The Egyptian Journal of Hospital Medicine (October 2021) Vol. 85 (2), Page 3498-3502

Role of Creatine Kinase MB in Diagnosis of Myocardial Injury after Neonatal Hypoxia-Ischemia

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ABSTRACT

Background: Creatine kinase MB (CK-MB), which exists mainly in the cytoplasm of myocardial cells, is currently accepted as an indicator and has high sensitivity and specificity for the diagnosis of myocardial injury.
Objective: This study was aimed to estimate serum creatine kinase MB (CK-MB) levels after asphyxia-induced myocardial injury in neonates. **Patients and methods:** 40 neonates were included in this study and divided into 20 cases with the diagnosis of perinatal hypoxia ischemia and 20 controls admitted to Neonatology Unit of Pediatric Department at Zagazig University. Serum CK-MB levels were estimated in all studied neonates**.**
Results: In the present study serum CK-MB levels in cases were significantly higher than controls. A significant area under curve with cutoff >14.5 (units /L) with sensitivity 99%and specificity 97.5% for CK-MB. Encephalopathy cases were significantly associated with higher HR and CKMB. Cases with organ failure were significantly associated with higher HR and CKMB. Cases with metabolic acidosis were significantly associated with higher HR and CKMB.
Conclusion: It could be concluded that cases with hypoxic ischemic encephalopathy (HIE) and those with multiple organ failure had a more pronounced elevation of serum CK-MB compared with cases of hypoxia-ischemia with no organ failure. Similarly, patients with HIE had significant elevation of cardiac enzymes. Collectively, these findings indicate more myocardial systolic dysfunction and damage in neonates with HIE and organ failure.
Keywords: Neonatal Hypoxia-Ischemia, Myocardial Injury, Creatine kinase -MB.

INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) is the most important reason for morbidity and mortality of newborns in all over the world although antenatal and neonatal cares have been improved in recent years. Neonatal HIE is not a rare condition, and its incidence is between 1 and 8 per 1000 live births in developed countries with rates as high as 26 per 1000 live births in the developing world [(1)].

Amongst those who survive the initial injury, rates of disability remain high throughout life. Of patients surviving neonatal HI, 5–10% of infants demonstrate persistent motor deficits, and 20– 50% display sensory or cognitive abnormalities that persist to adolescence [(2)].

A meta-analysis of seven studies including 386 infant patients investigated the average incidence of mortality and morbidity: 5.9% of all patients across all studies died, 16.3% suffered neonatal seizures, and 17.2% experienced neurological deficits, with 14.2% qualifying for a diagnosis of cerebral palsy [(3)]. Because of these high rates of morbidities caused by HIE, development of new treatment strategies has come into consideration. HI can develop acutely or chronically during the prenatal (hypotension, severe hypoxia, or infection), perinatal (cord occlusion or prolapse, abruption or placental insufficiency, uterine rupture), or postnatal periods (shock, respiratory, or cardiac arrest) [(4)].

The diagnostic criteria for neonatal HI are based on a set of markers demonstrated to correlate with clinical outcome. These include: 5-min Apgar score of less than 5; need for delivery room intubation or CPR; umbilical cord arterial pH less than 7.00; and abnormal neurological signs, such as hypotonic muscles or lack of sucking reflex [(5)].

Creatine kinase-muscle-brain isoenzyme (CK-MB**)** is one of the three isoenzymes of creatine Kinase and is expressed in myocardial muscle and in very small amounts in skeletal muscle. There is some evidence that CK-MB levels are significantly elevated in asphyxiated infants compared with controls. Levels of CKMB in asphyxiated infants rose to a significant peak at 12 h of life before returning to a low level at 48 h of life [(6)].

Other studies found that CK-MB was not helpful in predicting myocardial injury in a group of infants with neonatal hypoxic ischemia, and levels of CK-MB do not help distinguish between asphyxiated newborns and normal infants. Therefore, CK-MB may not be helpful in identifying infants with neonatal hypoxic ischemia who have cardiovascular compromise but may be more useful as part of a predictive model for poor outcome following neonatal hypoxic ischemia [(7, 8)].

