

Myocardial ischemia in neonate with perinatal asphyxia: Electrocardiographic, echocardiographic and enzymatic correlation

Saira Merchant, Rajkumar M Meshram, Devendra Khairnar

From Department of Paediatrics, Government Medical College, Nagpur, Maharashtra, India

Correspondence to: Dr. Rajkumar M Meshram, Department of Paediatrics, Government Medical College, Nagpur, Maharashtra, India.

Phone: +91-9822722315. E-mail: dr_rajmeshram@rediffmail.com

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ABSTRACT

Objective: The objective of this study is to evaluate the presence and severity of cardiac involvement in asphyxiated neonates and to establish which clinical and laboratory parameters (electrocardiogram [ECG], echocardiography [ECHO], and cardiac enzyme) are reliable predictors of myocardial ischemia. **Design:** Nested case-control study. **Setting:** Neonatology unit of tertiary care institute. **Materials and Methods:** The study group consist of 90 term neonates who had APGAR score <7 at 5 min as cases and 90 term neonate who had APGAR score >9 at 5 min as controls. On the 2nd day of life (between 24 and 36 h), all neonate underwent ECG, ECHO, and enzyme estimation (CK-MB). **Result:** The cases were divided into three groups according to SARNAT scale and Group I consist 25, Group II - 54, and Group - III, 11 neonates. The mean gestational age was 36.97±0.35 and 37.12±0.46 week for cases and controls respectively while mean birth weight was 2.79±0.36 kg and 2.68±0.76 kg for cases and controls, respectively. ECG changes were present in 70 (77.7%) of cases. ECG changes of Grade 3 and 4 were present in only Group III neonates and all neonates with Grade 4 changes were died in 1st week of life. Fractional shortening (FS) decreased progressively from Group I to Group III (p<0.001) and showed a significant difference between cases and controls as well as in different groups except in controls versus Group I. Peak aortic velocity behaved similarly. Concerning mean acceleration, the significant difference was observed between control and cases (all 3 groups). CK-MB activity increased from Group I to Group III and statistically significant difference was seen in controls and different Groups as well as in between different groups except in Controls versus Group I. **Conclusion:** Severe ECG changes (Grades 3 and 4), CK-MB elevation and reduced FS can be considered as reliable marker of myocardial ischemia in perinatal asphyxia.

Key words: Cardiac enzyme, CK-MB, Echocardiography, Electrocardiography, Ischemia, Myocardial perinatal asphyxia

Despite the important advances in perinatal care in the past decades, asphyxia remains a severe condition leading to significant mortality and morbidity. Estimated incidence of perinatal asphyxia is quite variable from one study to another. The reported incidence from hospital-based studies vary from 5 to 10 per 1000 live births [1,2]. Moreover, asphyxia has been shown to be the third most common cause of neonatal death after preterm birth and severe infection. Organ dysfunction in asphyxiated neonates depends on the duration of asphyxia and the early management. Although the myocardium in neonate is preferentially perfused during an episode of asphyxia, when such compensatory mechanism becomes compromised, the papillary muscle and subendocardial area appear to be particularly vulnerable to hypoxic injury [3-5].

Transient myocardial ischemia is a recognized association of perinatal asphyxia, with an incidence from 30% to 80% in severely asphyxiated neonates [6,7]. The recognition of myocardial ischemia is far more difficult in neonates than in adults. However, few investigations such as electrocardiogram (ECG), echocardiography (ECHO), and elevated levels of cardiac

enzymes (CK-MB and troponin) can detect ischemic insult to the heart.

Hence, the present study was conducted to evaluate the presence and extent of cardiac involvement in asphyxiated neonates to establish which clinical and laboratory parameters represented the reliable marker of cardiac damage in these patients.

MATERIALS AND METHODS

A hospital-based, prospective, nested case-control study was carried out in the neonatology unit of a tertiary care and referral institute of central India from October 2009 to September 2011. The cases and control were enrolled in the study after getting the approval of protocol from Institutional Ethical Committee and valid consent from parents. The study population comprised of 90 cases with completed 37 weeks of gestation with perinatal asphyxia evidenced by 5 min Apgar score of 7 or less [8]. The cases were divided into three groups according to SARNAT scale [9] which is used for staging of hypoxic ischemic encephalopathy. Neonates

with gestational age <37 weeks, congenital heart diseases, other congenital malformations, and sick neonates were excluded from study. Cord blood gas facility was not available at this institute; hence, could not be performed. 90 full-term neonates delivered without any evidence of asphyxia (5 min Apgar score 9 or more) were enrolled as control which was matched with cases for gestational age, sex, and birth weight.

