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ORIGINAL ARTICLE

N-terminal Pro-Brain Natriuretic Peptide in Preterm Neonates with Patent Ductus Arteriosus

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ABSTRACT

Background: N-terminal pro-BNP, the inactive by-product of Pro-BNP that is secreted from ventricular cardiomyocytes in response to volume or pressure overload, is more stable in serum samples and has a longer circulating half-life than active BNP. The study aimed to determine whether there was a correlation between plasma NT-proBNP level and echocardiographic assessment of ductal diameter and shunting to early predict cases that need treatment to decrease morbidities and mortalities of HSPDA or not**.**

Methods: The study was cohort control study performed on 30 preterm infants (20 males, 10 females) ages (28w to ≥ 37w) and admitted to Neonatal Intensive Care Unit at Zagazig University Children Hospital during the period from November 2017 to April 2018, were divided into 2 groups, Group 1: Comprised 13 neonates and they had HsPDA. Group 2: enrolled 17 cases and they had non HsPDA**.** Chest x-rays were done, Echocardiography (ECHO) at postnatal 48–72h using a vivid 7 dimension (general electric machine) Transthoracic complete M-mode, two-dimensional and Measurement of Plasma level of N-Terminal pro BNP is measured at day 1,2 and 3 by Elisa biomedica kits**.**

Results: There was a significant positive correlation on day 2 between N-terminal pro BNP and PDA Diameter. Moreover, ROC Curve detected that the cut off value for diagnosis of HsPDA was ≥ 4.55 pg/ml**. Conclusions:** N-terminal pro BNP can be considered as a sensitive diagnostic marker for detection of HsPDA and can be used early at day 2 for early diagnosis and proper management of HsPDA.

Keywords: N-terminal Pro-Brain Natriuretic Peptide, Patent Ductus Arteriosus (PDA), Neonates, Haemodynamically significant patent ductus arteriosus (HsPDA).

INTRODUCTION

Premature infants with a patent ductus arteriosus (PDA) who eventually develop PDA-related morbidities like death, intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), and chronic lung disease (CLD) have been more precisely described and characterized **[1]**.

The frequency of patent ductus arteriosus varies inversely with gestational age and can be as high as 60 percent in infants under 28 weeks **[2]**.

Morbidities linked to the patent ductus arteriosus are more likely to occur with a haemodynamically relevant PDA (hsPDA). Although the concept of a hsPDA remains uncertain, it is generally attributed to echocardiography and clinical evidence of systemic hypoperfusion and pulmonary overcirculation **[3]**.

Predicting morbidities associated with PDA will arise during the early neonatal period (within the first 48–72 h). It may promote targeted early care, reducing the number of children exposed to potentially harmful medicines **[4]**.

In response to volume or pressure overload, ventricular cardiomyocytes secrete pro-BNP to be involved in controlling the extracellular fluid volume and blood pressure. Pro-BNP is then split into the biologically active BNP and the inactive N-terminal pro-BNP by-product which is more stable in the serum sample and has a longer half-life in circulation **[5]**. The present study was conducted to determine the utility of cardiac biomarker N-terminal pro-Brain natriuretic peptide for detection of the presence of hsPD. (NTpBNP) may be useful in characterising shunt severity,

determining which PDAs warrant treatment, and predicting PDA related morbidities.

METHODS

The study was cohort control study performed on 30 preterm infants (20 males, 10 females) Their gestational ages ranged between 28 weeks to less than 37 weeks and admitted to Neonatal Intensive Care Unit at Zagazig University Children Hospital during the period from November 2017 to April 2018, were divided into 2 groups, Group 1:comprised 13 neonates and they had HsPDA. Group 2: enrolled 17 cases and they had non HsPDA**.**

Ethical Clearance: Written Informed consent was taken from the patient parents to participate in the study. Approval for performing the study was obtained from Neonatal Intensive Care Unit at Zagazig University Children Hospital after taking Institutional Review Board (IRB) approval. The research was carried out for studies involving humans in compliance with the code of ethics of the World Medical Association (Decleration of Helsinki). Haemodynamically significant patent ductus arteriosus (HsPDA) is defined according to echo (The gold standard) when patent ductus arteriosus diameter more than 1.5mm or Lt. atrium to aortic ratio more than 1.1 plus 2 or more clinical signs.

