

Original Article

Relationships between Troponin I and Hypoxic–Ischemic Encephalopathy among Newborn Babies

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ABSTRACT

Background: A proper evaluation of cardiovascular status, with a view to ensuring early diagnosis of cardiac dysfunction and prompt intervention where necessary, is a recognized approach in the management of asphyxiated neonates. Hence, we determined the levels of a cardiac biomarker (troponin I), its relationship with disease severity, and mortality in asphyxiated neonates with hypoxic–ischemic encephalopathy (HIE). **Methods:** This was a descriptive study that involved 85 asphyxiated, term appropriate-for-gestational age newborn babies with HIE (subjects) and 85 healthy controls within the first 72 h of life. Asphyxiated neonates were classified into HIE stages using Sarnat and Sarnat staging. Blood samples were collected between 24 and 72 h of life to determine the level of troponin I using enzyme-linked immunosorbent assay. The asphyxiated babies were followed up till discharge or death. **Results:** The median interquartile range level of troponin I in the subjects was higher compared with the controls, 1.26 (0.97–3.16) ng/ml versus 0.79 (0.79–1.42) ng/ml, $P < 0.001$. The levels of troponin I in HIE I, HIE II, and HIE III were 1.26 (1.00–2.37) ng/ml, 1.11 (0.86–2.96) ng/ml, and 3.58 (1.34–5.58) ng/ml, respectively. Nonsurvivors had a higher cardiac troponin I (4.00 [2.30–6.34] ng/ml) compared with survivors (1.21 [0.95–2.37] ng/ml), $P = 0.015$. **Conclusion:** Cardiac troponin I was significantly higher in asphyxiated subjects compared with healthy controls. Elevated troponin I was associated with higher mortality. Troponin I levels in the first 72 h can help as a prognostic indicator of HIE in term babies.

KEYWORDS: Hypoxic–ischemic encephalopathy, mortality, newborn babies, troponin I

INTRODUCTION

Perinatal asphyxia is a major public health problem, contributing 11.0% of under-five mortality (5.3 million) and 23.4% of neonatal death (2.5 million) in 2019.^[1] Despite the burden of perinatal asphyxia, there has been an improvement in the outcome of asphyxiated babies with the use of therapeutic hypothermia in several studies.^[2]

Perinatal asphyxia been a multisystemic disorder is faced with the challenges of appropriate diagnostic and prognostic indicators. Clinical assessment, serial level of cardiac enzyme, and other bedside laboratory indicators may assist in the early diagnosis and prognostication.

Cardiac dysfunction is one of the complications that could follow perinatal asphyxia. It is a late event as the heart receives preferential blood supply in the early phase of asphyxia.^[3] Cardiac enzymes are increasingly being used as a reliable marker of cardiac injury in the neonatal period, with the major benefit of being an early indicator of cardiac injury.^[4] Their roles complement clinical evaluation, electrocardiography, and echocardiography and are especially valuable

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as screening tools following myocardial injury in diverse settings.^[5,6] Troponin I is a highly sensitive and specific biomarker for diagnosing microscopic cardiac injury that is released early in response to myocardial ischemia.^[7,8] It is a significant prognostic tool in perinatal asphyxia.^[9,10] Troponins appear in blood 4–6 h after perinatal asphyxia with cardiac compromise. It peaks between 18 and 24 h and remains elevated for up to 21 days.^[8] However, there are limited studies on cardiac morbidity following perinatal asphyxia, especially in developing countries where perinatal asphyxia constitutes a major burden.^[11] Furthermore, the effects of cardiac dysfunction on survival have not been adequately explored. In view of the disease burden and aforementioned gaps in knowledge of cardiac function in perinatal asphyxia, this study determined the level of troponin I and its relationship with disease severity and survival in newborn babies with hypoxic–ischemic encephalopathy (HIE).

METHODS

This was a descriptive study of troponin I in term appropriate-for-gestational age (AGA) asphyxiated newborn babies with HIE as subjects and nonasphyxiated healthy babies <72 h of age as controls. We conducted this study at the neonatal intensive care unit (NICU) and postnatal ward of the hospital, a tertiary health facility in North-Central Nigeria.

Sample size

A sample size of 170 was calculated (85 each for subjects and controls) using the formula for comparison of two means.^[9] Hence, a total of 170 newborn babies consisting of 85 asphyxiated babies with HIE (subjects) and an equal number of age-matched healthy nonasphyxiated babies (controls) were recruited over a period of 7 months.

This study included AGA newborn babies with at least Stage I HIE, defined by Sarnat and Sarnat, admitted into NICU within 24 h of life. The controls included term AGA chronological and gestational age-matched nonasphyxiated healthy neonates with 5th-min Apgar score ≥ 7 or a history of cry immediately after birth and required no active resuscitation. These babies were recruited between 24 and 72 h of life.

This study excluded babies with clinical suspicion of congenital heart disease, major congenital anomalies, history of risk for sepsis, clinical suspicion of sepsis, and maternal use of medication such as diazepam and opioids within 24 h of delivery.

