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Original Article

Predictive value of cord blood myocardial enzyme and troponin levels for myocardial injury after neonatal asphyxia

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Abstract: Purposes: To assess the value of myocardial enzymes and troponins in cord blood in the early diagnosis of myocardial injury after neonatal asphyxia. Methods: We retrospectively analyzed the clinical data of 50 cases of perinatal asphyxia neonates and 40 normal newborns in this study. The clinical manifestation, electrocardiograph (ECG) and echocardiography result, and the cord blood myocardial enzyme and troponin levels were compared between the two groups. The receiver operating characteristic (ROC) curve analysis was used to explore the diagnostic value of cord blood myocardial enzymes and troponins for myocardial injury after neonatal asphyxia. Results: All cases in the asphyxia group had different degrees of clinical manifestations of myocardial injury, as well as ECG and echocardiography abnormalities. Compared with the control group, cord blood aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase isoenzyme MB (CK-MB), cardiac troponin T (cTNT), and cardiac troponin I (cTNI) levels in the asphyxia group were all elevated (all $P < 0.05$). Levels of the six biomarkers were all significantly higher in asphyxiated newborns with myocardial injury than in asphyxiated newborns without myocardial injury (all $P < 0.05$). ROC curve analyses showed that cord blood levels of CK-MB, cTNT, and cTNI could be used to differentiate asphyxiated newborn with and without myocardial damage. Calculation of AUC (area under curve) values indicated that CK-MB, cTNT, and cTNI had significant discriminatory ability (P=0.014, 0.021, and 0.009, respectively). The optimal cutoff value of CK-MB, cTNT, and cTNI were 135.4 U/L, 112.6 ng/L, and 55.3 ng/L, respectively. Conclusions: Cord blood CK-MB, cTNT, and cTNI levels could be used for early prediction of myocardial injury after neonatal asphyxia.

Keywords: Cord blood, myocardial injury, neonatal asphyxia, myocardial enzyme, troponins

Introduction

Neonatal asphyxia is a common disease of newborns, and its incidence in China can reach 10% [1]. Neonatal asphyxia refers to the inability of infants to establish normal breathing after birth [2], which will result in impaired oxygenation and perfusion of multiple organs, hypercapnia, acidosis, and is potentially fatal to the newborns.

Myocardial injury is the most common injury of neonatal asphyxia. It has been reported that the incidence of myocardial damage could be up to 73% in neonatal asphyxia [3]. However, due to the diversity of clinical manifestations of neonatal myocardial damage and the lack of specific diagnostic indicators in early stage, its miss diagnosis or misdiagnosis rates are high. If the myocardial injury develops to myocardial necrosis, the prognosis will be poor, and the mortality will be high. Therefore, new detection methods are urgently needed to predict myocardial damage in asphyxiated newborns.

Myocardial enzyme is an important index of myocardial injury after asphyxia. Under the circumstance of insufficient oxygen supply, the production of adenosine triphosphate (ATP) in myocardial cells decreases, which seriously affects the stability of cell membrane and lysosomal membrane. At the same time, the increase of lipid peroxidase and oxygen free radical directly damages and destroys the integrity

of biological membrane, leading to release of myocardial enzymes into the blood [4]. The commonly used myocardial enzymes include AST, LDH, CK, and CK-MB [5]. In recent years, two cardiac troponins, cTnI and cTnT, are recommended as the first-choice markers of myocardial injury because of their high specificity and sensitivity as compared with those commonly used myocardial enzymes [6, 7]. Umbilical cord is the pathway for material exchange between mother and fetus, and umbilical vein blood can reflect the metabolism of fetus and newborn. Besides, umbilical cord blood collection is easy to operate and has the least damage to infants.

In light of these, our study aimed to investigate the levels of myocardial enzymes and troponins in cord blood in newborns suffered from asphyxia. The findings will provide a basis for neonatal umbilical venous blood screening to predict myocardial injury after neonatal asphyxia.

