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N-Terminal Pro-brain Natriuretic Peptide in Myocardial Injury AfterNeonatal Hypoxia-Ischemia

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ABSTRACT

Background: Neonatal asphyxia is a common pediatric disease. Asphyxia causes hypoxia and leads to multiple organ damage of which heart damage is the most common. The aim of the present study was to evaluate the changes of serum NT-proBNP levels after asphyxia-induced myocardial injury in neonates. **Patients and methods:**A case-control study included forty neonates divided equally into: case group with the diagnosis of perinatal hypoxia ischemia and control group admitted to Neonatology Unit of Pediatric Department at zagazig University due to causes other than perinatal hypoxia and cardiovascular problems.Serum troponin T and NT-pro BNP were measured in all studied neonates**. Results:**Significant area under ROC curve was found with cutoff values >12.5 (ng/ml) and >22.5 (pg/ml) for troponin and BNP respectively. Sensitivity of 98% and 80% and specificity of 97.0% and 78% respectively were reported for troponin and pro-BNP serum levels.**Conclusion:**Our cases had myocardial damage evidenced by higher serum levels of troponin T and pro-BNP compared with control group. Serum troponin T and pro-BNP were 98 and 80 sensitive and 97 and 78 % specific for detection of myocardial injury in our patients. Cases with Hypoxic ischemic encephalopathy (HIE) and those with multiple organ failure had a more pronounced elevation of serum troponin T and pro-BNP compared with cases of hypoxia-ischemia with no HIE or organ failure.

Keywords: Myocardial Injury; NT-pro BNP; Neonatal Hypoxia-Ischemia

INTRODUCTION

Neonatal asphyxia causes hypoxia and leads to multiple organ damage, of which heart damage is the most common. Reports show that the occurrence of myocardial damage in neonatal asphyxia was 28–65% or even up to 73% **(1)**. However, the diagnosis of hypoxic–ischemic myocardial damage has been difficult because of the lack of sensitive laboratory tests for early diagnosis and the absence of standard diagnostic criteria **(2).**

Brain natriuretic peptide, or B-type natriuretic peptide (BNP), is a heart peptide hormone. When the tension of a blood vessel increases or its volume is overloaded, prepro BNP mRNA is rapidly transcribed in the myocardial cells of the ventricles. PreproBNP is then synthesized and processed to produce a signaling peptide and pro BNP. The pro BNP is then catalyzed to generate N-terminal (NT-pro BNP) and BNP, which are released into the blood **(1)**.

However, there are relatively few studies regarding BNP/NT-proBNP in the newborn. NT-proBNP does not pass the blood-placenta barrier; thus, any changes in the baby's body are autonomous. Myocardial ischemia and energy metabolism dysfunction lead to irreversible damage and even necrosis. Furthermore, during recovery, blood reperfusion can cause further damage to myocardial cells **(3)**.

Myocardial injury often occurs simultaneously with elevated ventricular tension and a compensatory increase in cardiac output. Particularly, in the event of heart failure, the ventricle is stretched by atrial and ventricular dilatation. At the same time, pulmonary vasodilation stimulates pulmonary and cardiac nerve receptors, regulating the release of BNP. The increase in the vascular BNP/NT-proBNP concentration leads to an increase of the ventricular volume. The elevated blood vessel pressure further induces the synthesis and secretion of BNP **(4)**.

Therefore, this study aimed to evaluate the changes of serum N-terminal pro- brain natriuretic peptide (NT-proBNP) levels after asphyxia-induced myocardial injury in neonates.

PATIENTS AND METHODS

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This case-control study included forty neonates and was carried out at Pediatric and Clinical Pathology Departments, Faculty of Medicine, Zagazig University**.** Patients were divided into 2 groups: Case group included 20 neonates (12 males and 8 females) with the diagnosis of perinatal hypoxia ischemia. Control group: included 20 age- and sex-matched neonates (13 males and 7 females) admitted to Neonatology Unit of Pediatric Department at zagazig University due to causes other than perinatal hypoxia and cardiovascular problems e.g. neonatal hyperbilirubinemia, neonatal vomiting and congenital anomalies not involving the heart.

