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# Brain Natriuretic Peptide (BNP) Correlates Echo Finding of Hemodynamic Patent Ductus Arteriosus

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## ABSTRACT

**Background**: When Doppler echocardiography is not readily available, a biomarker like NT-pro-Brain Natriuretic Peptide (BNP) can be used to diagnose patent ductus arteriosus (PDA) in premature infants.

**Objective**: To evaluate the diagnostic accuracy of the cardiac biomarkers BNP for detection of hemodynamically significant patent ductus arteriosus (hsPDA) in preterm newborns and their correlation to echocardiography results.

**Patients and Methods:** At tertiary care hospital at National Heart Institute, a total of 46 premature neonates (< 34 weeks gestation) or those whose birth weight was less than 1200 g who were admitted to Neonatal Intensive Care Units (NICUs) were included in this cross-sectional study. Patients with PDA were classified as having either hsPDA or non-hsPDA based on a large ductal flow with left to right shunt on colour Doppler echocardiography, and all participating neonates underwent this evaluation between 48- and 72-hours following birth.

**Results:** Serum brain-type natriuretic peptide was statistically significantly higher in cases with hsPDA. Serum brain-type natriuretic peptide statistically had significant high diagnostic performance in predicting hemodynamically significant patent ductus arteriosus. Serum brain-type natriuretic peptide at cut-off value of ≥108.0 pg/mL, had moderate sensitivity, but high other characteristics in diagnosing hsPDA.

**Conclusion:** Preterm newborns at risk for poor outcome due to PDA may be identified by serum brain-type natriuretic peptide in combination with echocardiography.

**Keywords**: Brain Natriuretic Peptide, Patent Ductus Arteriosus.

## INTRODUCTION

The ductus arteriosus or fetal circulation vessel, often closes shortly after birth in full term newborns. However, the prevalence of patent ductus arteriosus (PDA) decreases with increasing gestational age, and it is known to stay persistent in a high proportion of extremely low gestational age newborn newborns. Infants born weighing less than 1,000 grammes or those born before 28 weeks of gestation have a 66% chance of developing a persisting PDA [(1)]. Additionally, newborns with neonatal respiratory distress syndrome who require mechanical ventilation and those who did not get prenatal corticosteroids are less likely to close. There are a number of serious complications that can arise from having a PDA that won't go away, including intraventricular haemorrhage, pulmonary haemorrhage, necrotizing enterocolitis, and chronic lung disease/bronchopulmonary dysplasia, and an increased risk of death [(2)].

One cardiac peptide that rises in ventricular dysfunction is B-type natriuretic peptide (BNP). After being synthesized and secreted by the ventricle, this molecule is converted enzymatically in response to myocardial strain to pro-BNP. Many studies have demonstrated that measuring serum levels of natriuretic peptides is an accurate way to diagnose heart failure and predict the patient's prognosis [(3)].

Biochemical indicators, in addition to clinical and echocardiographic examination, may aid in determining the hemodynamic importance of a PDA. The brain-type natriuretic peptide (BNP) is a possibility since it is released by ventricular myocytes in response to volume excess. Premature newborns may benefit from BNP measures for the diagnosis and evaluation of PDA [(4)]. BNP has a half-life of 20 minutes; it produces diuresis, natriuresis, and arterial dilatation. A corresponding decrease in intravascular volume and ventricular preload is anticipated as a result. Previous research has shown a link between BNP and shunt volume size, suggesting its utility in assessing hemodynamically significant patent ductus arteriosus (hsPDA); however, its physiologic relationship with blood flow indices has not yet been investigated [(5)].

When it comes to making a clinical diagnosis of PDA, echocardiography is unrivalled. In addition to confirming a PDA diagnosis and ruling out or diagnosing a congenital heart defect, this test can be used to estimate the size of the shunt and evaluate its hemodynamic significance, specifically the impact on the body's circulation caused by the shunt's causing pulmonary over-circulation and systemic hypoperfusion [(6)].

## AIM OF THE STUDY

It was the goal of this study to evaluate the diagnostic accuracy of the cardiac biomarkers BNP for detection of hsPDA in preterm newborns and their correlation to echocardiography results.