Inclusion criteria: Any preterm less than 37 weeks gestational age admitted at NICU. All enrolled infants received standard NICU care which was both precise and supportive.

Exclusion criteria: Renal failure, Congenital heart failure, Significant congenital abnormalities, Birth asphyxia in 5min with apgar ranking, Minor to 3. Extreme sepsis Enterocolitis which necrotizes Adminstration of brufen before collection of blood samples.

Method: All children have had full history and comprehensive clinical review, such as gestational age, birth weight, sex, form of delivery, apgar scores, antenatal history (preeclampsia, premature rupture of membranes, chorioamnionitis), neonatal history [respiratory distress syndrome (RDS), mechanical ventilation, surfactant treatment, positive inotrop support].

Laboratory Investigations: Plasma N-Terminal proBNP. Complete blood count (CBC): Performed using Cell Dyne 1700, Leishman-stained smears tested for red blood cell morphology and differential white blood cell count. CRP using Highly Sensitive Elisa **[6]**. Kidney functions: Using Automated Autoanalyser COBAS 501. Electolytes (Na): using BIOLYTE 2000.

***Radiological investigations*:** Chest x-ray was done for preliminary diagnosis of any radiological abnormalities in the chest Echocardiography (ECHO) at postnatal 48–72h using a vivid 7 dimension (General Electric machine) Transthoracic complete M-mode, two-dimensional and Measurement of Plasma level of N-Terminal pro BNP is measured at day 1,2 and 3 by Elisa biomedica kits.

***Principle of the Assay*:**

This package is an immunoassay with a sandwich enzyme for evaluating NT-PRO-BNP in human serum. Sample and conjugate (cattle antihuman NT-PRO-BNP-HRPO) are pipetted into the microtiter's wills, which are precoated with polyclonal non-NT-Pro -BNP antibody cattle. NT – Pro – BNP present in the sample binds to the well's precoated antibody and forms a sandwich with the antibody for detection. In a second step, all non-specific unbound material is extracted in the washing stage. The substrate (TMP teramethyl-benzidine) is pipetted into the wells and the enzyme catalyzed color change of the substrate is directly proportional to the amount of NT-PRO-BNP This color change can be detected in the sample with a regular microtitre plate reader Elisa.

Statistical Analysis:

Based on Microsoft Excel software, data collected throughout history, basic clinical evaluation, laboratory tests, and outcome measures were marked, entered, and analyses. The data were then imported into the Social Sciences Statistical Package (SPSS version 20.0) (Social Sciences Statistical Package) for analysis tools.

RESULTS

Gestational age and baby weight were significantly lower in HsPDA group. **Table (1)**

Murmur, Apnea and Metabolic acidosis were significantly associated with HsPDA group. **Table (2)**

Left atrium/aortic ratio and mean Pulmonary artery pressure were significantly higher but EF was significantly lower among HsPDA group**. Table (3)**

NT-proBNP was significantly higher in HSPDA group at day 1,2&3. **Figure(1)**

There was no significant correlation found. **Table (4).** LF atrium/aortic ratio and mean Pulmonary artery pressure were significantly higher but EF was significantly lower among HsPDA group Table (5)

PDA Diameter was significantly positively correlated with NT-proBNP among HsPDA group . PDA Diameter was significantly positive correlated with NT pro BNP among HsPDA group Table (6)

There was a significant AUC with cutoff > 4.55 and with sensitivity 84.6% and specificity 88.2%

+ve predictive 83.3% negative 78.5% accuracy 82%. **Table (7)**

Table (1): Demographic characters of studied groups

		HsPDA (N=13) (Mean ±SD)		NON HsPDA (N=17) (Mean ±SD)		t/X^2	P
GA (weeks)		32.38±3.45		35.0±2.23		-2.515	0.018*
Weight (Kg)		1.75±0.58		2.26±0.51		-2.242	0.033*
		N	%	N	%		
Sex	Female	4	30.8%	6	35.3%	0.068	0.79
	Male	9	69.2%	11	64.7%		
Total		13	100.0%	17	100.0%		