Recruitment procedure

The study subjects were recruited from the NICU whereas the controls were recruited from the postnatal wards of the hospital. Consecutive term neonates with HIE admitted into the NICU within 24 h of life and fulfilled the study inclusion criteria were recruited after obtaining a written informed consent from the parent or caregiver. All the babies were assessed using Sarnat and Sarnat staging at presentation and thereafter daily. The highest stage of Sarnat and Sarnat was assigned to the subjects. All the babies had their anthropometric parameters recorded and were classified based on gestational age using Lubchenco chart.^[12] Besides, none of the asphyxiated babies underwent therapeutic hypothermia due to nonavailability of the required materials and equipment in our facility. Two milliliters of blood was collected from a peripheral vein of the dorsum of the hands and transferred into a plain bottle. The blood sample collected was allowed to clot and fully retract for 2 h at room temperature and then centrifuged at 1000 rpm for 15 min; serum was harvested and stored at -80°C in the chemical pathology laboratory. Serum troponin I was subsequently analyzed using Calbiotech human troponin I enzyme-linked immunosorbent assay (ELISA) kit (Catalog No. TI0 15C). The ELISA kit is an *in vitro* ELISA for the quantitative measurement of human troponin I in serum. The kit uses the principle of sandwich-based antibodies specific for human troponin I coated on a 96-well microplate.

Data analysis

Data obtained were entered into a computer and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 23.0 for Windows (SPSS Inc., Chicago, IL, USA). Mean and median were generated for normally distributed and nonnormal distribution, respectively. Tests of relationship (Mann–Whitney U and Kruskal–Wallis) and association (Spearman's correlation) were computed as appropriate. The results were presented using tables. $P < 0.05$ was considered statistically significant.

The hospital ethics review committee approved the study, and a written informed consent was obtained from parents after a clear explanation of the study objectives.

RESULTS

The median interquartile range (IQR) age at admission for subjects was 1.5 (0.5–6.0) h. The gestational age, anthropometry, gender, and age at sample collection of the subjects and controls were comparable, as shown in Table 1.

Regarding the distribution of the subjects according to HIE severity categories, 23 (27.0%) had HIE Stage I,

Table 1: General characteristics of the study population

Variable	Subjects	Controls	<i>t</i>	<i>P</i>
Age at sample collection (h), mean±SD	30.74±9.68	31.47±17.13	-0.344	0.731
Gestational age (weeks), mean±SD	39.45±1.37	39.12±1.45	1.523	0.130
Birth weight (kg), mean±SD	3.01±0.33	3.08±0.32	-1.432	0.154
Occipitofrontal circumference (cm), mean±SD	34.67±1.41	34.46±1.45	0.975	0.331
Length (cm), mean±SD	49.00±3.16	48.80±2.74	0.363	0.717
Sex, <i>n</i> (%)				
Male	51 (60.0)	44 (51.8)	$\chi^2=1.168$	0.280
Female	34 (40.0)	41 (48.2)		
Gestational age group (completed weeks), <i>n</i> (%)				
37-38	21 (24.7)	33 (38.8)	$\chi^2=1.858$	0.065
39-40	45 (52.9)	38 (44.7)		
41-<42	19 (22.4)	14 (16.5)		

SD - Standard deviation

52 (61.2%) had HIE Stage II, and 10 (11.8%) had HIE Stage III.

Table 2 compares serum troponin I between subjects and controls and shows that the subjects had significantly higher values of troponin I compared with the controls ($P < 0.001$).

There was no trend of increasing troponin I level from HIE I to HIE III. However, the median value associated with HIE III was nearly three times the value for HIE I and more than three times for HIE II. A Kruskal–Wallis test demonstrated no significant difference ($P = 0.075$) [Figure 1]. There was no significant difference in serum troponin I between HIE I and HIE II compared with a significant difference between HIE I and HIE III ($P = 0.041$). Similarly, there was a significant difference in troponin I values between HIE II and HIE III ($P = 0.034$) [Table 3].

Relationship between stages of hypoxic–ischemic encephalopathy and mortality

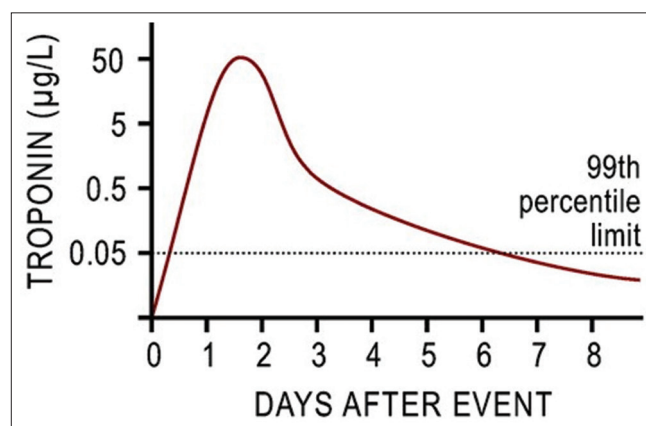
Five of the 85 subjects with HIE died, giving a case fatality rate of 5.9%. The case fatality was highest with Stage III disease (40.0%), and no mortality occurred among those with Stage I (0.0%). HIE Stage III constituted the highest proportion (80.0%) of the total mortality. There was a significant difference between the stages of HIE and mortality ($P < 0.001$) [Table 4].