## PATIENTS AND METHODS

**Subjects:**

At tertiary care hospital at National Heart Institute, a total of 46 premature neonates (< 34 weeks'



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gestation) or weighing less than 1200 g at birth admitted to the Neonatal Intensive Care Units (NICUs) were included in this cross-sectional study.

During this study 70 preterm neonates were assessed for eligibility and 46 preterm neonates. Of all eligible patients, 14 patients were excluded from the study based on inclusion criteria and 10 parents of patients refused to participate in the study.

Patients were separated into those with PDA that threatened their blood pressure and those without. The hemodynamically significant PDA were 16, the non-hemodynamically significant PDA were 30.

**Inclusion criteria:**

Premature neonates (< 34 weeks gestations) or weighing in at a birthweight of less than 1200 g.

**Exclusion criteria:**

- Maternal chronic disease e.g. DM, Hypertension • Autoimmune disease e.g. SLE, Rheumatoid Arthritis.
- Congenital heart defect other than PDA.
- Malformation present at birth that poses a risk of death.
- Fetal asphyxia of high severity.

Within the first 48-72 hours of life, all neonates were screened for PDA using colour Doppler echocardiography to distinguish between hsPDA and non-hsPDA. This was done by looking for a significant ductal flow with left-to-right shunt:

1) On day 2 of life, blood samples were taken for BNP measurement in addition to the standard blood tests.
2) Echocardiography was systematically performed.

This is what all of the participants in this research had to go through:
Full patient's medical history takes=n as well as general examination.

- **Investigations**

**BNP:** Routine blood samples were obtained in lithium-heparin tubes and centrifuged in the lab for 6 minutes after being kept at room temperature for transport. BNP was detected in plasma supernatant through enzyme-linked immunosorbent assay (ELISA).

**Echocardiographic measurements:**

An 8-MHz probe was used for the echocardiography (Philips CX 50). Measurements were taken using standard echocardiographic techniques as recommended by the American Society of Echocardiography[7].

**Diagnosis of hsPDA (Clinical criteria):**

The following criteria were used to establish a diagnosis of Echocardiographic hsPDA based on the data presented in the prior report: (1) ductal diameter ≥1.5 mm, (2) LA⁄Ao ratio ≥1.4 and (3) the ratio of diastolic retrograde flow TVI to systolic anterograde flow TVI through the descending aorta is less than 30%[5].

**Outcome Measurement:**

As a screening technique to predict hsPDA and provide further information regarding its spontaneous closure or lack thereof, the BNP level in conjunction with Echo measures of systemic blood flow indicators in babies with Hemodynamic PDA appears promising.

**Ethical consent:**

**An approval of the study was obtained from Zagazig University Academic and Ethical Committee (ZU-IRB#9488-8-5-2022). Every patient's parent signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

***Statistical analysis***

In order to analyze the data acquired, Statistical Package of Social Sciences (SPSS) version 20 was used to execute it on a computer. In order to convey the findings, tables and graphs were employed.

The quantitative data was presented in the form of the mean, median, standard deviation, and confidence intervals. The information was presented using qualitative statistics such as frequency and percentage. The student's t test (T) is used to assess the data while dealing with quantitative independent variables. Pearson Chi-Square and Chi-Square for Linear Trend (X2) were used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined.

**RESULTS**

Table **(1)** shows that: maternal age, neonatal gestational age and birth weight were 31.1±5.7 years, 30.8±2.3 weeks and 996.7±97.4 gm respectively. Males and females were almost equal in the studied cases (56.5% and 43.5% respectively).

**Table (1): Demographics**

| Variables | | Mean±SD | Range |
|---|---|---|---|
| **Maternal age (years)** | | 31.1±5.7 | 20.0–42.0 |
| **Gestational age (weeks)** | | 30.8±2.3 | 26.0–34.0 |
| **Birth weight (gm)** | | 996.7±97.4 | 742.0–1197.0 |
| | | **N** | **%** |
| **Sex** | **Male** | 20 | 43.5 |
| | **Female** | 26 | 56.5 |

**Figure (1)** shows that: About one third (34.8%) of the studied cases had hemodynamically significant patent ductus arteriosus (hsPDA).