Methods

Participants

50 full-term asphyxia neonates were retrospectively enrolled between June 2017 and May 2021 in the Department of Obstetrics, No. 215 Hospital of Shaanxi Nuclear Industry, China (Asphyxia group). The inclusion criteria of asphyxia neonates were as follows: Full-term neonates; Diagnosed with neonatal asphyxia; No serious congenital heart, lung and metabolic diseases; With written informed consent to use the clinical data of the newborns provided by the parents. Another 40 full-term normal neonates during the same time period were enrolled as controls. The controls came from the neonates whose indexes were within the normal range after examination for various reasons. The clinical data of these newborns were compared between the two groups.

Since 2015, all the guardians of the newborns in our hospital have signed a consent form on the premise of consent, agreeing that our hospital can use the clinical data of the newborns for possible retrospective studies.

Full term neonates refer to live born infants whose gestational age is 37-41+6 weeks. Neonatal asphyxia was determined in accordance with the "expert consensus on diagnosis of neonatal asphyxia" formulated by neonatal resuscitation group of perinatal medicine branch of Chinese Medical Association [8] using the following criteria: 1) Mild asphyxia: Apgar score ≤ 7 at 1 min or ≤ 7 at 5 min, with umbilical artery blood pH < 7.2 and -16 < BE ≤ -8; 2) Severe asphyxia: Apgar score ≤ 3 at 1 min or ≤ 5 at 5 min, with umbilical artery blood pH < 7. 0 and BE ≤ -16.

The exclusion criteria were as follows: Neonates with congenital heart diseases (such as atrial septal or ventricular septal defect, pulmonary artery stenosis, etc.), congenital pulmonary malformations (such as tracheoesophageal leakage, bronchopulmonary dysplasia, etc.), pneumothorax, congenital diaphragmatic hernia, congenital hypothyroidism, inherited metabolic diseases (such as phenylketonuria, congenital adrenal hyperplasia, etc.); Died within 1 week after birth; With incomplete clinical data after birth.

Clinical diagnostic criteria of neonatal myocardial injury

The clinical diagnosis of myocardial injury in asphyxiated newborns was made according to the Chinese standard [9]: 1) clinical features, including dysphoria; irregular breathing, such as tidal breathing, intermittent breathing, and sighing breathing; bradycardia (< 100 beats/min); low blunt heart sounds; poor circulation, such as pale face, cyanosis, capillary refill time (anterior chest) > 3 s; severe arrhythmia; cardiac arrest; and nervous system abnormalities, mainly manifested as weakening or disappearance of primitive reflex, increase or decrease of muscle tension, and irritation; 2) ST-T wave abnormalities lasting for more than 2-3 days; 3) echocardiography (recommended) showing the enlarged right heart, tricuspid regurgitation and abnormal left ventricular wall motion, decre ased ejection fraction, pericardial effusion, decreased myocardial contractility, decreased cardiac output and increased pulmonary artery pressure. Clinical diagnosis of cardiac damage can be made if one or more of the clinical features is met, together with abnormal ECG or echocardiography.

Although the increase of CK-MB (≥ 40 U/L) or cTnT (≥ 0.1 ng/ml) were also one of diagnostic

Table 1. Demographic features and clinical data

Variables	Asphyxia group (n=50)	Control group (n=40)	χ^2/t	*P* value
Gender (male/female)	26/24	21/19	0.002	1.000
Gestational age (weeks)	38.5±1.4	38.3±1.3	0.911	0.386
Birth weight (g)	3179±421	3291±392	0.237	0.818
Apgar scores at 1 minute	4.5±1.7	8.5±0.5	7.028	< 0.001
Apgar scores at 5 minutes	6.0±1.1	9.0±0.8	6.332	< 0.001
Cesarean section	31 (62%)	23 (57.5%)	0.188	0.672
Cord around the neck	6 (12%)	6 (15%)	0.173	0.760
MSAF	22 (44%)	11 (27.5%)	2.605	0.127

MSAF, Meconium-Stained Amniotic Fluid.

criterial for neonatal myocardial injury, they were not used in this study since our research was to evaluate their application value.

ECG and echocardiography examination

A 12-lead automatic analysis electrocardiograph FCP-7101 (Beijing Futian electronic medical instrument Co., Ltd., Beijing, China) was used for ECG examination. The newborn was in the supine position in a quiet state for examination and the process was carried out by professionals. The printing speed of the paper was controlled at about 25 mm/s, and the voltage range was about 10 mm/MV.