Table(2): Post natal Presentation

Variable	Group				X^2 Fisher	P
	HsPDA (N=13)		NON HsPDA (N=17)			
	N	%	N	%		
RD	13	100%	17	100%	----	-----
Heart Murmur	9	69.2%	3	17.6%	8.16	0.004*
M acidosis	7	53.8%	1	5.9%	11.94	0.001**
Convulsion	2	15.4%	0	0.0%	__	__
GIT	1	7.7%	0	0.0%	__	__
Apnea	12	92.3%	2	11.8%	18.3	0.00**

Table (3): ECHO parameters

	HsPDA (N=13)	NON HsPDA (N=17)	T	P
PDA(mm)	2.48±0.21	1.68±0.38	10.254	0.00**
L atrium /aortic ratio	1.28±0.08	0.95±0.1	9.589	0.00**
Mean Pulmonary arterypressure (mmHg)	36.92±1.89	29.94±1.85	10.136	0.00**
EF(%)	53.5±7.65	64.36±7.65	8.654	0.00**
FS(%)	42.65±8.65	48.65±5.92	1.874	0.067

Table(4): Correlations of NT pro BNP at day 2 with (demographic and basal clinical data and LAB. Finding)

	HsPDA		No HsPDA	
	NT pro BNP day 2		NT pro BNP day 2	
	r	P	R	P
demographic and basal clinical data				
GA(wk.)	-.065-	.833	-.061-	.818
Weight(kg)	-.253-	.404	-.110-	.675
APGAR_at_1st_min	-.331-	.269	.079	.763
APGAR_at_5_min	-.434-	.138	.346	.174
HR(beat\min.)	.359	.152	.352	.166
RR(breath\min.)	.471	.104	-.007-	.979
TEMP(c°)	.214	.478	.404	.087
SBP(mmHg)	-.287	.387	.087	.811
DBP(mmHg)	-.298-	.304	.238	.357

	HsPDA		No HsPDA	
	NT pro BNP day 2		NT pro BNP day 2	
	r	P	R	P
LAB. Finding				
WBC (10^3/ul)	-.309-	.304	.237	.361
Lymphocyte (10^3/ul)	-.125	.754	.122	0.796
Neutrophil (10^3/ul)	-.187	.621	.163	0.721
RBCs (10^6/ul)	-.125	.754	.122	0.796
HB (g/dl)	-.142	.644	.053	.840
MCHC (g/dl)	-.131-	.769	.079	.763
MCV (fl)	-.134-	.778	.346	.174
Platelet (10^3/ul)	-.238-	.434	.247	.339
Urea(mg/dl)	.097	.751	.408	.104
Cr (mg/dl)	.024	.938	.136	.603
Na(mEq/L)	.236	.459	-.239-	.356

Table(5): Correlations of NT pro BNP in day 2 with ECHO

	HsPDA		No HsPDA	
	NT pro BNP day 2		NT pro BNP day 2	
	R	P	R	P
PDA Diameter(mm)	0.495*	.011	-0.239	.356
L atrium/ aortic ratio	.221	.468	.416	.097
Mean Pulmonary artery pressure(mmHg)	.243	.423	.069	.791
EF(%)	-.341	.287	-.227	.388
FS(%)	.166	.624	.052	.840

PDA Diameter was significantly positive correlated with NT pro BNP among HsPDA grou