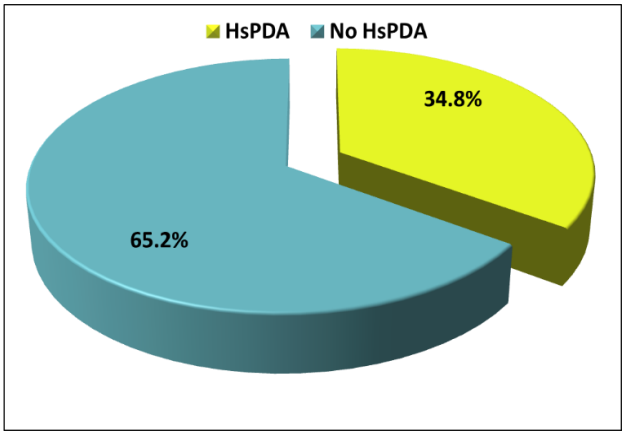


**Figure (1):** Patent ductus arteriosus (PDA) with hemodynamic significance (hsPDA) was found in the population of patients analyzed.

Table **(2)** shows that when comparing births of babies of different sexes and mothers of different ages, hsPDA found no statistically significant differences. Cases of hsPDA were associated with statistically decreased gestational age at birth and birth weight

**Table (2): Comparison according to HsPDA regarding demographic characteristics**

| Variables | | HsPDA (N=16) | No HsPDA (N=30) | p-value |
|---|---|---|---|---|
| Maternal age (years) | | 29.8±5.3 | 31.7±5.9 | ^0.281 |
| Gestational age (weeks) | | 29.7±2.2 | 31.4±2.1 | ^**0.015*** |
| Birth weight (gm) | | 953.8±80.9 | 1019.5±98.8 | ^**0.027*** |
| Sex | Male | 9 (56.3%) | 17 (56.7%) | #0.978 |
| | Female | 7 (43.8%) | 13 (43.3%) | |

**Table (3)** shows that: According to HsPDA, there were no discernible variations in CRP. Cases with HsPDA had statistically greater levels of serum brain-type natriuretic peptide.

**Table (3): Comparison of HsPDA and Non HsPDA regarding serum brain-type natriuretic peptide (pg/mL) among the studied cases**

| Measures | HsPDA (N=16) | No HsPDA (N=30) | p-value |
|---|---|---|---|
| CRP (mg/L) | 36.6±8.41 | 25.4±6.2 | ^0.183 |
| BNP (pg/mL) | 170.2±8.6 | 61.6±3.6 | ^<**0.001*** |

**Table (4)** shows that neonatal LA/AO, ductal diameter and left ventricular output statistically were significantly higher in cases with hsPDA. Right ventricular output statistically was significantly lower in cases with hsPDA.

**Table (4): Comparison of hsPDA to non hsPDA regarding echocardiography findings among the studied cases**

| Variables | HsPDA (N=16) | Non HsPDA (N=30) | p-value |
|---|---|---|---|
| LA/AO | 1.6±0.2 | 1.2±0.1 | ^<**0.001*** |
| Ductal diameter (mm) | 2.2±0.4 | 1.2±0.1 | ^<**0.001*** |
| RVO (ml/kg/min) | 234.8±30.1 | 264.7±28.0 | ^**0.002*** |
| LVO (ml/kg/min) | 328.9±31.7 | 295.1±26.0 | ^<**0.001*** |

Table **(5)** shows that: BNP statistically had no significant correlation with maternal age, neonatal gestational age, birth weight and CRP. BNP statistically had significant positive correlations with LA/AO, ductal diameter and left ventricular output as well as significant negative correlation with right ventricular output

**Table (5): Correlations of serum brain-type natriuretic peptide among the studied cases**

| Variables | r | p-value |
|---|---|---|
| Maternal age (years) | -0.032 | 0.831 |
| Gestational age (weeks) | -0.256 | 0.086 |
| Birth weight (gm) | -0.255 | 0.088 |
| CRP (mg/L) | 0.268 | 0.072 |
| LA/AO | 0.648 | <**0.001*** |
| Ductal diameter (mm) | 0.756 | <**0.001*** |
| RVO (ml/kg/min) | -0.432 | **0.003*** |
| LVO (ml/kg/min) | 0.371 | **0.011*** |

Table **(6)** and figure **(2):** Serum brain-type natriuretic peptide statistically had significant high diagnostic performance in predicting hemodynamically significant patent ductus arteriosus.

