blood CK activity.

In present study, mean Total CK as well as CK-MB and CK-BB activity were significantly elevated among those neonates at risk. On reviewing the literature, we did not come across any study evaluating the risk of various

antenatal and perinatal risk factors together. There are mixed findings on this issue in different studies. Some studies that have evaluated the cord blood total CK and CK isoenzyme activity with respect to prematurity have concluded that prematurity is associated with lower cord blood total CK and CK-MB/CK-BB activity while some others have indicated neonatal complications such as increased foetal heart rate (FHR) and asphyxia to be associated with elevated enzyme activity.^{34,37}

This is a complicated scenario, and in the absence of any clinical study being conducted using the same categorization pattern, we explored the independent role of different risk factors. We found a wide variability in total CK activity (Total CK=127.2 for breech presentation to 208.91 for PIH). However, for isoenzyme levels, we could find a significant association with different risk factors with value being of higher order for PIH, arrest in second stage of labour and NPOL, of middle order in leaking PV, fetal distress and others and it was of lower order in breech presentation. Unfortunately, owing to the limitation of our assay system, the pattern of relationship was similar for both the isoenzymes and we were unable to differentiate between events associated with damage to brain tissue and cardiac tissue.

Notwithstanding our inability to differentiate between the isoenzyme related risk of each event, the significant differences in isoenzyme activity of CK-MB and CK-BB clarified that the role of different risk factors needs to be studied independently and not in a clustered manner as done in our former analysis in which we had clubbed all the risk factors together and attempted to differentiate it from neonates at no risk but failed to find out a significant difference despite neonates at risk having higher mean total CK, CK-MB and CK-BB activity as compared to those not at risk. This implies that either the sample size of the study should be large enough to include substantial number of each type of risk or case-control studies using a purposive sampling design to observe role of each independent risk factor should be carried out separately with adequate number of cases and controls. In another study, Niklinski also failed to demonstrate the association between CK isoenzyme activity in different examined groups and were able to demonstrate the association of placental dysfunction with CK isoenzyme activity, thus stressing the need of having sufficient number of samples representing each entity independently.³⁸

In present study, we have considered maternal age as a surrogate risk factor, however, on analyzing the data statistically, we did not find a corresponding effect of age either on Total-CK or on its components CK-MB and CK-BB. On reviewing the literature, we did not find any study reporting such association. In fact, our hypothesis that extremes of maternal age, which are considered to be high risk pregnancies that affect the perinatal outcome, might influence the perinatal stress and in turn creatine

kinase activity seems to have no statistical outcome, however, we would like to mention here that the total CK activity were found to be maximum in cord blood of those neonates whose maternal age was <20 years and despite our inability to produce a statistically proven association these relationships worth further examination in larger trials. Interestingly, for advanced maternal age (>35 years), the componential CK activity, i.e. CK-MB and CK-BB were also much higher than the younger maternal age groups (CK-MB=98 U/L as compared to 49.21 to 57.42 U/L in younger age groups; CK-BB=49 U/L as compared to 24.61 to 28.71 U/L), thus potentiating our argument that this relationship should be explored further.

CONCLUSION

A total of 100 full-term newborns were enrolled in the study. Cord blood serum was analyzed for total CK, CK-MB and CK-BB activity by modified IFCC method. No significant association of cord blood CK-total, CK-MB and CK-BB activity was observed with maternal age. Mean total CK, CK-MB and CK-BB activities of neonates with presence of antenatal or perinatal risk factor were significantly higher as compared to that of neonates not having any risk factor. For different antenatal and perinatal risk factors, mean Total CK activity ranged from 122.34±24.24U/l (Arrest in second stage of labour; n=2) to 208.91±73.56U/l (PIH; n=3), however, the difference in Total CK activity among different risk factors was not significant statistically. For different antenatal and perinatal risk factors, mean CK-MB and CK-BB activities were maximum for PIH (139.10±52.29 and 69.55±26.15U/l respectively) and minimum for Breech presentation (34.62±2.77 and 17.31±1.39U/L respectively), thus showing statistically significant difference among different risk factors.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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