All the asphyxiated neonates were resuscitated according to guidelines recommended by the American Academy of Pediatrics. Gestational age was determined by New Ballard score [10], and neonates were screened for the presence of any major congenital malformation. On the second day of life (between 24 and 36 h), all neonates underwent ECG, ECHO, and enzyme estimation.

ECG

The 12-lead ECG was performed on a standard Schiller Cardiovit AT-101 12 lead machine after 24 h of birth. The ECG was evaluated by 2 independent observers who were unaware of clinical condition of patients. Tracing were analyzed according to criteria proposed by Jedeikin et al. [11]. Every 12-lead ECG were classified as follows.

Grade 1: The presence of flat or inverted T-wave in one or two leads (except aVR)

Grade 2: T-wave flat or inverted in 3 or more leads (except aVR)

Grade 3: T-wave flat or inverted in 3 or more leads and ST depression or elevation >2 mm in at least 2 chest leads or Q-wave abnormality defined as duration >0.02 s or amplitude >25% of R-wave in one anterior or 3 chest leads

Grade 4: Classical segmental infarction with abnormal Q-waves and markedly elevated ST-segment.

ECHO

ECHO evaluation was done on a standard Philips IE33 2D ECHO ultrasound imaging system using 50 Hz transducer for mono and two-dimensional imaging after 24 h of birth. All ECHOs were performed by the same cardiologist who was not aware about the clinical condition of patients. On M-mode images of the left ventricle, fractional shortening (FS) was determined by the formula.

$$FS = (LVED-LVES)/LVED$$

Where LVED is left ventricular, end-diastolic diameter and LVES is left ventricular end-systolic diameter.

The aortic flow curve was obtained using five chamber apical views. The following parameters of cardiac function were determined on each curve: Peak aortic velocity, mean acceleration, and stroke distance, namely, the area under the velocity curve, also known as velocity time integral. In addition, the function of the atrioventricular valve was assessed by Doppler study with particular reference to the presence of mitral and tricuspid regurgitation (TR). The pulmonary artery pressure was estimated

using TR jet if TR was present. Thus, the following parameters of cardiac function were determined: (1) FS, (2) peak aortic velocity, (3) mean acceleration, and (4) stroke distance.

Enzyme Estimation

For enzyme estimation of creatine kinase isoenzyme, 2 ml of venous blood collected by venipuncture. CK-MB was measured by qualitative test based on immunological principle of inhibition of CK-M monomer. A standard kit by Rashmi Diagnostics Pvt. Ltd., Bengaluru was used for enzyme estimation.

All patients were followed up to discharge or death and immediate outcome calculated in term of survival and deaths.

Statistical Analysis

For echocardiographic parameters and enzyme values, the mean and standard deviation were calculated. Comparison between cases and controls as well as a comparison between groups were performed by one-way variance multiple comparison Bonferroni test. Unpaired t-test was used to compare patients who survived to those who died from Group III.

RESULTS

90 cases (term neonates who had APGAR score <7 at 5 min) and 90 controls (term neonate who had APGAR score >9 at 5 min) were included in the study group. Cases were divided into three groups according to SARNAT scale and Group I consist 25, Group II - 54, and Group III - 11 cases. The mean gestational age was 36.97±0.35 and 37.12±0.46 week for cases and controls respectively while mean birth weight was 2.79±0.36 kg and 2.68±0.76 kg for cases and controls, respectively. Of the 90 cases, 18 had low birth weight, and 72 had a birth weight >2.5 kg. The lowest and highest birth weights were 2.2 kg and 3.4 kg, respectively. The male to female sex ratio was 1.25:1 in both cases and controls.

ECG changes of Grades 3 and 4 were present in only Group III infants with the incidence of 63.66% and all neonates with Grade 4 changes were died in the 1st week of life. ECG from Group III neonates showing small Q-waves in lead II, III, aVF, V2, and diffuse ST-T segment elevation. (Table 1)

FS decreased progressively from Group I to Group III (p<0.001) and showed significant difference between cases and controls as well as in different groups except in controls versus Group I. Peak aortic velocity behaved similarly and showed significant difference between cases and controls as well as in different groups except in Group I versus Group II. Concerning mean acceleration, the significant difference was observed between control and cases (all 3 groups). Analysis of stroke distance did not reveal any significant difference among all 3 groups. TR was observed in two neonates in Group I (8%), three in Group II (5.5%) and three in Group III (27.27%). Pulmonary hypertension was present in one and two neonates in Group II and III, respectively. The CK-MB activity increased from Group I

to Group III and statistically significant difference was seen in controls and different groups as well as in between different groups except in controls versus Group I (Tables 2 and 3).