**Table (6): Diagnostic performance of serum brain-type natriuretic peptide in predicting hsPDA**

| Factors | AUC | SE | p-value | 95% CI | Cut off |
|---|---|---|---|---|---|
| BNP | 0.961 | 0.001 | <**0.001*** | 0.904–1.000 | ≥108.0 pg/mL |

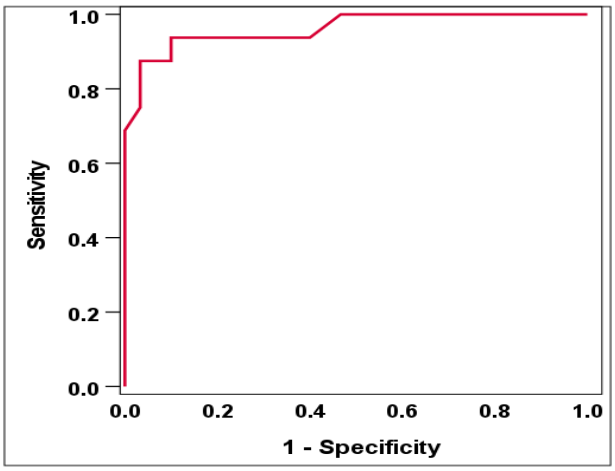


**Figure (2):** ROC curve for serum brain-type natriuretic peptide in predicting HsPDA

Table **(7)** serum brain-type natriuretic peptide 108.0 pg/mL had moderate sensitivity, but high other characteristics in diagnosing hsPDA.

**Table (7): Diagnostic characteristics of Serum brain-type natriuretic peptide suggested ≥108.0 pg/mL in diagnosing hsPDA**

| Characteristics | Value | 95% CI |
|---|---|---|
| **Sensitivity** | 87.5% | 61.7%–98.4% |
| **Specificity** | 96.7% | 82.8%–99.9% |
| **Diagnostic accuracy (DA)** | 93.5% | 82.1%–98.6% |
| **Youden's index** | 84.2% | 66.7%–101.6% |
| **Positive Predictive value (PPV)** | 93.3% | 68.1%–99.8% |
| **Negative Predictive value (NPV)** | 93.5% | 78.6%–99.2% |
| **Positive likelihood ratio (LR+)** | 26.25 | 3.79–181.92 |
| **Negative likelihood ratio (LR-)** | 0.13 | 0.04–0.47 |
| **Diagnostic odds ratio (DOR)** | 203.00 | 16.94–2433.20 |

Table **(8)** shows that mechanical ventilation and mortality were significantly more frequent in hsPDA cases.

**Table (8): Comparison of hsPDA regarding Clinical prognosis**

| Conditions | HsPDA (N=16) | Non HsPDA (N=30) | p-value |
|---|---|---|---|
| **Mechanical ventilation** | **16 (100.0%)** | **16 (53.3%)** | **§<0.001*** |
| **Mortality** | **14 (87.5%)** | **11 (36.7%)** | **#<0.001*** |

## DISCUSSION

Patients with hemodynamically significant PDA have an increased pulmonary blood flow accompanied by a decreased effective systemic blood flow due to substantial shunting of blood from the systemic to the pulmonary circuit. hsPDA is associated with a wide variety of comorbid illnesses in preterm babies and is therefore identified in over 30% of infants born to moms with gestational ages of 32 weeks or less [(2)]. Since NT-proBNP levels are significantly higher in preterm infants and correlate substantially with PDA diameter in the first three weeks of life, preterm birth is a strong risk factor for PDA, This method is helpful in detecting PDA in premature infants when Doppler echocardiography is unavailable [(8)].

The current study revealed that Mean ±SD of maternal age, neonatal gestational age and birth weight were 31.1±5.7 years, 30.8±2.3 weeks and 996.7±97.4 gm respectively. Males and females were almost equal in the studied cases (56.5% and 43.5% respectively) and Serum brain-type natriuretic peptide level was 99.4±66.2 pg/mL.

The current study results revealed that 34.8% of the studied cases had hemodynamically significant patent ductus arteriosus (hsPDA).

Results from our study showed that maternal age and newborn sex did not differ significantly between the hsPDA and non-hsPDA groups, however gestational age and birth weight did differ significantly less in cases with hsPDA. (p value= 0.015, 0.027) respectively.