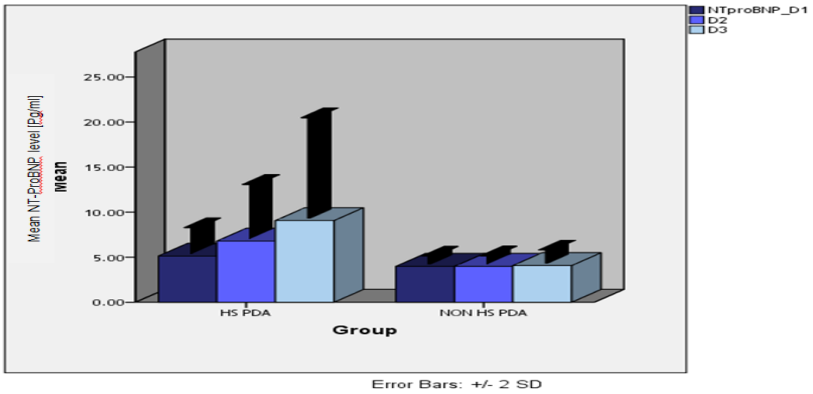
Table (6):NT pro BNP (pg/ml)distribution between groups at day 1, 2 and 3

	HsPDA (N=13)	NON HsPDA (N=17)	t	P
NT pro BNP_D1(pg/ml)	5.12±1.48	3.98±0.48	2.973	0.006*
NT pro BNP_D2(pg/ml)	6.79±2.3	3.98±0.49	3.741	0.001**
NT pro BNP_D3(pg/ml)	9.06±3.11	4.07±0.77	3.639	0.001**

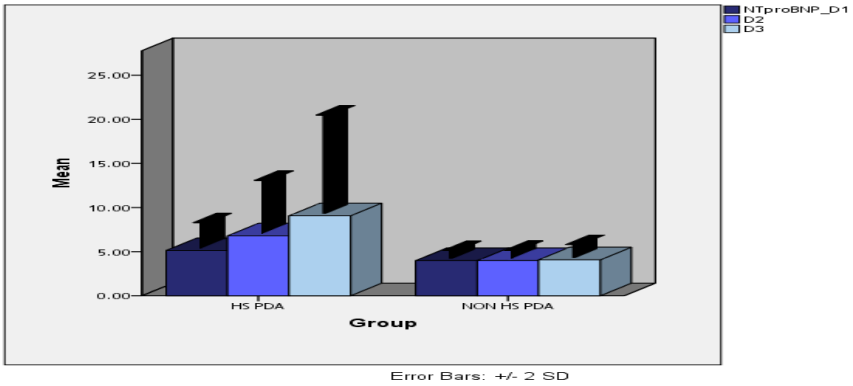
NT pro BNP was significantly higher in HSPDA group at day 1,2&3.

Table(7): Validity of NT-ProBNP in diagnosis of HsPDA at cut-off >4.55(pg/ml)

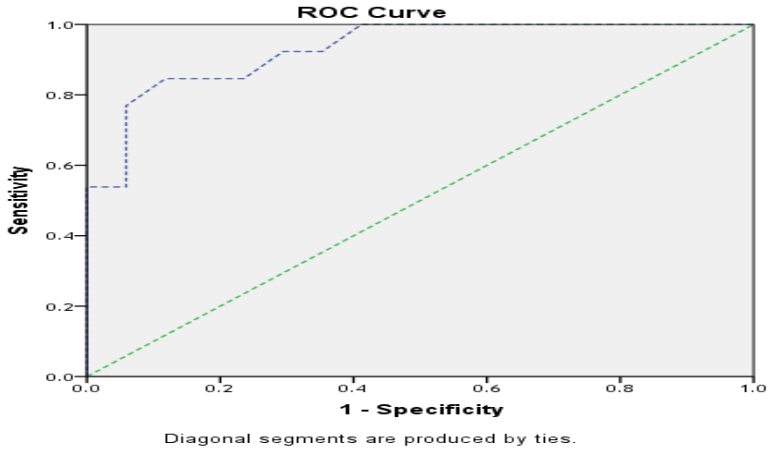
Area	Cutoff	P	95% Confidence Interval		Sensitivity	Specificity	+VE Predictive	-VE Predictive	Accuracy
			Lower Bound	Upper Bound					
0.930	>4.55(pg/ml)	0.00**	0.842	0.998	84.6%	88.2%	83.3%	78.5%	82.0%