Inclusion criteria:

Neonates admitted to Zagazig University Hospital with the diagnosis of perinatal hypoxia ischemia were included in the study if they met the diagnostic criteria of myocardial injury including at least 4 of the following including elevated level of serum troponin T **(5,6)**. History suggestive of perinatal hypoxia ischemia, Low intensity heart sounds and tachycardia, poor peripheral circulation, demonstrated by peripheral cyanosis, or prolonged capillary refill time over 3 seconds, heart failure, severe arrhythmias, cardiac arrest and elevated serum troponin T level.

Exclusion criteria:

Cases of perinatal hypoxia not fulfilling the criteria of myocardial damage.Neonates with water and electrolyte balance disorders and neonatal cardiovascular structural disease.Any disease elevating the BNP like kidney dysfunction, pulmonary disease e.g. chronic hypoxia.

Methods:

All patients were subjected to full prenatal and postnatal history including maternal age, consanguinity, history of previous abortions, any diseases either chronic diseases (cardiac, pulmonary or diabetes), hypertension, premature rupture of membranes, cord accidents, pregnancy complications, hemorrhage, toxemia, maternal infection or placental diseases. Neonatal resuscitation was required or not and the measures used either oxygen delivery by umbo bag or mask or required intubation. Occurrence of seizures or jitterness.

Neonatal assessment particularly:

1- Need for neonatal resuscitation with positive pressure ventilation.
2- Umbilical arterial / first postnatal pH.
3- Heart rate, respiratory rate, cyanosis not responding to resuscitative efforts, first day jaundice or pallor.
4- Assessment of gestational age according to new Ballard Score **(7)** as well as maternal history and prenatal ultrasound examination.
5- All infants were neurologically examined daily during the first week of life and classified according to presence or absence of encephalopathy into 2 groups. Patients with encephalopathy were subdivided according to the degree of HIE into mild, moderate or severe HIE based onSarnat's clinical staging of perinatal hypoxia ischemia **(8)**.
6- Patients were divided into 2 groups based on presence or absence of multiple organ failure. Patients who had more than one organ dysfunction in addition to cardiac and CNS involvement were included in multiple organ failure group e.g. patients with renal, pulmonary or GIT dysfunction after being initially normal at the diagnosis of hypoxic-ischemic insult.
7- Patients were divided into 2 groups based on acid-base disturbance using PH cut off value of 7.3.

Clinical Investigations:

1- Arterial blood gases.
2- Measurement of troponin T with an electrochemiluminescence kit (Roche, Shanghai, China), using the Elecsys 2010 instrument**.**
3- Measurement of NT-proBNP using a sandwich enzyme immunoassay (ELISA) for the determination of NT-proBNP in human serum. In a first step, sample and conjugate (sheep anti human NT-ProBNP-HRPO) are pipetted into the wills of the microtiter, which are precoated with polyclonal sheep and NT-ProBNP antibody. NT-ProBNP present in the sample binds to the precoated antibody in the well and forms a sandwich with the detection antibody **(2)**. The assay has been evaluated using a 4 pl algorithm method other curve fitting methods needs an evaluation by the user.The upper limit of normal for NT-proBNP was set at 450 pg/ml.

Statistical analysis:

Data were analyzed using Statistical Package for the Social Sciences (SPSS version 20.0) software. Qualitative data were represented as number and percentage, quantitative continuous data were represented by mean ± standard deviation (SD), the following tests were used to test differences of significance; difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups by unpaired student's t-test. Correlation between serum pro-

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BNP and the other parameters was tested by Pearson's or Spearman's correlation. P value was set at <0.05 for significant results &<0.001 for highly significant results.

