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Observational Study

Correlation of Cardiac Troponin T levels with inotrope requirement, hypoxic-ischemic encephalopathy, and survival in asphyxiated neonates

Cardiac Troponin T in neonatal asphyxia

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Abstract

BACKGROUND

Cardiac involvement in neonates with perinatal asphyxia not only complicates perinatal management but also contributes to increased mortality.

AIM

We aimed to assess Cardiac Troponin T (cTnT) levels in asphyxiated neonates and their correlation with echocardiography findings, inotrope requirement, hypoxic-ischemic encephalopathy (HIE) stages, and mortality.

METHODS

cTnT levels, echocardiographic findings, the requirement of inotropes, HIE stages, and outcome were studied in neonates of gestational age \geq 34 wk with

perinatal asphyxia.

RESULTS

Among 57 neonates with perinatal asphyxia, male gender, cesarean section, forceps/ vacuum-assisted vaginal delivery and late preterm included 33(57.9%), 23(40.4%), 3(5.3%), and 12(21.1%) respectively. The mean gestational age was 38.4 wk (1.6 wk). HIE stages I, II, and III were observed in 7 (12.3%), 37 (64.9%), and 9 (15.8%) neonates respectively. Twenty-six (45.6%) neonates had echocardiographic changes and 19 (33.3%) required inotropes. cTnT levels were elevated in 41(71.9%) neonates [median (IQR); 0.285(0.211-0.422)ng/mL]. The Median cTnT level showed an increasing trend with increasing changes in echocardiography (P = 0.002). Two neonates with mitral regurgitation and global hypokinesia had the highest cTnT levels (1.99 & 0.651ng/mL). Of 31 neonates with normal echocardiography, 18(58.06%) showed elevated cTnT. cTnT levels were significantly higher in those who required inotropic support than those who did not (P = 0.007). Neonates with HIE stage III had significantly higher cTnT levels compared to those with HIE stage I/II (P = 0.013). Survivors had lower median cTnT levels [0.210(0.122-0.316)ng/mL] than who succumbed [0.597(0.356-1.146)ng/mL].

CONCLUSION

cTnT levels suggestive of cardiac involvement were observed in 71.9% of asphyxiated neonates. cTnT levels correlated with echocardiography findings, inotrope requirement, HIE stages, and mortality.

Key Words: asphyxia; Cardiac dysfunction; inotropes; neonates; troponin T; survival

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Core Tip: Cardiac involvement in perinatal asphyxia complicates the management and increases mortality. We assessed cTnT levels in asphyxiated neonates and their correlation with echocardiography findings, hypoxic-ischemic encephalopathy (HIE) stages, and mortality. Elevated cTnT levels suggestive of cardiac involvement were found in 71.9% of neonates and correlated with increasing grades of ischemic changes in echocardiography. cTnT levels were elevated in 58% of neonates in the absence of echocardiographic findings. Significantly higher cTnT levels in neonates with HIE stage III than those with HIE stage I and II as well as higher cTnT levels in non-survivors than survivors show its predictive role.

INTRODUCTION

The myocardium is vulnerable to ischemic injury in asphyxiated neonates.¹⁻⁵ Perinatal asphyxia causes significant morbidity and mortality, especially in developing countries.⁶⁻⁹ The cardiac involvement in perinatal asphyxia varies. The reported asphyxial cardiomyopathy in neonates ranges from 24-78%.³⁻⁶ Ischemic cardiac dysfunction results in decreased cardiovascular reserve. The affected neonates may present with myocardial failure, bradycardia, and hypotension along with morbidities related to other systems. The assessment of the extent of myocardial injury and appropriate management influence treatment and outcome. Clinical assessment alone is considered inadequate to guide management or predict the outcome. Serum CK-MB lacks cardiac

specificity in the neonate and the levels are affected by gestational age, mode of delivery, and birth weight. CK-MB levels were reported to be 2 to 5 times higher in neonates born by normal vaginal delivery as compared to those born by cesarean section². Echocardiography helps in identifying the extent of cardiac dysfunction but needs expertise.

