

Original Research Article

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N-terminal pro brain natriuretic peptide as a marker of myocardial dysfunction in newborns with perinatal asphyxia

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ABSTRACT

Background: Perinatal asphyxia refers to a condition during first and second stage of labour in which impaired gas exchange leads to foetal hypoxemia. Perinatal asphyxia causes cardiac dysfunction in 24 to 60 percent of the cases. The reduced cardiovascular reserve is associated with hypoxic brain damage and has high impact on neonatal mortality and adverse neurological outcomes. It has been challenging to diagnose myocardial dysfunction in resource constraint setting. Aim and objective of this study was to Determine N-Terminal Pro BNP concentrations in perinatal asphyxia and correlate with modified Sarnat stages of hypoxic ischemic encephalopathy.

Methods: Among 120 Neonates admitted in neonatal intensive care unit with diagnosis of perinatal asphyxia were considered for the study. 2mL of venous blood drawn within 48hours of life was analyzed for quantitative N-Terminal Pro BNP and was correlated with modified Sarnat stages of hypoxic ischemic encephalopathy.

Results: A Total of 120 cases of perinatal asphyxia were considered for the study, among which 44 cases had HIE stage 1, 48 had HIE stage 2 and rest 28 had HIE stage 3. The mean and standard deviation of N-Terminal Pro BNP concentrations in stage 1 was $1,502.86 \pm 3,581.170$ pg/mL, stage 2 was $4,916.31 \pm 8,001.674$ pg/mL and stage 3 was $8,912.41 \pm 13,927.152$ pg/mL with significant p value of 0.003.

Conclusions: Early N-Terminal Pro BNP concentrations may provide a useful marker for the anticipated severity of myocardial dysfunction.

Keywords: Hypoxic ischemic encephalopathy, Modified Sarnat stages, N-terminal pro BNP, Perinatal asphyxia

INTRODUCTION

Asphyxia [as- ffik-se-ah] (Greek; “a stopping of the pulse”) Birth asphyxia is defined by the World Health Organization as “the failure to initiate and sustain breathing at birth immediately after delivery” (WHO).¹ Perinatal asphyxia is a common problem and has an incidence varying from 0.5 - 2% of live births.^{2,3} WHO estimates that 4 million neonatal deaths occur yearly due to perinatal asphyxia, representing 38% of deaths of children under 5 years of age.⁴

In India, the rural and urban regions of the Uttar Pradesh and Maharashtra have mortality of 23% and 25%

attributed to birth asphyxia, respectively.^{5,6} Perinatal asphyxia represents the third most common cause of neonatal death (23%) after preterm (28%) and severe infections (26%).⁷

Hypoxic ischemic organ damage can occur at ante partum period (50%), at intrapartum period (40%) or after delivery as postpartum asphyxia (10%).⁸ Hypoxic Ischemic Encephalopathy (HIE) should be suspected in encephalopathic newborns with a history of foetal and or neonatal distress and laboratory evidence of asphyxia.

Asphyxia may be suspected and HIE reasonably included in the differential diagnosis when there is:

- Prolonged (>1 hour) antenatal acidosis in newborn blood gas analysis.
- Foetal HR <60 beats per minute.
- Apgar score ≤ 3 at ≥ 10 minutes.
- Need for positive pressure ventilation for >1 minute or first cry delayed >5 minutes
- Onset of seizures within 12 to 24 hours of birth
- Burst suppression or suppressed background pattern on EEG or amplitude-integrated Electroencephalogram (aEEG).⁹