RESULTS

The present study showed age was distributed as 14.45±4.36 and 14.10±4.34 days respectively between groups. There was no significant difference regard GA, birth weight, sex distribution or mode of delivery **(Table 1)**. Cases were significantly associated with higher HR and RR. Also, cases were significantly associated with pallor and cyanosis **(Table 2)**. Cases were significantly associated with impaired Capillary perfusion and cases were significantly associated with hypoxic-ischemic Encephalopathy **(Table 3)**. Cases had significantly lower pH and PaO_2. Metabolic acidosis was significantly present in cases **(Table 4)**. EF and FS were significantly lower in cases compared to normal neonates **(Table 5)**. Cases were significantly higher than control subjects regarding serum levels of troponin and pro-BNP **(Table 6)**. Significant area was found under Receiver Operator Characteristic (ROC) curve with cutoff values>12.5 (ng/ml) and >22.5 (pg/ml) for troponin and BNP respectively. **(Table 7, Figure 1)**. Encephalopathy cases were significantly associated with higher HR, HCO_3, CKMB, troponin and significantly higher Pro-BNP but significantly lower regarding EF, FS and PaO_2.**(Table 8)**. Cases with organ failure were significantly associated with higher HR, PCO2, CKMB, troponin and also significantly higher Pro-BNP but significantly lower regarding EF, FS, HCO3, PaO_2 and pH **(Table 9)**. Pro-BNP was significantly negative correlated with EF **(Figure 2)**.Pro-BNP was significantly negative correlated with FS**(Figure 3)**.Pro-BNP was significantly positive correlated with troponinT**(Figure 4)**.

Table 1: Basic demographic distribution in studied groups

			Case (n = 20)	Control (n = 20)	t/ X^2	P
Age (days)			14.45±4.36	14.10±4.34	0.184	0.855
GA (weeks)			35.90±1.97	36.75±2.33	1.244	0.221
Birth weight (g)			2605.25±310.5	2790.0±278.90	1.979	0.055
Sex	Male	N	12	13		
		%	60.0%	65.0%		
	Female	N	8	7	0.10	0.74
		%	40.0%	35.0%		
Mode delivery	CS	N	14	14		
		%	70.0%	70.0%		
	NVD	N	6	6	0.00	1.00
		%	30.0%	30.0%		
Total		N	20	20		
		%	100.0%	100.0%		

CS: Cesarean Section; GA: Gestational Age; NVD: Normal Vaginal Delivery; t: student's t test; X^2: Chi-square

Table 2: Clinical characters distribution in studied groups

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			Group		t/X^2	P
			Case (n = 20)	Control (n = 20)		
HR (beat per minute)			157.30±14.3	116.0±9.49	10.756	0.00**
RR (breath per minute)			55.60±6.82	36.10±3.97	11.044	0.00**
Pallor	-VE	N	6	20		
		%	30.0%	100.0%		
	+VE	N	14	0	21.53	0.00**
		%	70.0%	0.0%		
Cyanosis	-VE	N	14	20		
		%	70.0%	100.0%		
	+VE	N	6	0	7.05	0.008*
		%	30.0%	0.0%		
Total		N	20	20		
		%	100.0%	100.0%		

HR: Heart Rate; RR: Respiratory Rate , t: student's t test; X^2: Chi-square

Table 3: Capillary perfusion and encephalopathy distribution in studied groups

			Group		X^2	P
			Case (n = 20)	Control (n = 20)		
Capillary perfusion	Normal	N	6	20		
		%	30.0%	100.0%		
	Impaired	N	14	0	21.53	0.00**
		%	70.0%	0.0%		
Total		N	20	20		
		%	100.0%	100.0%		
HIE stage	No	N	7	20		
		%	35.0%	100.0%		
	Mild	N	2	0		
		%	10.0%	0.0%		
	Moderate	N	6	0	19.25	0.00**
		%	30.0%	0.0%		
	Sever	N	5	0		
		%	25.0%	0.0%		
Total		N	20	20		
		%	100.0%	100.0%		

Table 4: ABG distribution in studied groups

			Case (n = 20)	Control (n = 20)	t/X^2	P
PH			7.27±0.10	7.32±0.02	2.054	0.047*
PCO2 (mmHg)			41.60±7.18	42.30±1.55	1.151	0.213
HCO3 (mEq/l)			20.21±3.63	22.10±2.10	2.459	0.023*
PaO2 (mmHg)			93.50±2.54	98.35±0.67	8.243	0.00**
Metabolic acidosis	-VE	N	13	20		
		%	65.0%	100.0%		
	+VE	N	7	0	8.48	0.004*
		%	35.0%	0.0%		
Total		N	20	20		
		%	100.0%	100.0%		