An ultrasonic instrument Philips iE33 (Netherlands) was used for cardiac ultrasound examination (probe S5-1, fusion frequency 2-4 MHz). The newborn was in the supine position in a quiet state and the angle between ultrasound beam and color flow beam was less than 20° and the sampling volume was placed at the valve orifice. Three cardiac cycles were taken, and the average value was taken. The indexes were ejection fraction (EF), shortening fraction (FS), peak early filling velocity (E, cm/s), peak late filling velocity (A, cm/s) and E/A.

Specimen collection and preparation

The umbilical cord was cut off immediately after delivery. 2-3 ml of umbilical vein blood was collected into dry coagulating-promoting tube. The umbilical cord blood sample was allowed to stand for 1 hour and then centrifuged for 10 min at 3000 r/min. Finally, the serum was harvested and stored at -80°C refrigerator for examination.

Measurement of cord blood myocardial enzyme and troponin levels

The myocardial enzymes (AST, LDH, CK, and CK-MB) levels in cord blood were determined using a SD-1 automatic biochemical analyzer (Seamaty Technology Co., Ltd., Sichuan, China). The cTnI in cord blood was determined by immunofluorescence chromatography using a Wanfu immunofluorescence detector FS-113 (Xiamen Haifei Biotechnology Co., Ltd., China) and the cTnT in cord blood was determined using an automatic electrochemiluminescence analyzer E601 (Roche Diagnostics, Mannheim, Germany).

Statistical analysis

All data were presented as mean ± standard deviation (SD) or percentage (%). One-way ANOVA was used to compare the differences between the two groups by using SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA). ROC curve analysis was used to evaluate the diagnostic values of the six biomarkers for the diagnosis of myocardial injury in asphyxiated newborns. The optimal cutoff value of ROC curve of each biomarker was determined by calculating Youden index. *P* values less than 0.05 were considered statistically significant.

Results

General information

There were no significant differences in general data, including gender, gestational age, and birth weight, between the two groups (all $P > 0.05$). The Apgar scores at 1 and 5 minutes were significantly lower in the asphyxia group than those in the control group (both $P < 0.05$). There were no significant differences in the proportion of neonates with cesarean section, cord around the neck, and meconium-stained amniotic fluid (MSAF) between the two groups (all $P > 0.05$) (**Table 1**).

Clinical manifestation and diagnosis of myocardial damage

In the control group, there was no obvious clinical manifestation of neonatal myocardial injury

Table 2. Comparison of clinical manifestation between the two groups

Clinical manifestation	Asphyxia group [n (%)]	Control group [n (%)]	χ^2	*P*
Irregular breathing	17 (34%)	0 (0%)	16.767	< 0.001
Poor circulation	37 (74%)	0 (0%)	50.264	< 0.001
Nervous system abnormalities	37 (74%)	0 (0%)	50.264	< 0.001

Table 3. Comparison of ECG abnormalities between the two groups

ECG abnormalities	Asphyxia group [n (%)]	Control group [n (%)]	χ^2	*P*
Bradycardia or tachycardia	30 (60%)	0 (0%)	36.000	< 0.001
Sinus arrhythmia	26 (52%)	0 (0%)	29.250	< 0.001
Atrial premature beat	20 (40%)	0 (0%)	20.571	< 0.001
Low or inverted T wave, ST segment reduction	9 (18%)	0 (0%)	8.000	0.004
Prolonged P-R interval with pathological Q wave	5 (10%)	0 (0%)	4.235	0.063
Degree I atrioventricular block	2 (4%)	0 (0%)	1.636	0.501

ECG, Electrocardiograph.