Severe perinatal asphyxia as defined by National Neonatal Perinatal Database as no breathing or an Apgar score of 0-3 at 1 minute of age results in myocardial ischemic injury.¹⁰ The incidence of clinical cardiac dysfunction in perinatal asphyxia varies from 24-60%.¹¹ Cardiac dysfunction is caused by transient myocardial ischemia. Neonate with cardiac dysfunction in perinatal asphyxia presents with respiratory distress, congestive heart failure, and myocardial ischemia leading to cardiogenic shock. The electrocardiogram (ECG) may show ST depression in the mid precordium and T-wave inversion in the left precordium. Echocardiographic findings include decreased left ventricular contractility, especially of posterior wall; elevated ventricular end-diastolic pressures; tricuspid insufficiency; and pulmonary hypertension. In severely asphyxiated newborns, dysfunction more commonly affects the right ventricle. A fixed HR may indicate severe brainstem injury. Myocardial involvement leading to cardiogenic shock remains one of the most challenging in the management and a significant cause of mortality in neonates suffering from perinatal asphyxia. Echocardiographic evaluation at bed side is not always available and has long learning with inter observer variation. Moreover, right ventricular dysfunction is difficult to detect and at the most semi quantitative.

B-type natriuretic peptide (BNP) and N-terminal-pro-BNP (NT-pBNP) have a crucial role in the screening and the diagnosis of cardiac disease, respiratory distress and monitoring of the treatment response in neonates and children. Natriuretic peptides are ring-shaped amino acid sequences with specialized actions. Four natriuretic peptides have been described till now, namely A, B, C and D.¹² Atrial natriuretic peptide (ANP) is synthesised and released by atrial myocytes. ANP lowers the blood pressure and has diuretic, natriuretic and kaliuretic properties.

Brain natriuretic peptide named after its discovery in porcine brains, is much higher in the ventricles of the heart.^{13,14} C-type natriuretic peptide is found in the brain and coronary vessels. It regulates vascular tone and lacks natriuretic properties.¹⁵ The D type known as Dendroaspis natriuretic peptide (DNP) is found in snake venom and it has no function in humans.¹⁶

BNP is a 32 amino acid ring structure, and the sequence is present on chromosome 1. BNP acts on a cyclic

guanosine monophosphate (cGMP)-coupled receptor via a transmembrane domain.¹⁷ The ring structure of the BNP must be intact to ensure receptor binding to natriuretic peptide receptors A and B (NPR-A/B). The ventricles of the heart are the main site of BNP synthesis and release in response to volume, pressure loading, and ventricular stress. Pro BNP is the inactive precursor and is cleaved into BNP, which is the active component, and N-terminal pro-BNP (NT-pBNP) is an inactive by product. The half-life of BNP is about 20 min and that of NT pBNP is 60 min.¹⁸ The actions of BNP are diuresis, natriuresis, arterial and venous vasodilatation, and antagonizing the renin-angiotensin system. The net effect is a reduction of intravascular volume, and ventricular preload and afterload. Recently, it has shown to be associated with the regulation of pulmonary vasculature.^{19,20} BNP is excreted after cleavage by membrane-bound neutral peptidase, which is found in the kidneys and vascular tree. It can also be cleared from the blood by direct binding to the natriuretic peptide receptor C, endocytosis and lysosomal degradation.²¹

There is a lack of data on normative values of BNP and NT-pBNP in neonates. The reference ranges quoted in the literature vary depending on timing of the test, the kits used and the population studied. Natriuretic peptides do not cross the placenta and therefore any variation in neonates must be explained intrinsically. This study was intended to know if any correlation in severity of perinatal asphyxia with concentrations of NT-pBNP and to establish if it is useful to identify in myocardial dysfunction.

METHODS

This study was conducted in the neonatal intensive care unit, Department of Pediatrics, Vani Vilas Hospital, Bangalore Medical College and Research Institute from Nov 2017 to May 2019. The study was cross sectional. Written Informed consent was taken from the parents of study subjects after fulfilling the inclusion criteria as soon as the neonate was admitted to NICU.²²

- Profound metabolic or mixed acidemia (pH < 7.00) in umbilical cord blood.
- Persistence of low Apgar scores less than 3 for more than 5 minutes
- Signs of neonatal neurologic dysfunction (e.g., seizures, encephalopathy and tone abnormalities).
- Evidence of multiple organ involvement (such as that of kidneys, lungs, liver, heart and intestine).

