ISSN: 0975-3583, 0976-2833 VOL14, ISSUE02, 2023

CREATINE KINASE-MYOCARDIAL BAND(CK-MB) IN NEONATAL SHOCK AND ITS CORRELATION WITH INOTROPIC SUPPORT AND OUTCOME

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ABSTRACT

OBJECTIVE: To evaluate creatine kinase-myocardial band(CK-MB) levels in neonatal shock and its relation to type ,doses and duration of inotropic support and outcome.

STUDY DESIGN: It was a prospective hospital based study , conducted over 2 years in neonatal intensive care unit of a government teaching hospital.

MATERIALS AND METHODS:Cases were selected by purposive-deliberate sampling as and when serially diagnosed.Shock was diagnosed clinically and was managed as per American College of Critical Care Medicine guidelines.CK-MB level was assessed by immunoinhibition enzyme assay method within 12-24 hours of onset of shock. Demographic and clinical profile of babies was noted on predesigned proforma.Primary outcome was time to come out of shock and secondary outcome was type of oxygen support, acute kidney injury and disseminated intravascular coagulation. Data was analyzed statistically by Kruskal Wallis , Mann-Whitney U test and Spearman's rho.

RESULTS: 211 babies formed the study subjects. There were119 male and 92 female babies.Maximum babies(45.97%) were between 32-34w gestation. The mean weight of babies was 1850.12±525.45g and mean gestation was 33.77±2.68w. Majority(58.77%) of babies were Appropriate for Gestational Age(AGA). Mean CK-MB level was 102.93±77.87 IU/L. The difference in levels of CK-MB in relation to types($p=0.846$) and doses of inotropes was statistically non significant($p>.05$).The CK-MB level was also non significant in relation to duration of inotropic support. The level of CK-MB was statistically significant in non survivors as compared to survivors($p=0.002$).

CONCLUSION: The CK-MB levels are not decisive in deterimining the type and doses of inotropes, but do predict mortality in neonatal shock.

KEY WORDS: Creatine Kinase-MB, Neonate, Shock, Inotropes

INTRODUCTION

Shock is a patho-physiologic state characterized by an imbalance between oxygen delivery and demand. Myocardial dysfunction, abnormal peripheral vasoregulation and hypovolemia leading to decreased delivery of oxygen and nutrients to tissues are often the primary sources of shock[1]. Cardiogenic shock due to myocardial dysfunction is seen commonly in Patent Ductus Arteriosus(PDA), intrapartum asphyxia,myocarditis, arrhythmias,metabolic abnormalities and cardiomyopathy[2].Even shock due to non-cardiogenic causes has myocardial dysfunction which effects the type and degree of inotropic support.

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The neonatal myocardium has fewer contractile elements compared with older children and adults and in particular immature myocardium has a higher basal contractile state and has higher sensitivity to changes in afterload. Early bedside focused echocardiography can help in early identification of underlying pathophysiology and targeting specific therapy. Bedside functional echocardiography may help in logical choice of medications depending on underlying physiology and desired hemodynamic effects. Patients with shock may warrant use of vasopressor therapy and patient with impaired cardiac function may need more inotropic therapy[1].Even American college of critical care medicine clinical practice parameters for hemodynamic support for pediatric and neonatal septic shock endorse the superior vena cava flow and cardiac index for management of shock in newborns[3].

Functional echocardiography to assess superior vena cava flow and cardiac index evaluation is not available in most of centers in India managing critically sick newborns.Estimation of cardiac enzymes (CK-MB and Troponin I) can be done to assess myocardial injury. Troponin I estimation is not available in our center. CK-MB was assessed in all neonates with shock and it was correlated with type , degree and duration of inotropic support and outcome.