Table 4. Comparison of cardiac function indexes between the two groups

Group	N	EF (%)	FS (%)	E (cm/s)	A (cm/s)	E/A
Asphyxia group	50	72.9±2.4	39.2±3.2	6.5±0.5	5.8±0.4	1.1±0.1
Control group	40	65.1±3.9	33.4±2.8	5.5±0.7	6.5±0.6	0.8±0.2
t		2.806	2.641	2.497	2.884	2.905
P		0.009	0.013	0.019	0.006	0.002

after birth. In contrast, all cases in the asphyxia group had different degrees of clinical manifestations of myocardial injury and abnormal manifestations of respiratory and nervous system after birth, including 17 cases of irregular breathing (34%), 37 cases of poor circulation (74%), and 37 cases (74%) of nervous system abnormalities (**Table 2**). The above clinical manifestations disappeared 7-14 days after birth after oxygen inhalation and myocardial protective therapy.

According to the clinical diagnostic criteria of myocardial damage in neonatal asphyxia mentioned above [9], there was no myocardial damage in the control group. In contrast, there were 28 cases (56%) diagnosed as myocardial damage in the asphyxia group.

ECG and echocardiography results

There were no obvious ECG abnormalities in the control group. In the asphyxia group, ECG abnormalities of various degrees occurred in all cases, including bradycardia or tachycardia in 30 cases (60%), sinus arrhythmia in 26 cases (52%), atrial premature beat in 20 cases (40%), low or inverted T wave in leads II, III and AVF, ST segment reduction in 9 cases (18%), prolonged P-R interval with pathological Q wave in 5 cases (10%), and degree I atrioventricular block in 2 cases (4%) (**Table 3**).

Echocardiography examination showed that compared with the control group, the EF, FS, E and E/A values in the asphyxia group were all decreased, while the A value was increased, and the difference was statistically significant (all $P < 0.05$) (**Table 4**).

Cord blood myocardial enzyme and troponin levels

Compared with the control group, cord blood AST, LDH, CK, CK-MB, cTNT and cTNI were significantly higher in the asphyxia group (all $P < 0.05$) (**Figure 1**).

Further analysis showed that compared with newborns with asphyxia but no myocardial damage, the umbilical cord blood myocardial

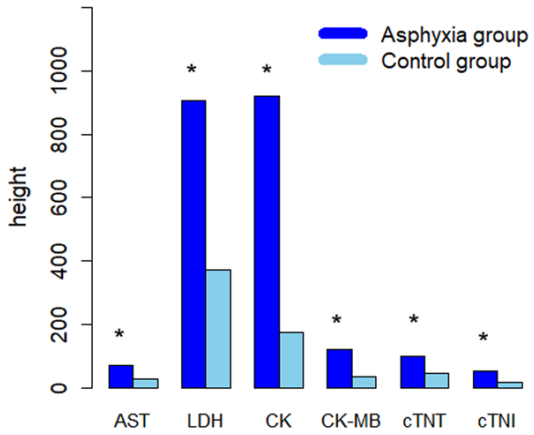

Figure 1. Comparison of myocardial enzymes and troponin levels in umbilical cord blood of newborns between asphyxia and control groups. $^{*}P < 0.05$ *vs.* Control group. AST, Aspartate Aminotransferase; LDH, Lactate Dehydrogenase; CK, Creatine Kinase; CK-MB, Creatine Kinase Isoenzyme MB; cTNT, serum Cardiac Troponin T; cTNI, serum Cardiac Troponin I.

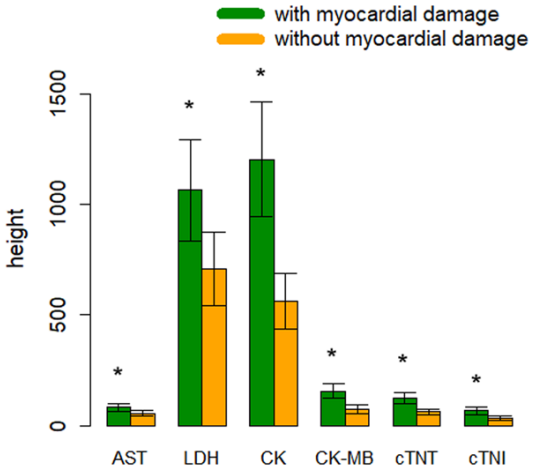

Figure 2. Comparison of myocardial enzymes and troponin levels in umbilical cord blood of newborns between asphyxia with and without myocardial damage groups. $^{*}P < 0.05$ *vs.* asphyxia without myocardial damage group. AST, Aspartate Aminotransferase; LDH, Lactate Dehydrogenase; CK, Creatine Kinase; CK-MB, Creatine Kinase Isoenzyme MB; cTNT, serum Cardiac Troponin T; cTNI, serum Cardiac Troponin I.

enzymes AST, LDH, CK, CK-MB, cTNT and cTNI in newborns with asphyxia combined with myocardial damage were significantly higher (all $P < 0.05$) (**Figure 2**).