Troponin I in association with mortality

The median (IQR) troponin I levels were significantly higher in fatal cases than in the survivors (4.00 [2.30–6.34] ng/ml) versus (1.21 [0.95–2.37] ng/ml: $U = 70.500$, $P = 0.015$).

DISCUSSION

Global assessment of the cardiovascular system is an integral part in the management of asphyxiated

**Figure 1:** Troponin I level following acute myocardial infarction^[11]

babies. This can be assessed by clinical methods, electrocardiography, echocardiography, and cardiac biomarkers. Studies have assessed myocardial dysfunction using each of these tools.^[4,13,14] The current study examined troponin I in a large sample of 85 asphyxiated neonates.

The median (IQR) serum troponin I in the asphyxiated neonates (subjects) in this study is comparable with 1.4 ± 1.1 ng/ml obtained among asphyxiated Indian neonates.^[15] It is, however, much higher than the values of 0.08–0.67 ng/ml obtained by other workers using different methods of immunoassay.^[16,17] Variation in serum level of troponin I has been shown by various immunoassay methods with fluorescent and chemiluminescent immunoassay having a lower limit of detection compared with the ELISA method which was used in the current study.^[18] On the other hand, the current study findings on troponin I level are lower than the 3.20 (1.15–6.30) ng/ml obtained by Pal and Goel^[19] among moderate-to-severely asphyxiated newborn babies in Indian.^[19] Majority of the subjects in the current study had mild-to-moderate HIE stage which could account

Table 2: Serum troponin I levels in the subjects and controls

Variable	Subjects	Controls	U	P
Troponin I (ng/ml), median (IQR)	1.26 (0.97-3.16)	0.79 (0.79-1.42)	965.500	<0.001

U: Mann-Whitney U-test. IQR - Interquartile range

Table 3: Serum troponin I levels across the stages of the disease

Variable	HIE I	HIE II	HIE III	K	P
Troponin (ng/ml), median (IQR)	1.26 ^a (1.00-2.37)	1.11 ^a (0.86-2.96)	3.58 ^b (1.34-5.58)	5.192	0.075

^{a,b}Values bearing the same superscript across row were not statistically different (*Post hoc* test for Kruskal-Wallis). HIE - Hypoxic-ischemic encephalopathy; IQR - Interquartile range

Table 4: Relationship between stages of hypoxic-ischemic encephalopathy and mortality

Disease stage	Outcome at discharge		F	P
	Survived, n (%)	Died, n (%)		
HIE Stage I	23 (100.0)	0 (0.0)	13.181	<0.001
HIE Stage II	51 (98.1)	1 (1.9)		
HIE Stage III	6 (60.0)	4 (40.0)		
Total	80 (94.1)	5 (5.9)		

HIE - Hypoxic-ischemic encephalopathy; F: Fisher's exact test

for the lower troponin I values compared with Pal and Goel.^[19]

The finding of higher serum troponin I in the subjects compared with healthy controls is consistent with previous studies.^[4,16,19] This buttresses the fact that hypoxic-ischemic injury in perinatal asphyxia is associated with elevated troponin I as reported in other studies.^[15,16]

Higher and significant values of troponin I were demonstrated in HIE III relative to HIE I and HIE II. This is comparable with previous studies that have reported significantly higher values with increasing disease severity.^[15-17] The finding of no significant difference in troponin I levels between HIE I and HIE II relative to HIE III may be related to the degree of myocardial ischemia. Myocardial ischemia consequent to perinatal asphyxia results in irreversible cell death and release of troponin I from the myocardium.^[20]

Troponin I was found to have a significant relationship with mortality in this study. This is consistent with findings documented by other workers.^[4,15,17] The relationship with mortality may be indicative of the degree of myocardial ischemia.^[20] Troponin I is a sensitive and early marker in the assessment of cardiac dysfunction related to perinatal asphyxia. There is no doubt that early diagnosis, adequate monitoring, and treatment will improve the health indices.

CONCLUSION

Cardiac troponin I was significantly higher in asphyxiated subjects compared with healthy controls.

Elevated troponin I was associated with higher mortality.

Limitations

The study defined perinatal asphyxia using clinical parameters rather than combination of clinical and documentation of metabolic acidosis. Besides, due to limited resources, we carried out a single measurement of troponin I among the asphyxiated neonates in this study, rather than serial measurement, which may produce additional information and noechocardiography was done to rule out congenital heart disease.

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The cost of the study was borne by the study authors.

Conflicts of interest

There are no conflicts of interest.

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