The current study was aimed to estimate serum creatine kinase MB (CK-MB) levels after asphyxia-induced myocardial injury in neonates.

PATIENTS AND METHODS

This study included a total of forty neonates divided into 20 cases diagnosed as perinatal hypoxia ischemia and 20 controls, attending at Neonatology Unit, Departments of Pediatric, Faculty of Medicine, Zagazig University Hospitals.

Received: 20 /6 /2021
Accepted: 16 /8 /2021

Case group included 20 neonates (12 males and 8 females) with the diagnosis of perinatal hypoxia ischemia. Control group included 20 age- and sex-matched neonates (13 males and 7 females) admitted due to causes other than perinatal hypoxia and cardiovascular problems e.g., neonatal hyperbilirubinemia, neonatal vomiting and congenital anomalies not involving the heart.

Inclusion criteria: Neonates with diagnostic criteria of myocardial injury.

Exclusion criteria: Neonates with any disease as kidney dysfunction, pulmonary disease.

All patients were subjected to full history taking, clinical examination, and laboratory determination of CK-MB.

Collection of blood samples: A 2 ml blood sample was withdrawn from the femoral vein of neonates on 2nd day of hospital admission. The serum was collected for the detection of CK-MB.

Measurement of CK-MB: by electrochemiluminescence kit (Roche, Shanghai, China), using the Elecsys 2010 instrument.

Ethical approval:

The study was approved by the Ethical Committee of Zagazig Faculty of Medicine. An informed consent was obtained from all patients in this research. Every patient received an explanation for the purpose of the study. All given data were used for the current medical research only.

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. Qualitative data were represented as number and percentage, quantitative continuous data were represented by mean ± SD, and the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups by unpaired student's t-test. P value was set at <0.05 for significant results &<0.001 for highly significant result.

RESULTS

In the present study serum CK-MB levels in cases were significantly higher than controls **(Table 1**).

Significant area under curve with cutoff >14.5 (units /L) with sensitivity 99%and specificity 97.5% for CK-MB **(Table 2 & Figure 1)**.

Encephalopathy cases were significantly associated with higher HR and CKMB **(Table 3**).

Cases with organ failure were significantly associated with higher HR and CKMB **(Table 4)**. Cases with metabolic acidosis were significantly associated with higher HR and CKMB **(Table 5)**.

Table (1): CKMB distribution in studied groups.

	Case (n = 20)	Control (n = 20)	t	P
CKMB (units/L)	**25.60±8.57**	**10.30±3.01**	**7.496**	**0.00****

CKMB: Creatine Kinase MB t: Student t test

Table (2): Area under curve, cutoff and validity of CKMB.

Test Result Variable(s)	Area	Cutoff	P	95% Confidence Interval		Sensitivity	Specificity
				Lower Bound	Upper Bound		
CKMB	**0.976**	**>14.5 (units/L)**	**0.00****	**0.934**	**0.99**3	**99.0%**	**97.5%**