HCO_3: Bicarbonate ion; PCO_2: Partial carbon dioxide pressure; PaO_2: Partial oxygen pressure
t: student's t test; X^2: Chi-square

Table 5: LV systolic function in studied groups

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	Case (n = 20)	Control (n = 20)	t	P
LVEF (mm)	47.70±5.79	66.75±5.37	10.774	0.00**
LVFS (mm)	26.70±5.13	39.60±2.81	9.856	0.00**

LVEF, Left Ventricular Ejection Fraction; LVFS: Left Ventricular Fractional Shortening
t: student's t test

Table 6: Troponin T and pro-BNP distribution in studied groups

	Case (n = 20)	Control (n = 20)	t	P
Troponin T (ng/ml)	42.60±11.1	1.60±0.55	16.488	0.00**
Pro-BNP (pg/ml)	30.90±9.98	18.35±.6.61	4.223	0.00**

Pro-BNP: Pro-Brain Natriuretic Peptide; t: student's t test

Table 7: Validity of troponin T and pro-BNP in diagnosis of myocardial injury

Test Result Variable(s)	Area	Cutoff	P	95% Confidence Interval		Sensitivity	Specificity
				Lower Bound	Upper Bound		
Troponin T	0.989	>12.5 (ng/ml)	0.00**	0.965	0.995	98.0%	97.0%
Pro-BNP	0.836	>22.5 (pg/ml)	0.00**	0.712	0.960	80.0%	78.0%

Pro-BNP: Pro-Brain Natriuretic Peptide

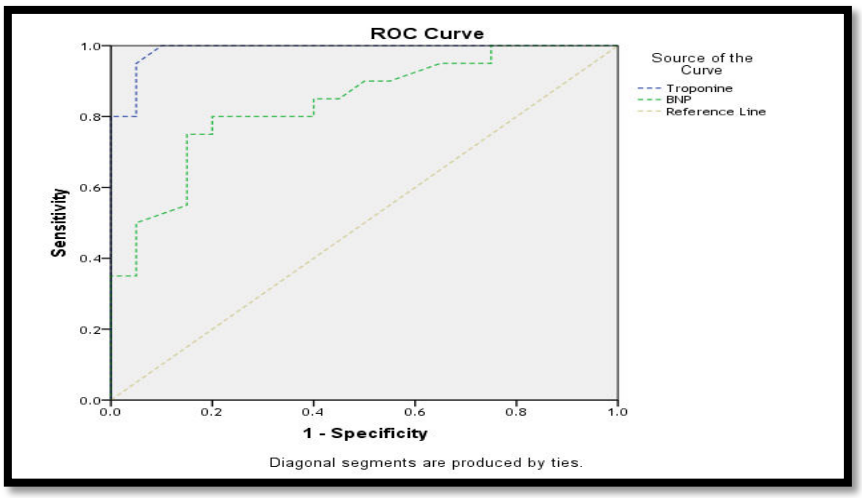

Figure (1): ROC curve for troponin T and BNP in cases

Table 8: Studied parameters in cases according to presence or absence of hypoxic-ischemic encephalopathy

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	No (n = 7)	Encephalopathy (n = 13)	t	P
Age (days)	15.57±5.21	13.84±4. 12	0.605	0.553
GA (weeks)	36.42±1.98	35.61±2.01	0.875	0.393
Birth weight (g)	2707.14±279.0	2550.38±323.2	1.081	0.294
HR (beat/minute)	148.57±12.0	162.0±13.54	2.193	0.042*
RR (breath/minute)	58.28±6.57	54.15±6.75	1.316	0.205
LVEF (mm)	51.14±3.80	45.84±5.94	2.121	0.048*
LVFS (mm)	31.57±4.31	24.07±3.32	4.336	0.00**
pH	7.32±0.03	7.24±0.12	1.751	0.097
PCO_2 (mmHg)	41.48 ± 5.86	42.01 ± 8.40	1.816	0.069
HCO3 (mEq/l)	19.9±.3.34	20.10±3.69	2.207	0.041*
PaO_2 (mmHg)	95.14±1.46	92.61±.59	2.360	0.030*
CKMB (units/L)	17.57±5.60	29.92±6.06	4.217	0.001**
Troponin T (ng/ml)	32.71±8.42	45.0±14.89	2.381	0.023*
Pro-BNP (pg/ml)	22.42 ± 5.74	35.46 ± 11.37	2.819	0.011*