Figure(1): Mean NT-ProBNP level (Pg/ml)in day1,2 and 3 of the studied groups



Figure(2): Mean NT-ProBNP level (Pg/ml)in day1,2 and 3 of the studied groups



Figure(3): ROC Curve for detection of NT pro BNP CUTOFF regarding HsPDA

DISCUSSION

In response to volume or pressure overload, ventricular cardiomyocytes secrete pro- BNP to be involved in the regulation of extracellular fluid volume and blood pressure. Subsequently, Pro-BNP is divided into the biologically active BNP and the inactive N-terminal pro-BNP by-product which is more stable in the serum sample and has a longer half-life in circulation **[5].**

There was a statistically significant difference between both groups about gestation age (P= 0.018) in the present sample. In addition, there was a statistically significant difference regarding weight in both groups (P= 0.033) .These results indicate that with younger gestational ages, a better chance for PDA is available. They are also concomitant with **Koch et al. [9]** who examined 122 preterm infants at Parkland Memorial Hospital from February 2001 till December 2003 and stated that spontaneous permanent DA closure is less in low gestational ages and certainly small weights. **Nuntnarumi et al. [10]** agreed with the present work also as in their study on 35 preterm infants they found a statically significant relationship between low gestational ages and increased significance of PDA (P= 0.01). Similar results were mentioned by **Bernati et al. [11]** performed a cross-sectional study at the Neonatal Ward, Neonatal Intensive Care and Rooming-in-Nursery at Mohammad Hoesin Hospital, Indonesia and

reported that PDA has a good opportunity to occur in younger preterm infants as well as smaller body weights. This can be explained by 2 things, one is that in premature infants The DA is poorly responsive to oxygen, while the other is due to impaired or defective respiratory function that indicates a delay in prostaglandin lung metabolism leading to delay or failure of DA closure.

There was no substantial difference between the two classes with respect to infant sex in the present study (P= 0.79).This finding agrees with that of **Nuntnarumi et al. [10]** who declared no relation between infant sex and significance of PDA. Also, the current results run in agreement with those of who reported no effect of sex over significance of PDA.

As a result of being preterm, all cases included in the study had respiratory distress whether HSPDA (13/13; 100%) or non-HsPDA groups (17/17; 100%). On the other hand, Apnea was significantly evident in HsPDA groupcompared with non-HsPDA group. **Dice and Bhatia [12]** mentioned the same results as they reported that newborn infants with hemodynamically significant PDA experience multiple episodes of apnea. **Nuntnarumi et al. [10]** also stated that apnea was evident in 42% of infants with HsPDA included in their study. **Zhao et al. [13]** also reported that frequent episodes of apnea are usually present in preterm infants with PDA with large shunting through it. While premature apnea (PA) is a developmental condition, impaired pulmonary reflexes and respiratory responses to hypoxia and hypercapnia are likely to lead to the incidence or severity of AOP.

The present study revealed that HsPDA group had a significantly higher heart rate, higher respiratory rate, lower systolic blood pressure and lower blood pressure by diastolic compared to non-HsPDA. In addition, cyanosis, wide pulse pressure and increases O2 demand were significantly higher in HsPDA group compared with the non-HSPDA group. The current results agreed with those of **Dice and Bhatia [12]** who reported that HSPDA is associated with tachycardia, tachypnea, decreased blood pressure and wide pulse pressure. **Nuntnarumi et al. [10]** according to the present work on tachycardia (above 160 bpm) and small pulse pressure, systolic ejection whispering, and broad pulse pressure were the most common clinical findings observed in infants with HsPDA and occurred in around 50% of their cases. **Tanabe et al. [7]** also described tachypnea, respiratory distress, tachycardia, and wide pulse pressure as suggestive signs of HsPDA.

