Original Research Paper

Volume - 13 | Issue - 10 | October - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Neonatology

# ROLE OF CARDIAC TROPONIN I CONCENTRATIONS IN ASSESSING MYOCARDIAL DYSFUNCTION AND PREDICTING THE NEUROLOGICAL OUTCOME AND SEQUELAE IN NEONATES ≥ 36 WEEKS WITH BIRTH ASPHYXIA

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**ABSTRACT** HIE is caused by prolonged perinatal asphyxia which may lead to affecting the functioning of multiple organs causing impairment or even death. HIE stands as one of the most common etiology for neurological consequences and neonatal death.This study aims to assess the prognostic ability of Cardiac Troponin I in assessment of Myocardial dysfunction and predicting neurological outcome. A total of 84 infants have been enrolled and categorised accordingly depending on different grades of HIE based on NICHD assessment. Cardiac troponin I concentration levels were measured at baseline, in patients belonging to all three grades of HIE, and the levels were investigated in abnormal patients as assessed by Echo findings and Hammersmith neurological examination for neonates at 14 days after birth and for infants at 3 months after birth. ROC curve analysis was also performed to determine it's prognostic value as a biomarker for neurological sequelae and its outcome. All the observations from the study suggested Cardiac Troponin I can be used as reliable and clinically significant biomarker for assessing the Myocardial Dysfunction and as a fairly independent biomarker for neurodevelopmental outcome and sequelae in patients having HIE.

**KEYWORDS :** Hypoxic-Ischemic Encephalopathy, Cardiac Troponin I, Myocardial dysfunction.

## INTRODUCTION

Birth asphyxia is the leading cause for neonatal mortality and morbidity.The shortage of oxygen in the body initiate cascade of events like cell necrosis and death leading to hypoxic- ischemic encephalopathy HIE. HIE can cause Multiorgan dysfunction affecting the vital organs like Brain, heart, liver , kidney, hemopoietic system causing altered conscious state, absence of primitive reflexes, instability in autonomic system, seizures, liver and renal impairments, decreased cardiac output. Early prediction of the outcomes following perinatal asphyxia is necessary to identify babies at higher risk resulting in neurological sequelae and limit the damage.

Clinical assessment of hypoxic-ischaemic encephalopathy (HIE) with a scoring system is currently the simplest cot-side method for predicting neurological outcomes in asphyxiated infants.[4] Babies with mild HIE usually have a good prognosis, however, those with severe HIE usually show poor outcomes.[5] The outcome of babies with moderate HIE varies depending on the duration and persistence of the signs of encephalopathy. In some cases, the signs of encephalopathy may persist longer. Babies with signs lasting more than seven days are at a greater risk of neurodevelopmental problems

In this clinical study we studied the prognosis of Cardiac Troponin I as potential Cardiac biomarker for the Myocardial Dysfunction and neurological outcome and its sequelae resulting from neonatal HIE. Cardiac Troponin I levels in blood are very low for the new borns (<30 pg/mL). But incase of any cardiac injuries or Myocardial Ischemia the levels can significantly increase. Early elevation of Cardiac troponin I in asphyxiated neonates is a predictor for Myocardial dysfunction. Presence of Echo findings with early elevation in levels of Cardiac troponin -I correlates with Myocardial dysfunction. In this study a significant direct relationship was observed between Cardiac Troponin-I concentration levels and grades of HIE and this study also aims to establish its prognostic value as a predictor for neurological sequelae in HIE patients.

## MATERIALS AND METHODS

### Study Design and Setting

This was an observational correlational clinical study carried on from September 2016 to march 2017 at Department of neonatology, Madras Medical College (MMC), Chennai. Also involved are out-born unit of Institute of Child health and hospital for children (part of MMC) and inborn unit of Institute of Obstetrics and Gynaecology, Chennai (part of MMC). A written consent of willingness for enrolment of the infants in the study was obtained from the parents / care-givers of the infants selected. All 84 infants selected belonged to any of the three stages of Hypoxemic ischemic encephalopathy (HIE).

### Eligibility

All new borns admitted in the intramural and extramural, with perinatal asphyxia were eligible for this study

### Inclusion Criteria

Neonates born at ≥36 weeks of gestation and of >1800 g birth-weight, and with perinatal asphyxia were eligible. Perinatal asphyxia in patients born at the study hospital was defined as the need for resuscitation at birth, along with the presence of one or more of the following:

1. Apgar score of <6 – at 5 min after birth,
2. Continued need for resuscitation, for > 5 mins
3. umbilical cord pH or any arterial pH of <7.00 within 60 mins of birth, and base deficit of >16 mmol/L within 60 mins of birth

Written consent was obtained from the parents/caregivers of the infants selected for willingness for enrolment in the study (Annexure I).