CKMB: Creatine KinaseMB; GA: Gestational Age, HCO_3: Bicarbonate ion; HR: Heart Rate; LVEF: Left Ventricular Ejection Fraction; LVFS: Left Ventricular Fractional Shortening; PaO_2: Partial oxygen pressure; PCO_2: partial pressure of carbon dioxide; Pro-BNP: Pro-Brain Natriuretic Peptide; RR: Respiratory Rate., t: Student's t test

Table 9: Studied parameters in cases according to presence or absence of multiple organ failure

	No (n = 14)	Organ failure (n = 6)	t	P
Age (days)	15.71±5.21	11.50±3.78	1.491	0.153
GA (weeks)	35.50±1.91	36.83±2.13	1.423	0.172
Birth weight (g)	2557.14±332.1	2717.5±241.1	1.062	0.302
HR (beat/minute)	152.57±13.41	168.33±10.07	2.569	0.019*
RR (breath/minute)	56.57±7.37	53.33±5.16	0.971	0.344
LVEF (mm)	50.14±4.89	42.0±3.09	3.733	0.002*
LVFS (mm)	28.50±5.01	22.50±2.07	2.793	0.012*
pH	7.31±0.04	7.16±0.14	3.709	0.002*
PCO_2 (mmHg)	40.36 ± 3.96	45.66 ± 2.16	7.856	0.00**
HCO3 (mEq/l)	23.14±2.24	16.66±1.36	6.500	0.00**
PaO_2 (mmHg)	94.85±1.23	90.33±1.86	6.462	0.00**
CKMB (units/L)	22.07±7.67	33.83±.18	3.581	0.002*
Troponin T (ng/ml)	37.50±12.97	48.16±9.88	2.230	0.041*
Pro-BNP (pg/ml)	27.21±7.84	39.50±14.76	2.457	0.024*

CKMB: Creatine KinaseMB; GA: Gestational Age, HCO_3: Bicarbonate ion; HR: Heart Rate; LVEF: Left Ventricular Ejection Fraction; LVFS: Left Ventricular Fractional Shortening; PaO_2: Partial oxygen pressure; PCO_2: Partial carbon dioxide pressure; Pro-BNP: Pro-Brain Natriuretic Peptide; RR: Respiratory Rate. ,t: student's t test

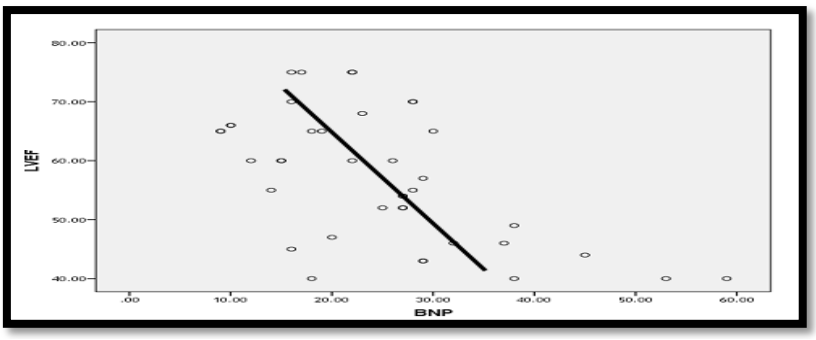

Figure (2): Correlation between LVEF and BNP

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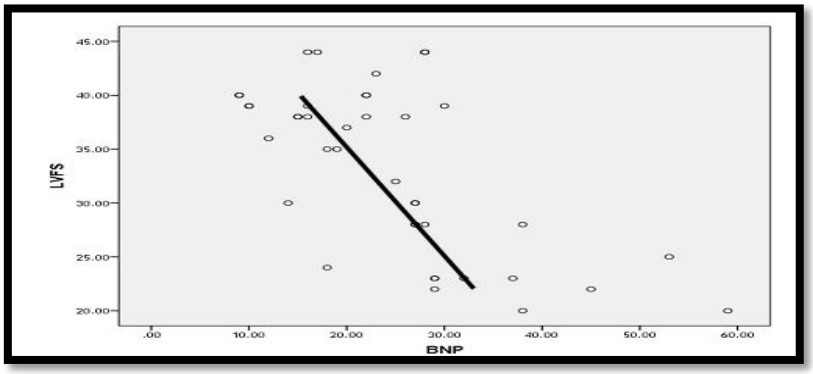

Figure (3): Correlation between LVFS and BNP.