ROC analysis

ROC curve analyses were used to evaluate the diagnostic values of the six biomarkers for myocardial injury in asphyxiated newborns, namely, differentiating between asphyxia with and without myocardial damage groups (**Table 5**). Calculation of AUC values showed that CK-MB, cTNT, and cTNI had significant discriminatory ability (P=0.014, 0.021, and 0.009, respectively) (**Figure 3**). The AUC values for CK-MB, cTNT, and cTNI were 0.727, 0.698, and 0.752, respectively. The optimal cutoff value of CK-MB, cTNT, and cTNI for differentiating asphyxiated newborns with myocardial damage from those without myocardial damage group were > 135.4 U/L, > 112.6 ng/L, and > 55.3 ng/L, respectively. Cord blood CK-MB, cTNT, and cTNI levels could correctly predict myocardial injury in 20, 19, and 22 cases, respectively, in the asphyxia with myocardial damage group (n=28), and correctly exclude 22, 22, and 22 cases, respectively, in the asphyxia without myocardial damage group (n=22).

Discussion

Neonatal asphyxia can lead to multiple organ function damage, and the heart is one of the most common affected organs [10]. The reason is that cardiomyocytes are highly sensitive to hypoxia, which can lead to abnormal metabolic function and structure of cardiomyocytes [11]. However, due to the lack of typical clinical manifestations and specific symptoms in the early stage of myocardial injury, and as a special group, neonatal examination is often limited, so it is easy to be misdiagnosed [12].

At present, the detection of cardiac biomarkers in children with suspected myocardial injury mainly includes myocardial enzymes and troponins. Myocardial enzymes (AST, LDH, CK, and CK-MB) can reflect the integrity of cardiomyocytes, but they exist in a variety of tissues and organs in vivo. Although the sensitivity is high, their specificity is not high. Among them, CK-MB mainly exists in the cytoplasm of cardiomyocytes, with few in skeletal muscle cells and brain cells. Therefore, CK-MB has relatively good specificity and is recognized as a better index for diagnosing myocardial injury [13]. Cardiac troponin is a group of proteins related to cardiac contractile function and consist of cTnI, cTnT and cTnC [14]. Among them, CTnI and cTnT have high myocardial specificity and sensitivity. Compared with CK-MB, cTnI and cTnT have longer window period, higher specificity and sensitivity, and were regarded as ideal

Table 5. ROC curve analysis of each biomarker for differentiating the myocardial damage in neonates with asphyxia

Biomarker	AUC	P	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
AST	0.652	0.322	> 62.4	73%	65%	74%	62%	69%
LDH	0.588	0.602	> 922.6	69%	61%	72%	58%	66%
CK	0.557	0.564	> 1022.3	67%	61%	71%	56%	65%
CK-MB	0.727	0.014	> 135.4	57%	95%	82%	74%	78%
cTNT	0.698	0.021	> 112.6	61%	94%	74%	72%	74%
cTNI	0.752	0.009	> 55.3	58%	96%	91%	75%	81%

AST, Aspartate Aminotransferase; LDH, Lactate Dehydrogenase; CK, Creatine Kinase; CK-MB, Creatine Kinase Isoenzyme MB; cTNT, serum Cardiac Troponin T; cTNI, serum Cardiac Troponin I.