Cardiac troponin T (cTnT) has been explored as a more specific biomarker for the diagnosis of myocardial injury in asphyxiated neonates. ^{10, 11} Troponin T can be detected at earlier stages than CK-MB and it also remains high for a longer period.¹⁰ Further, cTnT levels are found to be elevated in 30-50% of cases having normal CK-MB levels². The levels also may correlate with mortality. In this context, we aimed to evaluate the role of cTnT in perinatally asphyxiated neonates as a marker of myocardial injury and assess its correlation with inotrope use, hypoxic-ischemic encephalopathy (HIE), and mortality.

MATERIALS AND METHODS

Neonates of gestational age ≥ 34 wk with perinatal asphyxia were prospectively studied over two years in a neonatal intensive care unit of a University teaching hospital. The demographic and birth details, clinical examination data were collected. cTnT levels, echocardiographic findings, the requirement of inotropes, evidence of other system involvement, HIE in particular, and outcome were collected.

About 0.5 mL of blood collected using standard sampling tubes (BD red vacutainers) was processed for estimation of cTnT levels. Biochemical analysis of cTnT levels in this study was done with an Elecsys 2010 and Cobas e 411 analyzer using the Elecsys Troponin T hs (high sensitive) STAT (short turnaround time) Immunoassay (Roche Diagnostics, Germany). This is an

electrochemiluminescent sandwich enzyme-linked immunosorbent assay. The total duration of the assay is 9min. The lower limit of detection is 3ng/L or 3pg/mL, if the values are below this level it was reported as <3ng/L. The upper limit of detection is 10000ng/L or 10000pg/mL, if the values are above this level it was reported as >10000ng/L or up to 100000ng/L for the 10-fold diluted sample. The kit specifications include the sensitivity of 99% and specificity of 98% at 100ng/L and, the sensitivity of 100% and specificity of 75% at 14ng/L. Normal values for cTnT: Interquartile Range: 0.01–0.062 /mL⁶³, 95th centile: 0.153 ng/mL⁶³, 99th centile: 0.244ng/mL⁸⁹. For the study purpose, cTnT levels of more than 0.15ng/mL were considered elevated.

Neonate was considered to have perinatal asphyxia if he/she met any of the following criteria: need of bag and mask or bag and tube ventilation at birth with Apgar score of \leq 6 at 5 minutes; hypoxic encephalopathy features (lethargy, seizures, hypotonia, coma or irritability); cord blood pH \leq 7.0, or arterial pH in neonates \leq 7.2. Neonates with congenital heart defects, major anomalies, and those who expired within the first hour of birth were excluded. HIE was considered in asphyxiated neonates if they had neurologic manifestations (seizures, coma, hypotonia). HIE was divided into Sarnat stages 1, 2, and 3 based on standard clinical features.^{3, 4, 12} Heart rate <100/min was considered bradycardia. Systolic and or diastolic blood pressure (BP) equal to or lower than the 5th percentile for age and sex was considered hypotension. Capillary filling time (CFT) > 3 s was considered as increased CFT.

Echocardiograph was obtained with the "Philips CX-50" machine. Following echocardiographic findings were considered as suggestive of myocardial ischemia: mitral regurgitation (MR) or right ventricular (RV) /Left ventricular (LV)/global hypokinesia, tricuspid regurgitation (TR), and pulmonary artery hypertension (PAH) with TR.² Renal dysfunction was considered if creatinine

level was more than the upper limit of the normal reference range for gestational age with or without urine output <1 mL/kg/hour.² Transaminase levels more than twice the normal levels (normal aspartate transaminase (AST) up to 40U/L and alanine transaminase (ALT) up to 45U/L) were considered as hepatic dysfunction.

The results are expressed as frequencies and percentages. Data were analyzed using SPSS v16.0 software. Differences in the median of quantitative data among different stages of HIE and echocardiographic changes were compared by Kruskal- Wallis test and proportions by Chi-Square tests. A 'p' value of <0.05 was considered statistically significant. Ethical approval was obtained from the Institutional Ethical Committee. Informed consent was obtained from the parents.

RESULTS

This study included 57 neonates with perinatal asphyxia (Figure 1). Male gender, lower segment cesarean section (LSCS), forceps or vacuum-assisted vaginal delivery, and late preterm included 33(57.9%), 23(40.4%), 3(5.3%), and 12(21.1%) respectively. The mean gestational age was 38.4 ± 1.6 wk.