CK-MB: Creatine Kinase MB

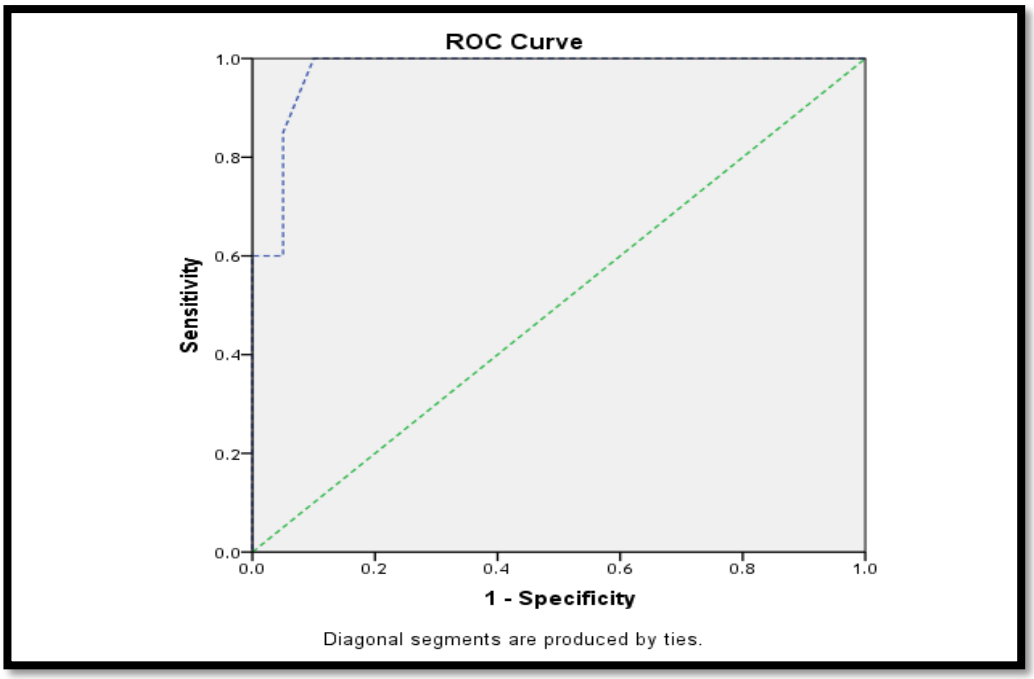

Figure (1): ROC Curve for CK-MB in cases.

Table (3): Studied parameters in cases according to presence or absence hypoxic- ischemic Encephalopathy.

	No (n = 7)	Encephalopathy (n = 13)	t	P
Age (days)	15.57±5.21	13.84±4. 12	0.605	0.553
GA (weeks)	36.42±1.98	35.61±2.01	0.875	0.393
Birth weight (g)	2707.14±279.0	2550.38±323.2	1.081	0.294
HR (beat/minute)	148.57±12.0	162.0±13.54	2.193	0.042*
RR (breath/minute)	58.28±6.57	54.15±6.75	1.316	0.205
CKMB (units/L)	17.57±5.60	29.92±6.06	4.217	0.001**

CKMB: Creatine Kinase MB; GA: Gestational Age,; HR: Heart Rate; RR: Respiratory Rate. t: Student t test

Table (4): Studied parameters in cases according to presence or absence of multiple organ failure.

	No (n = 14)	Organ failure (n = 6)	t	P
Age (days)	15.71±5.21	11.50±3.78	1.491	0.153
GA (weeks)	35.50±1.91	36.83±2.13	1.423	0.172
Birth weight (g)	2557.14±332.1	2717.5±241.1	1.062	0.302
HR (beat/minute)	152.57±13.41	168.33±10.07	2.569	0.019*
RR (breath/minute)	56.57±7.37	53.33±5.16	0.971	0.344
CKMB (units/L)	22.07±7.67	33.83±.18	3.581	0.002*

CKMB: Creatine Kinase MB; GA: Gestational Age,; HR: Heart Rate;; RR: Respiratory Rate. t: Student t test

Table (5): Relation of different parameters with PH among cases.

	PH >7.3	PH <7.3	t	P
Age (days)	14.92±4.5	13.57±4.03	0.472	0.642
GA (weeks)	35.84±2.03	36.0±2.0	0.162	0.873
Birth weight (g)	2600.0±343.3	2615.0±263.6	0.100	0.921
HR (beat/minute)	152.30±12.69	166.57±13.10	2.371	0.029*
RR (breath/minute)	56.92±7.0	53.14±6.20	1.195	0.248
CKMB (units/L)	22.23±7.70	31.85±6.61	2.790	0.012*

CKMB: Creatine Kinase MB; GA: Gestational Age,; HR: Heart Rate;; RR: Respiratory Rate. t: Student t test