The neonates that were excluded from the study were preterm infants, antenatally diagnosed cardiac disease and with major congenital malformation.

Based on previous study P.S. Rajakumar et al, myocardial dysfunction in newborns with perinatal asphyxia was 76.6%.¹¹

$$n = Z^2 \alpha pq \quad Z\alpha = \text{the standard table value at 95% CI}$$

$$d^2 \quad p = 76.6 \quad q = 100-p = 23.4$$

$$n = 117.3 \text{ or approximately } 120 \quad d = 10\% \text{ of } p = 7.66$$

The details were entered in a predesigned proforma. This included history regarding antenatal risk factors for perinatal asphyxia such as age of the mother, history of pregnancy induced hypertension, anemia, bleeding, infection and systemic disease. Intrapartum factors like mode of delivery, history of prolonged rupture of membrane, difficult labor, meconium staining of amniotic fluid, malpresentation and cord prolapse were also entered. Examination findings including vitals and detailed anthropometry were recorded and a complete neurological examination and other systemic examination were done as per established standards. The neonates were treated as per the NICU treatment protocol for birth asphyxia of the hospital. During the NICU stay, heart rate, respiratory rate, blood pressure and oxygen saturation are monitored continuously. Clinical assessments included assessments of the neurologic status twice daily, the grade of HIE (Stage I, Stage II or Stage III), the type of respiratory support needed, the presence of seizures, involvement of multiorgan dysfunction. Hospital recommended guidelines for investigations were done as and when needed. 2ml of venous blood drawn in plain tube between 3- 6 hours of life from asphyxiated infants is analyzed for NT-pBNP.²³ The Hotgen kit was used for quantitative measurement of human NT-ProBNP in serum or plasma employing combination of up converting phospher technology and immunochromatography. The Microsoft Excel and SPSS (SPSS Inc, Chicago v 18.5) software packages were used for data entry and analysis respectively. The results were averaged (mean±standard deviation) for each parameter

for continuous data was analyzed using student t test and for proportions using chi-square test.

RESULTS

Among 120 neonates 88(73.3%) were male and 32(26.7%) were female. In the study group, 30(25%) babies were of low birth weight (<2500 grams) and 90(75%) babies were having normal weight at birth (>2500 grams). 77.5 percent of babies (93) were born between 37 -39 weeks and 22.5 percent were born after 40 weeks (postdated). The mean and standard deviation of birth weight was 2786.9±475.684 grams and range of 1800 to 3820 grams. 41.7 percent of babies (50) delivered had meconium staining of the liquor and 58.3 percent had clear liquor. 80 percent of the babies (96) were born vaginally, 4.2 percent of deliveries were assisted with either forceps or vacuum. Rest 15.8 percent were taken for emergency lower segment caesarean section. 40 babies were resuscitated with tactile stimulation, 53 babies were resuscitated with positive pressure ventilation using bag and mask. 26 newborns were intubated and 1 newborn required chest compressions and endotracheal adrenaline. APGAR scores at 1 minute of life following resuscitation, 5.8 percent had score of less than 3, 70.8 percent had scores between 3 and 5 and 23.3 percent had score above 5. No babies had Apgar score of less than 3 at 5 minutes of life. 32.5 percent had scores between 3 and 5; rest 67.5 babies had scores above 5. Among 120 newborns in the study with perinatal asphyxia 44 (36.7%) babies had stage 1, 48 (40.0%) babies had stage 2, and rest 28 (23.3%) babies had stage 3. Stages were done according to modified Sarnat stages of hypoxic ischemic encephalopathy. 55.8 percent had respiratory distress and 19.2 percent had shock at the time of admission in neonatal intensive care unit following perinatal asphyxia. Table1.