### Exclusion Criteria

1. Neonates with major congenital anomalies
2. Neonates presenting after 24 hours of birth
3. Neonates enrolled in the therapeutic Cooling Study

Primary outcome measure is to study the correlation between Cardiac Troponin- I and Echo findings and Hammersmith neurological examination in predicting the neurological outcomes (survival with sequelae) at 14 days or later after birth asphyxia and at three months of age.

### Non-parametric Setting For Qualitative Data Analysis

Pearson correlation between study variables is performed to find the degree of relationship, Pearson correlation co-efficient ranging between -1 (weak correlation) to 1 (strong correlation) between two biomarkers. The stronger the correlation, stronger is the ability to influence the other biomarker with which there is a correlation.

Classification of Correlation Co-efficient ®

| | |
|---|---|
| Up to 0.1 | Trivial Correlation |
| 0.1-0.3 | Small Correlation |
| 0.3-0.5 | Moderate Correlation |
| 0.5-0.7 | Large Correlation |
| 0.7-0.9 | V.Large Correlation |
| 0.9- 1.0 | Nearly Perfect correlation |
| 1 | Perfect correlation |

ROC curve analysis is performed to find the predictability of study variables (biomarkers) in prognosis of advanced HIE stage. The biomarkers with higher sensitivity and specificity, PPV (Positive Predictive Value) and NPV (Negative Predictive Value) suggest their correlation beyond their individual cut-off values to be prognostic markers for the neurological sequelae. Diagnostic markers based on Area under curve AUROC signifies the following result –

| | |
|---|---|
| 0.9 - 1.0 | Excellent test |
| 0.8 - 0.9 | Good test |

| | |
|---|---|
| 0.7 - 0.8 | Fair test |
| 0.6 - 0.7 | Poor test |
| 0.5 - 0.6 | Fair |

**Statistical Methods**

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean+ SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

The following assumptions on data are made

1. Dependent variables should be normally distributed,
2. Samples drawn from the population should be random,
3. Cases of the samples should be independent

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

## RESULTS AND DISCUSSION

84 infants with a gestation age of > 36 weeks of gestation were included in the study. 19% (16/84) of infants were delivered through LSCS mode of delivery while the remaining infants delivered through normal route. 90% (76/84) of infants are of birthweight 2.5kg-3.5kg and 79 infants were AGA. Respiratory support was given 79 infants.

**Demographic Data Of The Patients**

Patients enrolled are of both genders – 35 male and 49 female. 39/84 patients were of gestational age less than 38 weeks. Except 8 neonates who are below 2500g, remaining 76 neonates enrolled have a birth weight between >2500g and 3500g. Only five were small for gestational age. 79 neonates required respiratory support on admission (CPAP or mechanical ventilation or O2). Oxygen saturation was still less than 90 in case of 42 neonates upon admission and in 76 neonates mean arterial pressure upon admission is <30 mm to 40 mm of Hg. Upon admission, patients were categorized based on the severity of encephalopathy – 34 patients were assessed mild (HIE1), 37 were assessed moderate (HIE2) and 13 were assessed severe (HIE3). All three grades of encephalopathy are identified among neonates upon admission – 34 neonates with mild encephalopathy (HIE1), 37 neonates with moderate encephalopathy (HIE2), 13 neonates with severe encephalopathy (HIE3). All patients were assessed with APGAR score at 1 minute as <7 and at 5 minutes the score is <7 in 28 patients. Around 54% of patients in both HIE2 and HIE3 groups still have APGAR score <7 at 5 min. The demographic data is summarized in Table 1.