Mode of resuscitation at birth included intubation in 26(45.6%) and bag and mask ventilation in 15(26.3%). Organ involvement in perinatal asphyxia included brain in 53(93%), hepatic in 35(61.4%), renal in 26(45.6%), and cardiac in 30(52.6%). Mechanical ventilation was needed in 20(35.1%) neonates. HIE stage 1, 2 and 3 were observed in 7 (12.3%), 37 (64.9%) and 9 (15.8%) neonates respectively. Four neonates did not have HIE. Six neonates died.

Of 57 asphyxiated neonates, 26 (45.6%) neonates had echocardiographic changes. Mitral regurgitation with global hypokinesia was observed in two

(3.5%) neonates. Inotropic support was required in 19 (33.3%) neonates. Elevated cTnT levels were observed in 41(71.9%) neonates studied, with median (IQR) of 0.285(0.211-0.422) ng/mL. The maximum value observed was 1.99ng/mL. (Table1)

The median cTnT level showed an increasing trend with the increase in changes in echocardiography (P = 0.002 Kruskal Wallis Test) (Table 2). Mitral regurgitation with global hypokinesia was observed in two neonates with high cTnT levels (1.99, 0.651ng/mL) who eventually succumbed. Of 31 neonates with normal echocardiography findings, 18(58.06%) cases had elevated cTnT levels. cTnT levels in those who required inotropic support were significantly higher when compared to those who did not require inotropic support (P = 0.007, Chi-Square test) (Table 3).

Neonates who had HIE stage III had significantly higher levels of cTnT levels when compared to neonates with HIE stage I and II (P = 0.013 Kruskal-Wallis test) (Table 4). Six out of these 9 neonates with HIE stage III, having much higher cTnT levels succumbed.

Six neonates among 57 enrolled with perinatal asphyxia died. Median cTnT levels in those who survived were 0.210(0.122-0.316)ng/mL which is comparatively lower than the median cTnT level in those who succumbed [0.597(0.356-1.146)ng/mL] (Table 5).

DISCUSSION

Cardiac involvement secondary to tissue ischemia in neonates with perinatal asphyxia can occur as a part of a multi-organ involvement or isolated cardiac event. 12-16 Myocardium involvement not only complicates perinatal management but also increases mortality. The present study has identified the significant role of cTnT levels in identifying cardiac involvement, its correlation

with echocardiography findings, inotrope requirement, HIE stages, and mortality.

In severely asphyxiated infants, cardiac dysfunction more commonly affects the right ventricle. The various manifestations related to cardiac dysfunction are respiratory distress, congestive cardiac failure, hypotension, delayed capillary refilling time, bradycardia, cardiogenic shock, and systolic murmur due to mitral regurgitation and tricuspid regurgitation. 8, 17 Sinus bradycardia and lowered systemic blood pressure are commonly seen in neonatal hypoxic ischemia. These features are observed in the present study. Costa et al looked at blood pressure in asphyxiated newborns. They observed significantly lower systolic and diastolic blood pressures in asphyxiated neonates compared to control newborns. 18 Hypotension is a late sign of under-perfusion.

Hypotension is often due to peripheral vasodilatation or poor cardiac output. de Dios et al studied cardiac involvement (n = 31) in 156 asphyxiated term neonates. They categorized dysrhythmias and mild hypotension as minor cardiac involvement and tricuspid regurgitation, myocardial ischemia, cardiogenic shock, or hypovolemic shock as major cardiac involvement. 19 Echocardiography certainly could guide the management of these infants about fluid resuscitation and choice of inotropic support. Echocardiography is helpful in the early identification of tricuspid insufficiency, compromised left ventricular output, and stroke volume in infants who suffer from perinatal asphyxia. Echocardiographic findings such as regional wall abnormalities, increased echogenicity of papillary muscle, compromised left ventricular function, and tricuspid or mitral valve insufficiency resulting in reduced contractility, low cardiac output, decreased stroke volume, and elevated pressure of pulmonary artery suggest myocardial ischemia. 17, 19 The mitral valve insufficiency and patent ductus arteriosus correlate with severe degrees

of asphyxia injury. Tricuspid insufficiency was observed significantly at a higher rate in asphyxiated neonates than healthy neonates and it was more frequent with increasing severity of asphyxia.¹⁸ Most of these features were observed as the main findings in echocardiography in the present study.