Our study results revealed that serum brain-type natriuretic peptide was evaluated within the first 48-72 h of life and was statistically significantly higher in cases with hsPDA (p value<0.001).

In concordance with our results, **Alenazi *et al.*** [(5)] as a predictor of hsPDA, NT-pro-BNP levels were studied in a prospective blind study of 33 infants born at fewer than 31 weeks of gestation or weighing less than 1200 g at birth and demonstrated that, with the exception of newborns with severe hsPDA, Plasma NT-pro-BNP levels were highest on day one of life and decreased until day seven. The hsPDA group had significantly (p0.001) higher plasma NT-pro-NBP levels on day 2 than the non-HPDA group. The non-hsPDA group showed a peak in plasma NT-pro-BNP levels within the first two postnatal days, followed by a gradual decline over postnatal days 3-7; this is highly indicative of a ductus that will close on its own [(9)].

Our findings are also consistent with those of **El-Khuffash and colleagues [(10)],** who found a significantly elevated level of NT-pro-BNP on Day-2, not Day-1, in preterm children with hsPDA, and a quick drop following successful PDA. Plasma NT-pro-BNP levels on day 3 were considerably greater in babies with hsPDA compared to either day 1 or day 10, according to a study by **Farombi-Oghuvbu and colleagues [(11)]**. These results, together with our own, indicate that days 2-3 of life are optimal for measuring NT-pro-BNP level in order to predict hsPDA.

As regards brain-type natriuretic peptide, our study results revealed that BNP statistically had no significant correlation with maternal age, neonatal gestational age and birth weight while it had statistically significant positive correlations with LA/AO, ductal diameter and left ventricular output as well as significant negative correlation with right ventricular output (p value<0.001).

Consequently, Serum brain-type natriuretic peptide had statistically significant high diagnostic performance in predicting hemodynamically significant patent ductus arteriosus. Serum brain-type natriuretic peptide at cut-off value of ≥108.0 pg/mL, had moderate sensitivity, but high other characteristics in diagnosing hsPDA. In agreement with our findings, **Alenazi and colleagues [(5)]** compared hsPDA and non-hsPDA infants for Left Atrial to Aortic Ratio (LA/AO) thickness (p<0.002), interventricular septum thickness (p0.03),

and diastole PDA gradient ($p<0.005$) using echocardiography.

Also, **Occhipinti *et al.*** [12] NT-pro-BNP plasma concentrations associated with ductal size and left atrial dilatation in preterm neonates. Our investigation demonstrated that the LA/AO ratio was related to plasma NT-pro-BNP concentration after adjusting for potential confounding variables.

Also, **Khosroshahi *et al.*** [2] study utilizing cross-sectional data from 60 infants and children diagnosed with VSD, ASD, or PDA based on echocardiographic and hemodynamic evaluations, the authors conclude that there is a significant link between the blood level of pro-BNP and the degree of shunt in these patients. ($P = 0.01$) Serum levels of pro-BNP were positively correlated with the Qp/Qs ratio. At a concentration of 40.36 pg/mL, the sensitivity and specificity for detecting pro-BNP with a Qp/Qs ratio greater than 1.5 were 92% and 79%, respectively.

In light of the fact that traditional echo-graphic signals are not particularly good predictors of PDA spontaneous closure, a low NT-pro-BNP level may serve as a useful independent marker of PDA spontaneous closure. The strongest predictive values for hsPDA were found in the peak plasma NT-pro-BNP level on day 2, which was 75.52 pg/ml [5].

Findings were consistent with a previous study that identified hsPDA in premature newborns by measuring NT-pro-BNP on day 3 [13].

As a result, a preterm infant's NT-pro-BNP level on days 2-3 may be utilised as a screening tool to anticipate hsPDA and guide physicians to seek early echocardiographic assessment [5].

## CONCLUSION

Newborns with hsPDA had significantly elevated plasma BNP levels on Day 2, and their plasma NT-pro-BNP levels peaked between days 1 and 3 after birth. As a result, its concentration may serve as a screening tool to foretell hsPDA and shed light on whether or not the condition resolves on its own. The measurement of serum brain-type natriuretic peptide and the performance of an echocardiography can help physicians identify preterm children with PDA who are at risk for a poor outcome and may benefit from targeted medicinal therapy of PDA. We recommend screening for hsPDA by measuring plasma BNP levels within the first three days of life.

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