MATERIALS AND METHODS

It was a prospective hospital based study conducted in inborn Neonatel Intensive Care Unit(NICU) of department of pediatrics Government medical college /Rajindra hospital Patiala. The study period was from January 2021 to December 2022.The approval to conduct the study was taken from institutional ethical committee vide letter number 3459.Informed consent was also obtained from parents. Neonates with clinical diagnosed shock were included in study.Cases were selected by purposive-deliberate sampling as and when serially diagnosed.Babies with birth asphyxia ,congenital heart disease, cardiac failure, cardiomyopathy, arrhythmias, metabolic disturbances and gross congenital malformations were excluded from study. Shock was managed as per American College of Critical Care medicine guidelines[3].Demographic profile of babies including gender,gestation, birth weight , clinical parameters,type , dose and duration of inotropic support was noted along with outcome on a predesigned proforma. Gestational age in completed weeks was assessed form last menstrual period of mothers and confirmed if needed be by modified New Ballard Scoring System. Neonates were designated as Appropriate for Gestational Age(AGA) when birth weight was between 10th and 90th percentile of the weight for that gestational age,Small for Gestational Age (SGA) when birth weight was <10th percentile for that gestational age and Large for Gestational Age(LGA) when birth weight was> 90th percentile for that gestational age[4].CK-MB levels in serum was assessed within 12-24 hours of onset of shock.It was analyzed by immunoinhibition enzyme assay method. CK-MB upto 25 IU/L was taken as normal. Babies were monitored clinically and biochemically.Primary outcome was time to come out of shock and secondary outcome was type of oxygen support, acute kidney injury(AKI) and disseminated intravascular coagulation(DIC). AKI was diagnosed if serum creatinine level was>upper limit of normal reference range for gestational age with/without urine output<1cc/kg/h[5].DIC was diagnosed in a sick baby with bleeding from multiple sites with thrombocytopenia and derranged Prothrombin Time. Data was analyzed statistically by Kruskal Wallis , Mann-Whitney U test and Spearman’s rho. Statistical

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significance level (p value) was determined as ≤ 0.05 for all analyzes. IBM SPSS version 22 was software used for analysis.

RESULTS: Out of 251 neonates included in study , 40 were excluded.16 babies expired while on treatment,8 left against medical advice and 16 had to be referred due to non-availability of mechanical ventilator at that time in NICU.So 211 formed the subjects of the study.Baseline characteristics of the babies were as shown in table1.

Table 1: Baseline characteristics of study neonates (n=211)

Characteristic		Number	Percentage
Gender	Male	119	56.4
	Female	92	43.6
Gestational Age (w)	<32	39	18.48
	32-34	97	45.97
	35-36	39	18.48
	37-41	36	17.06
	Mean±SD	33.77±2.68	
	Median	33.00	
	Range	26-40	
Birth Weight (g)	<1000	3	1.42
	1000-1499	53	25.12
	1500-1999	87	41.23
	2000-2499	39	18.48
	≥ 2500	29	13.74
	Mean±SD	1850.12±525.45	
	Median	1750.00	
	Range	760-4050	
Weight for Gestation	SGA	53	25.12
	AGA	124	58.77
	LGA	4	1.90
	Tw	30	14.22
CK-MB(IU/L)	Mean±SD	102.93±77.87	
	Mean Rank	149.88	

SGA: Small for Gestational Age, AGA: Appropriate for Gestational Age, LGA:Large for Gestational Age

Mean gestation was 33.77±2.68w and mean weight was 1850±525.4g.CK-MB level was normal in 3 babies whereas in rest it was elevated. Mean ±SD CK-MB level(IU/L) in study subjects was 102.93±77.87. Majority(58.77%) of babies were AGA.

Respiratory Distress Syndrome(RDS) was seen in 179 babies. 157 babies had neonatal sepsis,51 babies had Necrotizing enterocolitis(NEC).AKI was seen in 54 and DIC in 32 babies.Persistent pulmonary Hypertension of Newborn(PPHN) was observed in 11 babies.87 babies received mechanical ventilation,whereas 115 babies were on Non-Invasive Ventilation(NIV).The difference in CK-MB levels in relation to type of inotropic support was statistically non significant(p=0.846)(table 2).

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Table 2: CK-MB level in relation to type of inotropic support

Inotrope	Number of Cases	CK-MB(IU/L)(Mean±SD)	p value
Dopamine	209	154.65±104.13	0.846 (Kruskal Wallis=0.814)
Dopamine+Dobutamine	204	155.07±105.10	
Dopamine +Dobutamine+Adr	146	149.97±105.08	
Dopamine+Dobutamine+Adr+Noradr	39	172.31±112.54	

Adr-Adrenaline, Noradr- Noradrenaline

Though babies on 4 inotropes(Dopamine, Dobutamine, Adr, Noradr) had highest value of CK-MB levels.CK-MB level in relation to different doses level of inotropes was statistically non significant (table 3).