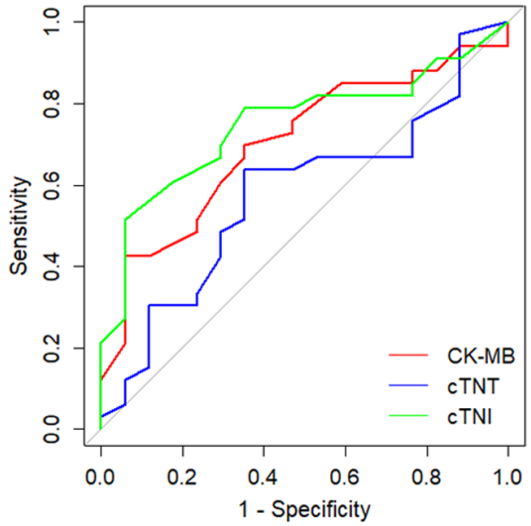

Figure 3. Receiver operating characteristic (ROC) curve of CK-MB, cTNT, and cTNI. CK-MB, Creatine Kinase isoenzyme MB; cTNT, serum Cardiac Troponin T; cTNI, serum Cardiac Troponin I.

markers for clinical detection of early myocardial injury [15, 16]. However, both CK-MB and troponins usually rise a few hours after the onset of symptoms, making it impossible to diagnose myocardial injury immediately through these biomarkers [17].

In recent years, the clinical application value of neonatal umbilical cord blood enzymology analysis has gradually attracted the attention of perinatal medicine [18-20]. Studies have reported that umbilical cord blood myocardial enzymes in neonates with intrauterine distress are significantly increased [21]. Umbilical cord blood CK-MB and cTnT could be used as important indicators to monitor neonatal myocardial injury [22]. As the most simple and noninvasive screening method, cord blood can be used to detect fetal myocardial enzymes for early detection of myocardial injury, which is helpful to improve the quality of life of newborns with myocardial damage. However, due to the different detection methods, reagents and ranges in previous studies [23, 24], so far, there is no unified standard for umbilical cord blood enzymological indexes in diagnosing myocardial injury in asphyxia newborns.

In this study, we investigated the clinical manifestation, ECG and echocardiography result, especially the cord blood myocardial enzyme and troponin levels in newborns suffered from asphyxia. We found that all cases in the asphyxia group had different degrees of clinical manifestations of myocardial injury, as well as ECG and echocardiography abnormalities. Cord blood AST, LDH, CK, CK-MB, cTNT and cTNI levels in asphyxia newborns were all significantly higher than that in controls. 28 cases (56%) in the asphyxia group were diagnosed with myocardial damage. These results were consistent with previous reports that neonatal asphyxia can cause serious damage to fetal heart and other organs [25, 26].

Our results also demonstrated that in the asphyxia group, the six biomarkers in newborns with myocardial damage were significantly higher than that in newborns without myocardial damage. Most importantly, ROC curve analyses indicated that cord blood CK-MB, cTNT, and cTNI had significant discriminatory ability and could correctly predict myocardial injury in newborns suffered from asphyxia. Except for AST, the sensitivity of indicators examined in this study were all relatively low. However, the PPV, NPV, accuracy, and especially the specificity of CK-MB, cTNT, and cTNI were all considerably

higher than that of other indicators. We further calculated the optimal cutoff values of these biomarkers for diagnosing myocardial injury in asphyxia newborns. Notably, all neonates without myocardial injury in the asphyxia group were diagnosed as negative according to the levels of CK-MB, cTNT, and cTNI, which suggested a low false positive rate. These results were consistent with previous reports that CK-MB, cTnT, and cTnI were all valuable diagnostic markers of myocardial injury [27-29]. Besides, our results provided the potential for early noninvasive diagnosis of myocardial injury in asphyxiated newborns using these biomarkers.

There are some limitations in the present study. Firstly, the number of cases is small, and it is a single center sample, so its representativeness needs to be further verified in the later multi center large sample study; secondly, the study period was relatively short, and a longer follow-up time is needed to verify our findings.

In conclusion, our results demonstrated that cord blood AST, LDH, CK, CK-MB, cTNT and cTNI levels were significantly increased in newborns with perinatal asphyxia. ROC curve analysis showed that cord blood CK-MB, cTNT, and cTNI had significant discriminatory ability for myocardial injury in newborns suffered from asphyxia. Umbilical cord blood test, as the most simple and noninvasive screening method, could be used for early prediction of myocardial injury in asphyxia newborns.

Disclosure of conflict of interest

None.

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