In asphyxiated neonates, despite preferential myocardial perfusion, hypoxia leads to myocardial damage. If ischemia progresses, especially beyond 20 minutes, over 60% of the cellular adenosine triphosphate will be used up, lactate in myocardial tissue increases about 12 times, glycogen and creatine phosphate reserves decrease resulting in dramatic structural changes. ^{10, 20, 21} This also causes damage to the cell membrane and releases creatinine kinase muscle-brain isoenzyme (CK-MB) and cTnT into the bloodstream. CK-MB levels although significantly elevated in asphyxiated infants they do not appear to discriminate well those infants with cardiovascular compromise. ^{10, 21} The highest levels occur at 12 h following birth and the levels decrease by 48 h of life.²⁰

The structure of troponin T is unique to the myocardium. Troponin concentration in the myocardium is much higher compared to CK-MB. In healthy humans, troponin levels in plasma are negligible. The troponin levels raise within a few hours after the acute ischemic episode and remain high for 10–14 days. This increases the diagnostic time range.²

The present study has identified elevated cTnT levels in 71.9% of asphyxiated neonates and established a correlation of these levels with echocardiographic findings. Costa et al reported significantly higher cTnT in neonates having echocardiograph signs of myocardial damage.¹⁸ They also found that cTnT

levels in neonates suffering from asphyxia with echocardiography changes were higher compared with those of normal newborns. Tricuspid regurgitation was observed in all asphyxiated neonates. The cTnT levels ≥ 0.21 ng/mL had a significant association with abnormal echocardiographic findings. This cTnT level had 100% specificity and 39% sensitivity. The authors suggested the cTnT 0.19 ng/mL as the differentiating cut-off level. In the present study, all neonates with echocardiographic findings of asphyxia had cTnT levels beyond this cut of value. The two neonates with global hypokinesia on echocardiograph had the highest cTnT levels and both of them died.

Myocardial dysfunction also impacts cerebral hemodynamics and decreases cerebral perfusion.22-25 Cerebral hemodynamic disturbances such as a decreased rate of flow of blood including the velocity of highest systolic blood flow and velocity of blood flow at the end of diastole, raised index of pulsatility and resistance observed among neonates suffering from perinatal asphyxia are more frequent in infants who have cardiac dysfunction affecting the left ventricle. In the present study, neonates with HIE stage 3 had the highest cTnT levels. Higher cTnT levels in neonates with HIE and its correlation with mortality was also reported by Bhasin et al 24 The limitation of the present study includes not analyzing the values of cTnT during therapeutic hypothermia and its changes as a prognostic marker of the final outcome.

CONCLUSION

Elevated cTnT levels suggestive of cardiac involvement in 71.9% of asphyxiated neonates establish its importance. The cTnT levels correlate with an increasing grade in echocardiography findings. Elevated cTnT levels in 58% of neonates with normal echocardiography findings suggest its biomarker role even in the absence of echocardiographic findings. Elevated cTnT levels in neonates with

HIE stage III being significantly higher than those with HIE stage I and II show its predictive role. cTnT levels in non-survivors are likely to be much higher than those among survivors.

ARTICLE HIGHLIGHTS

Research background

The myocardial ischemic injury in asphyxiated neonates complicates management and may lead to higher mortality. Cardiac troponin T (cTnT) levels are expected to rise early in myocardial ischemia and remain high for about two weeks.

Research motivation

cTnT levels are better markers than Serum CK-MB levels and could be predictive of mortality

Research objectives

The present study determined cTnT levels in asphyxiated neonates and found out its relationship with echocardiography findings, inotrope requirement, hypoxic-ischemic encephalopathy (HIE) stages, and mortality.

Research methods

cTnT levels are estimated in all asphyxiated neonates along with echocardiography evaluation

Research results

Among asphyxiated neonates, cTnT levels were elevated in 71.9%. Further, the cTnT levels correlated with increasing grades of ischemic changes in

echocardiography. Elevated cTnT levels in 58% of neonates with normal echocardiography findings suggested its role as a biomarker. cTnT levels in neonates with HIE stage III were significantly higher than those with HIE stage I and II. cTnT levels were higher in non-survivors than survivors.

Research conclusions

cTnT could be a potential and clinically useful biomarker for asphyxia related myocardial injury in neonates

Research perspectives

Further studies to determine the exact cut of levels of cTnT predicting mortality are needed

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Footnotes

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STROBE statement: The authors have read the STROBE Statement—a checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—a checklist of items.

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Figure Legends

Figure 1. Study flow chart