In the present study, there was a highly significant difference between both groups regarding PDA diameter, left atrium to aortic ratio and pulmonary artery pressure all were higher in the HsPDA group compared with the non-HsPDA group(P≈0.00). In addition, Ejection fraction was significantly lower in HsPDA group. **Nuntnarumi et al. [10]** mentioned similar results as they reported larger PDA in HsPDA infants that reached 2.7±1.1 vs 1.2±0.3mm in the non-HsPDA infants.

Arlettaz [13] reported that the main echocardiographic criteria mentioned in diagnosis of HsPDA is enlargement of the left atrium to an aortic valve ratio of 0,5 and absent or retrograde diastolic flow in the descending aorta, absent or retrograde diastolic flow in the upper mesenteric and/or anterior cerebral arteries. The previous author also added that HsPDA is characterized by increased pulmonary blood flow and blamed the volume of blood flowing back through PDA, known as steal phenomenon, from the descending aorta into the lung circulation.

In the current study, NT-ProBNP was significantly higher in HsPDA group with increasing titres throughout the three days compared with the non-HsPDA group that showed nearly stationary titres. This agreed with **Nuntnarumi et al. [10]** Who found NT-ProBNP peak plasma was in the first 48hrs. Of life and then rapidly deteriorated within the first 7 days except for those with HsPDA where NT-ProBNP rates were around 5-8 times higher.

EL-Khuffash et al. [14] Significant NT-ProBNP high was registered at 48hr. Not at 12hrs of age. In premature infants with HsPDA, there is a rapid decline following positive PDA closure.

Farombi-Oghuvbu et al.[15] examined NT-ProBNP serial plasma levels in 49 infants less than 34wks on day 1,3,5 and 10 of life. Of gestation and found that NT-ProBNP plasma was substantially higher in premature neonates ith HsPDA on days 3 and 5, not on day 1 or day 10. These findings as well as ours indicate that the best timing for calculating the amount of NT-ProBNP to predict HsPDA should be at day 2-3 of life. Recent studies have shown that on day 1 of birth, NT-ProBNP level was affected by gestational age, where the level was higher in the more premature infants. High at day 10 was more linked to sepsis infants **[15].**

BNP and NT-ProBNP plasam concentrations are roughly similar in normal subjects, but NT-ProBNP is 2-10 times higher in heart failure patients, which can be explained by cardiac secretion changes ± clearance mechanisms **[16].** Also, the current study revealed that the only element that showed statistically significant

positive correlation- throughout the study- with NT-Pro BNP was PDA diameter.

This agreed with **Nuntnarumi et al. [10]** who showed that in day 3 NT-ProBNP was significantly correlated with LA/AO ratio and PDA diameter, whereas **EL-Khuffash et al. [17]** at 12 o'clock NT-ProBNP was posted. Of age substantially associated with RDS and LA / AO but not ductal. The conflicting results of the correlation between plasma levels and related variables at the time of the measurements indicate the difference in postnatal age. Moreover, ROC Curve was made to detect the cut off value of NT-Pro BNP at the second day and revealed that area under curve (AUC) reached 0.93 with a cutoff value of >4.55, sensitivity 84.6% and specificity 88.2%. Such finding indicates that NT-ProBNP can considered as a potential diagnostic marker for detection of HsPDA.

Nuntnarumi et al. [10] reported similar results throughout their study as they declared that high NT-ProBNP plasma levels were observed in infants who developed HsPDA on the second day which suggests a good screening tool of NT-ProBNP to predict HsPDA. They added that AUC of 0.964 with a cutoff value of >10.18, sensitivity 100% and specificity 91.3%.

CONCLUSIONS

N-terminal pro BNP can be considered as a sensitive diagnostic marker for detection of HsPDA and can be used early at day 2 for early diagnosis and proper management of HsPDA.

Limitations of our study: While infants at the extreme viability (around 26 wks) are most likely to be treated for HsPDA, they are under-represented in studies to date, resulting in a potentially significant gap in information about the efficacy of applying reported concentration thresholds of natriuretic peptides to this high-risk population.

RECOMMENDATIONS

Further study is warranted by the ability of natriuretic peptides to predict associated PDA complications which aid in the development of PDA staging system.

Declaration of interest: The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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