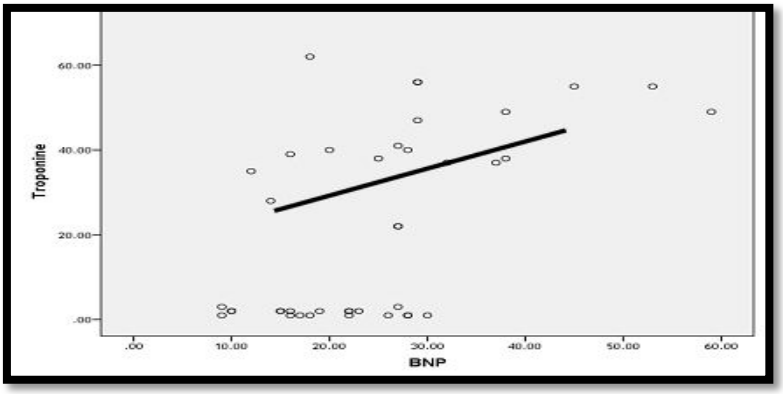

Figure (4): Correlation between troponin T and BNP.

DISCUSSION:

Early detection of myocardial damage presents an ongoing challenge for the neonatologist. Little is known about changes in myocardial function during the first days of life, when the hemodynamic circulatory system changes from two parallel to one serial circuit **(9).**

ProBNP has attracted clinical attention as a marker of cardiac function and as an indicator of left ventricular dysfunction **(10)**. In heart disease, **Costello et al. (11)** have evaluated the role of B-type natriuretic peptide (BNP). Increasing experience with BNP in pediatric heart disease has led to a greater interest in this protein as a potential marker of heart disease in children. BNP is part of a family of natriuretic peptides that affect the cardiovascular system**.**

An increase in the BNP/NT/proBNP level appears to be correlated with the timing and extent of myocardial infarction **(12)**. **Goetze et al. (13)** showed that myocardial hypoxia affects ventricular BNP gene expression and increases the plasma BNP/NT/proBNP concentration, suggesting that the elevated plasma BNP/NT/proBNP levels in the acute phase of myocardial injury in children are correlated with acute phase-localized myocardial ischemic injury.

As regard to mode of delivery, cesarean sections were higher than normal vaginal deliveries in our cases and control groups, with no significant difference between CS and NVD among studied groups ($p > 0.05$). This was in agreement with **Clark et al. (14)** found that there was no significant difference between high risk neonates and control group as regards the mode of delivery. **Szymankiewiczet al. (15)** found that asphyxiated neonates were more delivered by cesarean section than normal vaginal delivery. Also, **Masyhur et al., (16)** reported that incidence of asphyxia was higher among babies delivered by CS.

The asphyxiated cases in our study showed higher HR (157.3 ± 14.3 beats/minute in cases versus 116 ± 9.49 beats/minute in control group) and RR (55.6 ± 6.82 breaths per minute in cases versus 36.1 ± 3.97 breaths/minute in control group). Our cases were significantly associated with pallor and cyanosis unlike **Masyhur et al. (16)** reported normal heart rate examinations in asphyxiated cases**.**

In our study, a significant number of cases had poor capillary perfusion, hypoxic-ischemic encephalopathy and multiple organ failure ($p < 0.001$). In agreement with our results, a study made by **Groenendaal et al. (17)** revealed that central nervous system was the organ most frequently involved in severely asphyxiated neonates.