There was no mortality in Groups I and II. Among 11 neonates in Group III, five neonates (45.45%) have died and 6 (54.54%) survived. Comparison of these subgroups (non-survivors vs. survivors) revealed no significant difference in ECHO parameters, but the CK-MB level was significantly higher ($p=0.037$) in an infant whose outcome was unfavorable and most of the neonates with unfavorable outcome had multiorgan dysfunction.

DISCUSSION

Perinatal asphyxia remains one of the most important fields of research for pediatricians, and innumerable studies have been conducted on the various aspect of perinatal asphyxia. However, cardiac dysfunction in asphyxia is a neglected area with very few clinical studies on it because infants with cardiac dysfunction are those who are severely asphyxiated. The clinical picture among them is dominated by neurological changes resulting in high mortality. The contribution of cardiac dysfunction to mortality and the fate of cardiac status among the survivors have not been extensively evaluated. Hence, this study in tertiary care institute attempts to exemplify the magnitude and the nature of cardiac dysfunction in perinatal asphyxia and to evaluate clinical and laboratory parameters which are reliable predictors of myocardial ischemia.

In the present study, both groups (cases and controls) were comparable with each other with respect to sex, birth weight as controls were matched and selected. A similar type of comparable study was reported by Rajakumar et al. [12].

In this study, electrocardiographic (ECG) changes were present in 70 (77.7%) of cases. Previous studies have given wide variation in the incidence ranging from 45% by Pal et al. [13], to 73.3% by Rajakumar et al. [12], and 76.7% by Agrawal et al. [6]. The significant Q-wave was present in 3 (3.33%) in our study and Rajakumar et al. have reported 10% incidence of Q-waves. This corresponds to Grade 4 of Jedeikin grading criteria. These Q-waves were found in inferior leads-III and aVF suggesting inferior wall infarction. There has been no study, which clearly delineates which part of ventricular wall is damaged in perinatal asphyxia. Further studies are required to identify the particular patterns of infarction seen in asphyxia.

An important role is played by ECHO which may show two basic pattern representative of myocardial damage: (1) A depressed left ventricular function, expressed by reduction in both FS and aortic velocity (2) TR, eventually associated with pulmonary hypertension. M-mode Doppler imaging allows measurement of FS and ejection fraction (EF), which are more quantitative measures of the contractility of the ventricles. In a group of asphyxiated neonates, there was a gradual decrease in the FS with increasing degree of asphyxia in this study. Similar trends were also seen in aortic peak velocity and the mean acceleration used as the indices of left ventricular function. These results were similar to the ventricular dysfunction trends as represented by Barberi et al. [14].

Although a mild TR is relatively common in normal newborn infants, a moderate to severe valve insufficiency is often associated with pulmonary hypertension, as in some of our Group II and III neonates (1 from Group II and 2 from Group III). Barberi et al. studied cardiac involvement in asphyxiated neonate using ECG, ECHO, and cardiac enzyme reported FS, peak aortic velocity and mean acceleration were significantly reduced in severe asphyxia,

Table 1: ECG changes in cases (3 HIE groups) and controls

Study population	n	Normal (n, %)	ECG changes (n, %)			
			Grade 1	Grade 2	Grade 3	Grade 4
Controls	90	81 (90)	9 (10)	-	-	-
Group I	25	20 (80)	4 (16)	1 (4)	-	-
Group II	54	-	2 (3.7%)	52 (96.3)	-	-
Group III	11	-	-	4 (36.36)	4 (36.36)	3 (27.3)

HIE: Hypoxic ischemic encephalopathy, ECG: Electrocardiogram

Table 2: ECHO parameters and CK-MB isoenzyme (mean±SD) in cases and controls

Study population	FS (%)	Peak aortic velocity (cm/s)	Mean acceleration (cm/s ²)	Stroke distance (cm)	CK-MB (IU/L)
Controls	39.2±3.28	81.88±10.18	1117.08±101.70	9.212±1.55	13.92±2.89
Group I	37.7±3.17	80.24±6.14	1462.24±153.99	11.36±0.91	14.92±3.44
Group II	29.8±3.74	74.96±9.66	1387.67±215.74	11.00±1.44	137.65±102.81
Group III	20.1±3.40	66.64±8.51	1394.73±116.91	10.94±0.98	345±242.18