**Table 1 Demographic Data**

| | Final Diagnosis | | | P value |
|---|---|---|---|---|
| | HIE 1 (n=34) | HIE 2 (n=37) | HIE 3 (n=13) | |
| Gender | | | | |
| • Female | 24(70.6%) | 19(51.4%) | 6(46.2%) | 0.162 |
| • Male | 10(29.4%) | 18(48.6%) | 7(53.8%) | |
| Gestation age (weeks) | | | | |
| • 36-37 | 19(55.9%) | 12(32.4%) | 8(61.5%) | 0.070+ |
| • 38-40 | 15(44.1%) | 25(67.6%) | 5(38.5%) | |
| Birth weight (g.) | | | | |
| • <2500 | 7(20.6%) | 1(2.7%) | 0(0%) | <0.001* |
| • 2500-3000 | 21(61.8%) | 17(45.9%) | 9(69.2%) | * |
| • 3000-3500 | 6(17.6%) | 19(51.4%) | 4(30.8%) | |
| Mode of delivery | | | | |
| • LSCS | 0(0%) | 11(29.7%) | 5(38.5%) | <0.001* |
| • Vaginal | 34(100%) | 26(70.3%) | 8(61.5%) | * |
| APGAR score 1 min. | | | | |
| • <7 | 34(100%) | 37(100%) | 13(100%) | 1.000 |
| • >7 | 0(0%) | 0(0%) | 0(0%) | |
| APGAR score 5 min. | | | | |
| • <7 | 1(2.9%) | 20(54.1%) | 7(53.8%) | <0.001* |
| • >7 | 33(97.1%) | 17(45.9%) | 6(46.2%) | * |
| Cord ABG (pH, Base deficit) | | | | |
| • <6.8 | 0(0%) | 0(0%) | 0(0%) | <0.001* |
| • 6.8-7.2 | 20(58.8%) | 26(70.3%) | 13(100%) | * |
| • >7.2 | 14(41.2%) | 11(29.7%) | 0(0%) | |
| Severity of encephalopathy @ admission (NICHD assessment) | | | | |
| Mild | 34(100%) | 0(0%) | 0(0%) | <0.001* |
| Moderate | 0(0%) | 37(100%) | 0(0%) | * |
| Severe | 0(0%) | 0(0%) | 13(100%) | |

** Chi-Square test/Fisher Exact test

At base line, blood samples were taken upon admission and after 24 hrs and 72 hrs to analyse for Cardiac troponin I concentrations. ECHO for myocardial dysfunction and Hammersmith neurological examination have been done. Baseline investigations of the biomarker are presented in table 2.

**Table 2: Baseline Investigation Of Cardiac Troponin-I**

| Marker | Upon admission** | | | 24 hrs after admission** | | | 72 hrs after admission** | | |
|---|---|---|---|---|---|---|---|---|---|
| | HIE 1 | HIE 2 | HIE 3 | HIE 1 | HIE 2 | HIE 3 | HIE 1 | HIE 2 | HIE 3 |
| Cardiac troponin I | 0.04 ±0.00 | 0.05 ±0.01 | 0.07 ±0.01 | 0.04 ±0.00 | 0.06 ±0.02 | 0.08 ±0.01 | 0.04 ±0.00 | 0.04 ±0.00 | 0.07 ±0.02 |

P<0.001**, ANOVA test, P=0.03*

Cardiac troponin I levels are correlated to the severity of HIE. Increase in the levels was observed from HIE 1 to HIE 2 and HIE 3.On admission patients in HIE grade 3 have 75% more levels of Cardiac Troponin I than HIE grade 1 patients. On observation at 24hrs after admission patients with grade 2 HIE and grade 3 HIE have 50 % and 100% increase in concentration levels of Cardiac troponin I respectively from HIE grade 1. Further after 72hrs of admission Cardiac troponin I levels have 75% increase in concentration from HIE 1 to HIE 3. Significant increase in the levels were observed as the severity of HIE increases. Across all the individual groups the mean concentration levels of Cardiac Troponin levels remained constant with increase in time. The levels were observed to be more or less constant from admission to after 24 hrs to 72 hrs after admission among individual groups.

To observe these patients and to assess prognostic value of the Cardiac Troponin-I in predicting neurological sequelae, blood samples were again taken for neonates after 14 days and infants at 3 months of age, and were observed for Cardiac troponin, the biomarker of interest in the current study. The mean serum concentrations (with standard deviation) of Cardiac Troponin- I were studied in normal and abnormal subjects as assessed by ECHO findings (possibility of myocardial dysfunction) during final diagnosis.

Cardiac Troponin I have been measured in normal and abnormal patients as assessed by Hammersmith neurological examination to understand the possible correlation to predict neurological outcomes with such assessment of the biomarker.

**Table 3: Cardiac Troponin I In Relation To ECHO Findings**

| Cardiac troponin I | Echo Absent | Echo Present | P value |
|---|---|---|---|
| Admission | 0.04±0.01 | 0.06±0.02 | <0.001** |
| 24 hrs | 0.04±0.02 | 0.06±0.01 | <0.001** |
| 72 hrs | 0.04±0.00 | 0.05±0.02 | <0.001** |

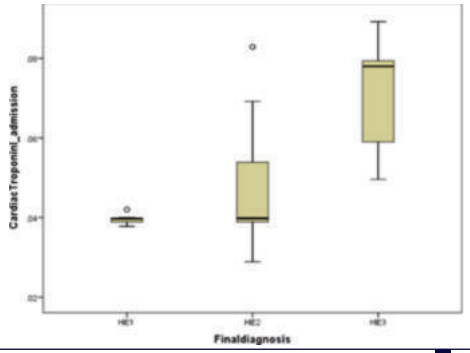


**Table 4: Cardiac Troponin I In Relation To Hammersmith Neurological Examination @ Neonates (at 14 days)**

| Cardiac troponin I | Normal | Abnormal | P value |
|---|---|---|---|
| Admission | 0.04±0.00 | 0.05±0.02 | <0.001** |
| 24 hrs | 0.04±0.00 | 0.06±0.02 | <0.001** |
| 72 hrs | 0.04±0.00 | 0.05±0.02 | 0.002** |