In our study, cases had significantly lower pH (7.27 ± 0.1 in cases versus 7.32 ± 0.02 in control group), HCO_3 (20.21 ± 3.63 mEq/L in cases versus 22.1 ± 2.1 mEq/L in control group) and PaO_2 (93.5

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± 2.54 mmHg in cases versus 98.35 ± 0.67 mmHg in control group). Marked acidosis could play an important role in myocardial injury and cerebral vasodilatation in perinatal asphyxia with subsequent circulatory insufficiency which may lead to cerebral hypoperfusion. Severe metabolic as well as respiratory acidosis develop within minutes of the onset of total fetal hypoxia **(18)**, while the metabolic acidosis occurs due to anaerobic metabolism and increased lactic acid production. Similar findings were reported by **Trevisanuto et al. (19)** showed that asphyxiated neonates had pH < 7. 18 and had low bicarbonate level, and increased lactic acid.

Cardiac troponin T is considered the preferred and gold standard biomarker for myocardial injury. Troponin is a complex of three regulatory proteins (troponin c, troponin T, troponin I) that is crucial to muscle contraction in skeletal and cardiac muscle **(20)**. Our study showed that cases were significantly higher than control subjects regarding serum level of troponin T (42.6 ± 11.1 ng/ml in cases versus 1.6 ± 0.55 ng/ml in control group) ($p < 0.001$) indicating presence of myocardial injury in our patients.

Our results showed that cases were significantly higher than control subjects regarding serum level of pro-BNP (30.9 ± 9.98 pg/ml in cases versus 18.35 ± 6.61 pg/ml in control group)(($p < 0.001$). **Ke-yu (21)** found that increased plasma NT-proBNP levels may reflect the severity of the impairment of cardiac function and myocardial damage in newborns with asphyxia.

Plasma NT-proBNP levels increase in neonates with HIE complicated by myocardial ischemic injury in the acute phase. Detection of NT-proBNP levels may be useful in the diagnosis of myocardial ischemic injury and the severity evaluation of HIE **(22).**

Regarding validity of troponin T, we found significant area under ROC curve with a cutoff value >12.5 ng/ml for troponinT, sensitivity of 98% and specificity of 97%.Regarding validity of pro-BNP, we found significant area under curve with cutoff >22.5 pg/ml for BNP with sensitivity 80% and specificity of 78%. **Gu (4)** suggested that serum NT-proBNP sensitivity can be increased to 90% and the specificity to 87% for detection of myocardial injury.

We demonstrated that NT-proBNP is a potentially useful marker of myocardial damage. NT-proBNP serum level was unaffected by gestation, birth weight, sex, chorioamnionitis and mode of delivery. **El-Khuffash and Molloy (23)** showed that myocardial hypoxia affects ventricular BNP gene expression and increases the plasma BNP/NT-proBNP concentration, suggesting that the elevated plasma BNP/NT-proBNP levels in the acute phase of myocardial injury in children are correlated with acute phase-localized myocardial ischemic injury. **Zhu and Nie (2)** demonstrated that the serum NT-proBNP level can reflect myocardial injury in neonates with asphyxia and can guide its diagnosis.

Jiang et al., (24) showed BNPsensitivity of 72.2% at 12 hours and 88.9% at 7 days of occurrence of hypoxia ischemia. However, the specificity, positive predictive value, and accuracy of BNP were low but troponin I showed a considerably higher specificity than BNP.

Wei et al. (25) found out that ventricular systolic and diastolic dysfunction increases plasma BNP levels. Left and right ventricular systolic dysfunction was associated with a higher level of plasma BNP than left ventricular diastolic dysfunction. This comes in agreement with our results. We showed that Pro-BNP was significantly negatively correlated with LVEF.Pro-BNP was significantly negatively correlated with LVFS

CONCLUSION:

Our cases had myocardial damage evidenced by higher serum levels of troponin T and pro-BNP compared with control group. Serum troponin T and pro-BNP were 98 and 80 sensitive and 97 and 78 % specific for detection of myocardial injury in our patients. Cases with HIE and those with multiple organ failure hadmore myocardial systolic dysfunction and damage evidenced by a more pronounced elevation of serum troponin T and pro-BNP compared with cases of hypoxia-ischemia with no HIE or organ failure.

Long term prospective studies are recommended to evaluate usefulness of pro- BNP as a prognostic parameter of myocardial injury in patients with neonatal hypoxia ischemia.

No Conflict of interest.

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