DISCUSSION

Neonatal hypoxia is a common pediatric disease-causing hypoxia and leads to multiple organ damage, of which heart damage is the most common. Perinatal asphyxia constitutes an important cause of mortality and both short- and long-term morbidity in neonates. Asphyxia can compromise the blood supply of organs other than CNS and lead to irreversible damage and increased morbidity and mortality**.** Hypoxic-ischemic insults are the most common cause of brain lesions in the neonates**.** Multiorgan dysfunction is a constant feature of the neonatal hypoxia. Cardiac dysfunction is reported in up to 62–78% of cases. The reduced function could also have been caused by a depletion of energy substrate within the myocardium due to the asphyxia [(9)].

Myocardial injury occurs because of decreased myocardial perfusion resulting in ischemia of the papillary muscle and subendocardial tissue. The reduced function could also have been caused by a depletion of energy substrate within the myocardium due to the asphyxia [(10)].

Our study was conducted to measure the serum level of CK-MB in neonates with hypoxia-ischemia on 20 asphyxiated neonates (case group) and 20 healthy neonates who were not exposed to risk factors as proved by medical, obstetric history and history of present pregnancy, and signs of perinatal asphyxia as evidenced by complete thorough examination (control group).

Our results show that cases were significantly higher than control subjects regarding serum level of CK-MB (25.6 ± 8.57 units/L in cases versus 10.3 ± 3.01 units/L in control group) ($p < 0.001$).

Zhu *et al.* [(11)] stated that levels of CK-MB began to rise within the first few hours of life and were significantly higher in moderate and severe grades of neonatal hypoxia ischemia compared with mild grades and normal controls within the first 2–4 h. Levels of CKMB in asphyxiated infants rose to a significant peak at 12 h of life before returning to a low level at 48 h of life. There was no significant difference in the serial serum CKMB levels during the first 48 h of life between asphyxiated infants with and without hypotension, between infants who had normal or abnormal ECGs, between infants with and without heart failure, between infants with low and normal EF or between infants who survived or died.

Kanik *et al.* [(12)] found that CK-MB was not helpful in predicting myocardial injury in a group of infants with neonatal hypoxia ischemia, and levels of CK-MB do not help distinguish between asphyxiated newborns and normal infants. Therefore, CK-MB may not be helpful in identifying infants with neonatal hypoxia ischemia who have cardiovascular compromise but may be more useful as part of a predictive model for poor outcome following neonatal hypoxia ischemia.

Regarding validity of CKMB, we found significant area under curve with cutoff >14.5 units/L for CKMB with sensitivity 99% and specificity of 97.5% for CKMB serum level (table 9 and figure 8) for diagnosis of myocardial injury. CKMB (17.57 ± 5.6 units/L in cases without encephalopathy versus 29.92 ± 6.06 units/L in encephalopathy patients) ($p = 0.001$), CKMB (22.07 ± 7.67 units/L in patients without organ failure versus 33.83 ± 18 units/L in organ failure patients) ($p = 0.002$). In sepsis, myocardial depression usually occurs within 2–3 days after the onset of sepsis and is characterized by acute increases in ventricular volume and a marked deterioration of left ventricular ejection fraction.

Post *et al.* [(13)] showed that 59% developed myocardial dysfunction, as defined by deteriorated left ventricular systolic function of <50%. Another study by **Ver Elst *et al.*** [(14)] reported left ventricular dilation in combination with an impaired LVEF.

CONCLUSION

It could be concluded that cases with hypoxic ischemic encephalopathy (HIE) and those with multiple organ failure had a more pronounced elevation of serum CK-MB compared with cases of hypoxia-ischemia with no organ failure. Similarly, patients with HIE had significant elevation of cardiac enzymes. Collectively, these findings indicate more myocardial systolic dysfunction and damage in neonates with HIE and organ failure.

Financial support and sponsorship: Nil.

Conflict of interest: Nil.

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