**Table 5: Cardiac Troponin I In Relation To Hammersmith Neurological Examination @ Infants (at 3 Months)**

| Cardiac troponin I | Normal | Abnormal | P value |
|---|---|---|---|
| Admission | 0.04±0.01 | 0.07±0.02 | <0.001** |
| 24 hrs | 0.05±0.02 | 0.07±0.01 | <0.001** |
| 72 hrs | 0.04±0.00 | 0.06±0.02 | <0.001** |

**Assessment Of Possible Correlation Of Cardiac Troponin I To Echo Findings.**

The patients with abnormal echo findings had significant elevation of mean concentration levels of Cardiac Troponin I of 50 % compared to normal infants upon admission and similarly at 24 hrs. 25 % increase is still evident after 72 hrs.It is observed that over 72 hrs period, the mean concentration of cardiac troponin levels remains constant in the normal group and decrease in the abnormal group.

**Assessment Of Cardiac Troponin I In Relation To Hammersmith Neurological Examination Of Neonates (14 Days Old) And Infants (at 3 Months Of Age).**

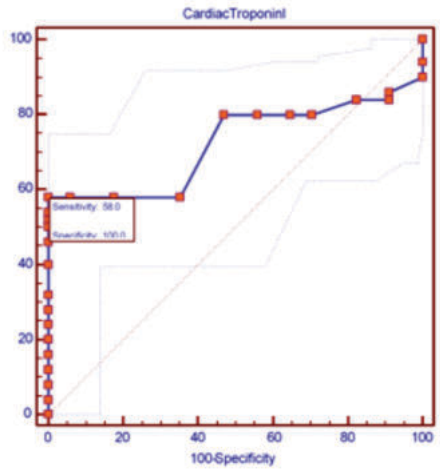
Up on admission it is observed that abnormal neonates show 25 % higher mean concentrations of Cardiac Troponin I than normal neonates which is even 50% higher at 24 hrs of admission, but still have 25% of elevation at 72 hrs in abnormal patients. At 3 months of age the mean concentration of Cardiac Troponin I is 75% high in abnormal group than the normal group up on admission and and still the same after 24 hrs of admission. There is an elevation of 50% in the levels of cardiac troponin after 72 hrs of admission as compared to patients in normal group.

**ROC Curve Analysis To Predict Advanced Stage**

ROC curve analysis was done to have sensitivity value, specificity value, the cut off value of biomarker and the AUROC (Area under ROC curve) in predicting the neurological sequelae in patients with birth asphyxia. ROC curve analysis was shown in Table 6.

**Table 6: ROC Curve Analysis**

| Variables | ROC results to predict Advanced Stage | | | | Cut-off | AUROC | SE | P value |
|---|---|---|---|---|---|---|---|---|
| | Sensitivit | Specificit | LR+ | LR- | | | | |
| Cardiac troponin I | 58.00 | 100.00 | 0.00 | 0.42 | >0.042 | 0.722 | 0.056 | <0.001** |




Cardiac troponin I had exhibited high specificity than high sensitivity and with AUROC of 0.722 makes it a fairly independent prognostic biomarker for Neurological sequelae in patients with birth asphyxia. The cutoff value of > 0.042 and p value (<0.001**) suggests Cardiac Troponin I can be used a fairly independent prognostic biomarker to predict the neurological sequelae.

## CONCLUSION

As observed during the study the mean concentration levels of Cardiac Troponin I have statistically significant correlation with severity of HIE. The severe the grade of HIE the higher concentration of Cardiac Troponin I among the patients. The patients with abnormal echo findings having high concentrations of Cardiac Troponin I before 72 hrs of admission may infer to the presence of Myocardial dysfunction. This study suggests that early elevation of Cardiac troponin -I indicates the presence of Myocardial dysfunction and its increasing levels as the time period increases may have clinical significance in predicting the increase in severity of HIE. Cardiac Troponin levels in neonates at 14 days and in infants after 3 months are observed to be high in abnormal patients , if witnessed beyond the cutoff value (> 0.042) and the AUROC analysis establishes cardiac troponin I as an fairly independent biomarker for predicting the Neurological sequelae among HIE patients. Further studying on the correlation between extent of severity of Myocardial dysfunction with the severity of HIE in relation to Cardiac Troponin I levels may have valuable clinical implications.

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