ECHO: Echocardiographic, SD: Standard deviation, FS: Fractional shortening

Table 3: Comparison of ECHO parameters and serum CK-MB in cases and controls (p-value)

Study population	FS (%)	Peak aortic velocity (cm/s)	Mean acceleration (cm/s ²)	Stroke distance	CK-MB
Control versus Group I	0.1	0.002	0.0001	0.0001	1.000
Control versus Group II	0.0001	<0.0001	0.0001	0.0001	<0.001
Control versus Group III	0.0001	<0.0001	0.000	0.005	0.001
Group I versus Group II	<0.0001	0.131	0.291	1.00	0.000
Group II versus Group III	<0.0001	0.05	1.000	1.00	0.000
Group I versus Group III	<0.0001	0.001	0.186	1.00	0.000

ECHO: Echocardiographic, FS: Fractional shortening

whereas the only abnormality found in moderate asphyxia was a reduced FS. In this study, FS and peak aortic velocity decrease progressively from Group I to Group III. Analysis of stroke distance and mean acceleration did not reveal any significant difference among three groups.

TR and pulmonary hypertension were documented in 11 (22.22%) cases in the present study. The most common finding was TR in 8 (8.8%) cases. This is less than that in the previous studies by Rowe et al. [15], Martein et al., and Rajakumar et al. who documented 12%, 21%, and 23.3%, respectively. However, Herdy et al. [16] have observed these changes in 7% of cases. TR could be due to papillary muscle ischemia or persistent pulmonary hypertension. The wide variation in the incidence of TR may be due to the type of cases selected, presence or absence of pulmonary hypertension and the timing of ECHO. Three neonates with TR had pulmonary hypertension by ECHO evaluation in our study, which could be contributed to TR. Although mitral regurgitation (MR) has been documented in previous studies (Rowe et al.), none of the babies in our study had MR.

Creatinine kinase is released during muscular trauma and myopathic disorder as well as myocardial infarction. In neonates, the total CK activity rises dramatically after delivery and falls to normal after 2-3 days [17]. Because of the association between the height of CK peak and obstetric difficulties, the peripartum release of this enzyme is generally thought to be due to muscle trauma, with or without anoxic damage. In adults, CK-MB is relatively specific to the myocardium. CK-MB release during newborn period has been studied by Jouppila et al. [18] who did not find significant elevation in the fractional CK-MB level during the first 3 days of life in healthy infants. Cuestas [19] mentioned the extreme elevation of CK-MB activity in some asphyxiated neonates. Nelson et al. using a single sample found the elevation of fractional and absolute CK-MB activities in the first few days of life in some infant with asphyxia.

Cardiac enzyme was estimated in all cases and controls. CK-MB estimated in the study was significantly elevated in cases when compared to controls. Mean CK-MB level among cases and controls were 122.46 IU/L and 13.92 IU/L, respectively. This is lower than the value reported by Agrwal (147±161.0 IU/L), Rajakumar et al. [20] (121±77.4 IU/L in cases and 28.8±20.2 IU/L in controls), Mandal Ravi et al. [21] (823.5 IU/L in cases), and Fonseca et al. [22] 212±90.8 IU/L in cases and 106±48.1 IU/L in controls).

The CK-MB activity increased from Group I to Group II and statistically significant difference was seen in controls and different groups as well as in between different groups. Thus, indicating CK-MB is a very sensitive marker of myocardial ischemia. Whereas Barberi et al. observed that CK, CK-MB, CK-MB/CK ratio and lactate dehydrogenase were all increases in Group III, while only in Group II only CK-MB and the CK-MB/CK ratio were abnormal.

Main limitation of our study was that estimation of cardiac enzyme troponin T, which is very specific for myocardial ischemia, was not done because of financial constraints as this facility was not available in our institute and study population belonged to poor socioeconomic class.

CONCLUSION

Severely asphyxiated neonates reflect relevant ischemic ECG changes, depressed left ventricular function, and marked cardiac enzyme increases. These alterations are far less pronounced in neonates with mild to moderate asphyxia. Our results suggest that severe ECG changes (Grades 3 and 4) are present only in very sick neonates, and should be considered as a specific marker of severe myocardial injury. CK-MB elevation and reduced FS should be regarded as most reliable marker of ischemia as they are detectable even in mildly compromised neonates. Asphyxiated neonates with Grades 3 and 4 ECG changes and high CK-MB activity have very poor prognosis due to extensive myocardial damage and concomitant multiorgan involvement.

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