Table 1: Mean, standard deviation, minimum and maximum values of birth weight (grams), gestational age (week), pH, sodium bicarbonate meq/L, and BNP ng/mL.

	HIE	N	Mean	SD	Min.	Max.	F value*	p value
Birth weight (grams)	Stage 1	44	2743.9	501.297	1800	3820	0.290	0.749
	Stage 2	48	2817.3	460.013	1800	3650		
	Stage 3	28	2802.5	473.072	1900	3700		
Gestational Age (Wk)	Stage 1	44	38.3	1.102	37.0	41.0	2.543	0.083
	Stage 2	48	38.7	1.371	37.0	42.0		
	Stage 3	28	38.9	1.079	37.0	41.0		
pH	Stage 1	44	7.37	0.074	7.21	7.68	62.073	<0.001
	Stage 2	48	7.24	0.147	7.01	7.66		
	Stage 3	28	7.01	0.185	6.54	7.30		
Sodium Bicarbonate (meq/L)	Stage 1	44	19.89	3.218	14.90	28.60	62.595	<0.001
	Stage 2	48	15.72	4.665	10.10	28.70		
	Stage 3	28	9.36	3.358	3.70	16.30		
BNP (ng/mL)	Stage 1	44	1,502.86	3,581.170	5	19,803	6.301	0.003
	Stage 2	48	4,916.31	8,001.674	5	35,000		
	Stage 3	28	8,912.41	13,927.152	6	35,000		

DISCUSSION

Perinatal asphyxia remains a severe condition leading to significant neonatal mortality and morbidity, although important advances made in past decade. The exact pathogenesis of myocardial dysfunction in birth asphyxia is still not clear; the role of hypoxia induced pulmonary vasoconstriction is the main precipitating cause of disturbed circulatory dynamics. There are logistic difficulties such as expertise and equipment in assessment of myocardial dysfunction. There are reports of NT-pBNP levels in perinatal asphyxia as a marker of cardiac dysfunction. The reduced cardiovascular reserve is associated with hypoxic brain damage and it has a high impact on neonatal mortality and adverse neurological outcomes.

In the present study, a total of 120 neonates with evidence of birth asphyxia were selected and studied. The babies were stratified based on the severity of asphyxia into three stages using modified Sarnat staging. The

results and interpretations of the findings were based on the severity of HIE stages.

The gender, birth weight and gestational age distribution of the babies and colour of the liquor was not found to have a significant correlation with the severity of HIE staging in the present study. This was similar to the results shown by Agarwal et al, and Jain et al.^{24,25} Among the total 20 deaths, 9 babies had a meconium stained liquor at birth and all babies were graded with severe HIE stage 3. This difference was not significant statistically and the findings were in accordance with the reports* of Lakshmanan et al.²⁶ The findings of this study suggest that both the 1 minute and 5-minute APGAR scores were having a significant correlation stage of perinatal asphyxia. This was in contrary to the studies by Shadique AM et al, where statistical significance was not seen, however studies by Lakshmanan et al, showed statistical significance of APGAR scores with stages of perinatal asphyxia.^{26,27}

Table 2: Reference ranges for B-type natriuretic peptide (BNP) in neonates.

Study	Sample size	Age range Source	Kit	BNP levels
Koch and Singer ²⁸	12	Day 0 to day 1 Plasma	Biosite	Mean: 231.6 pg/ml SD: 197.5
Koch and Singer ²⁸	14	Day 4 to day 6 Plasma	Biosite	Mean: 48.4 pg/ml SD: 49.1
Kunii et al ²⁹	11	Day 0 Cord blood	Shiono RIA BNP	Mean: 10.4 pg/ml SD: 11.9
Kunii et al ²⁹	11	Day 1 Plasma	Shiono RIA BNP	Mean: 118.8 pg/ml SD: 83.2
Kunii et al ²⁹	11	Day 7 Plasma	Shiono RIA BNP	Mean: 15.3 pg/ml SD: 7.8
Bar-Oz et al ³⁰	122	Day 1 Cord blood	Elecsys 1010/2010	Mean: 578.8 ng/l SD: 351.3
Bar-Oz et al ³⁰	33	Day 1 Plasma	Elecsys 1010/2010	Mean: 3042.4 ng/l SD: 1783.2
Mir et al ³¹	153	Day 1 Venous/cord	Biomedica	Mean: 641 fmol/mL Range: 254-1272
Mir et al ³¹	153	Day 3 Venous/cord	Biomedica	Mean: 246 fmol/ml Range: 110-430