Table 3: CK-MB level in relation to doses of inotropes

Inotrope	Dopamine			Dobutamine				Adrenaline					Noradrenaline			
Dose(µ/kg /min)	≤6	7-10	11-14	≤6	7-10	11-14	15-20	0.05	0.1	0.2	0.3	0.4	0.05	0.1	0.2	0.3
Number of Neonates	100	98	11	11	59	47	89	11	62	37	33	3	4	19	5	9
CK-MB(IU/L) (Mean±SD)	151.74±115.59	150.26±74.39	220.18±185.93	169.00±72.95	148.29±96.49	154.53±124.58	158.70±102.86	143.73±70.12	146.73±92.71	158.22±135.87	153.70±102.53	97.00±85.07	133.50±14.80	165.37±125.62	190.60±77.68	145.67±73.01
Mean Rank	97.99	109.62	127.59	122.68	99.28	98.40	106.62	77.95	74.15	71.72	74.52	54.50	18.25	17.76	24.30	19.00
p value	0.178			0.568				0.935					0.690			
Kruskal Wallis	3.450			2.022				0.827					1.467			

Babies who were on inotropic support for 8-10 days had highest level of CK-MB levels(table 4).

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Table 4: CK-MB level in relation to duration of inotropic support

Days of Inotropic Support	Number of neonates	CK-MB (IU/L)(Mean±SD)	Mean Rank	p value
1-4	119	163.18±104.91	112.07	0.305 (Kruskal Wallis=3.626)
5-7	68	138.32±86.83	96.86	
8-10	19	171.05±145.99	107.58	
11-14	5	121.40±89.81	79.90	

Babies with AKI had highest level of CK-MB levels , though comparison between co-morbid conditions was statistically non significant as shown in table 5.

Table 5: CK-MB level in relation to co-morbid conditions in study neonates

Co-morbid Condition	N	CK-MB (IU/L)	Mean Rank	p value
MV	87	169.56±126.23	89.71	0.271 (Kruskal Wallis=2.612)
AKI	54	173.93±135.36	90.29	
DIC	32	130.44±73.31	74.09	

MV: Mechanical Ventilation, AKI: Acute Kidney Injury, DIC: Disseminated Intravascular Coagulation

28 babies expired while on treatment.CK-MB level in these babies was statistically significant as compared to study subjects(p=0.002).

Table 6: CK-MB level in non-survivors as compared to study neonates

	N	CK-MB (IU/L)	Mean Rank	p value
Non -Survivors	28	166.79±127.77	129.46	0.002 (Mann-Whitney U=3.120)
Study neonates	211	102.93±77.87	93.34	

Mean duration of inotropic support was 4.49±2.41 days.None of the inotropic drug showed significant coefficient of correlation with CK-MB levels.Spearman's rho correlation coefficient was 0.088, 0.005,-0.110 and 0.034 in relation of Dopamine, Dobutamine, Adrenaline, Noradrenaline individually with CK-MB levels(all p values>0.05).

DISCUSSION: CK-MB has been studied in birth asphyxia,sepsis, congenital heart disease and respiratory distress in newborn.

In the present study , CK-MB level was not statistically significant associated with types of inotropic support as well doses of inotropes.So it is not decisive in choice of inotropes and doses of inotropes.That is to be decided clinically /bedside echocardiography.Though CK-MB level was significantly elevated in non-survivors as compared to the survivors.Oman et al[6] in their study found no difference in CK-MB levels between survivors and non-survivors.It is in contrast to present study, though Oman et al did their study on septic babies without shock while present study was done on babies with shock.

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CK-MB level was significantly elevated in non -survivors as compared to survivors in study conducted by Aggarwal J et al[7].Though the subjects of their study were babies with birth asphyxia with hypoxic ischemic encephalopathy(HIE). Such babies were excluded in the present study.CK-MB level was elevated in neonatal sepsis as a marker of myocardial dysfunction in study conducted by Krestu N et al[8]. They concluded that increase of CK-MB serum activity can be considered as a sign of myocardial dysfunction caused by neonatal sepsis. However, Singh V et al [9] in their study observed CK-MB elevation in 15% of babies and inotrope use in 32 % of babies with birth asphyxia.Hence CK-MB level was not true reflector of myocardial dysfunction, as also observed in present study as CK-MB levels were not statistically related to use of different inotropes as shown in table 2.

Zhang S et al[10] in their study measured levels of CK-MB, alpha hydroxybutarate dehydrogenase in neonatal septic shock and found that the levels of above enzymes are elevated in septis shock and decrease was observed 2 weeks after treatment.Elevation was significant statistically in cases with severe septic shock as compared with mild septic shock($p<0.05$).There was gradual increase in the level of CK-MB with progression of shock.But their study , did not observe the outcome.

CONCLUSION: Estimation of CK-MB in neonatal shock is not useful in tailoring the type and doses of inotropes, but it does help in predicting mortality.

CONTRIBUTORS: TT and MS conceptulized the study, BK and MS analyzed and interpreted the data. KS collected the data.MS wrote the manuscript,TT critically revised it. All authors approved the final manuscript.

Funding: Nil

Conflicts of Interest: None

Competing Interest: None

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