Table 3: Comparison of mean, standard deviation of B-type natriuretic peptide (BNP) in neonates with Stages of hypoxic ischemic encephalopathy.

Study -BNP level pg/ml	Stage 1HIE	Stage 2 HIE	Stage 3 HIE	p value
Dharmendra Jain et al ³³	n = 10 482.40±114.83	n = 10 957.00±336.94	n = 11 1823.27±477.91	<0.001
Present study	n = 44 1,502.86±3,581.17	n = 48 4,916.31±8,001.674	n = 28 8,912.41±13,927.152	0.003

Table 4: Comparison of mean, standard deviation of B-type natriuretic peptide (BNP) in neonates of hypoxic ischemic encephalopathy with mortality.

Dharmendra Jain et al ³³	Death	1888.6±598.6 pg/ml	p value < 0.01
	Discharge	961.8±571.2 pg/ml	
Simovic AM, et al ³⁴	Asphyxiated newborns (n = 55)	993.05±1259.51 pg/ml	p value 0.003
	Healthy newborns (n = 36)	278.98±190.47 pg/ml	
Present study	Death (n = 20)	10,319.52±14,742.4 pg/ml	p value 0.002
	Discharge (n = 100)	3,452.66±6,984.858 pg/ml	

This difference could probably be attributed to the difference of the number of newborns enrolled in the studies with severe asphyxia.

Koch and Singer determined the concentration of NT-Pro BNP in 12 normal newborns on day one with a mean of 231.6 pg/ml and standard deviation 197.5pg/ml.²⁸ Subsequently on day 4 to day 6 found a lower mean of 48.4 pg/ml and standard deviation of 49.1pg/ml. Table 2.

Levels of BNP and NT-p BNP surge at birth, plateaus on day 3-4. This is followed by a steady fall to reach a constant level in infancy.³¹ The surge is multifactorial, including the loss of the placental low-pressure system. Exposure to the initially supra-systemic pulmonary pressures subjects the ventricle to greater volume and pressure loading. Furthermore, the placenta has a role in clearance of natriuretic peptides and loss of this clearance system contributes to the high levels.³² Therefore high levels of BNP at birth have a crucial regulatory role in the hemodynamic changes associated with transition to extra uterine life. Kidney maturation, a rise in systemic vascular resistance and a fall in pulmonary pressures explain the subsequent fall in the peptide levels.

Dharmendra Jain et al, published a similar study determining the levels of B type natriuretic peptide concentrations in HIE stages.³³ This study was in accordance to the increasing concentrations of B type natriuretic peptide with increasing severity of hypoxic ischemic encephalopathy. The myocardial dysfunction was most severe in stage 3 perinatal asphyxia with highest BNP values with statistical significance p value. Table 3.

The mean B type natriuretic peptide concentrations were significantly elevated in non survivor group. This was attributable to higher level of cardiac dysfunction in the newborns with perinatal asphyxia. NT-Pro BNP can serve as a marker of cardiac dysfunction and higher levels was associated with poor outcome. Table 4.

CONCLUSION

N-Terminal Pro BNP levels within the first 48hrs after birth was significantly higher in newborns with perinatal asphyxia, with the levels rising proportionally to the clinical stages of HIE. Early N-Terminal Pro BNP concentrations may provide a useful marker for the anticipated severity of myocardial dysfunction.

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