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ESTIMATION OF SERUM N-TERMINAL BRAIN NATRIURETIC PEPTIDE LEVELS IN PRETERM NEWBORNS WITH PATENT DUCTUS ARTERIOSUS(PDA) – A ONE-YEAR HOSPITAL-BASED PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Patent ductus arteriosus (PDA) is a common cardiovascular condition in preterm neonates, often diagnosed using clinical and echocardiographic markers. N-terminal pro-brain natriuretic peptide (NT-proBNP) has been proposed as a potential biomarker for PDA screening and severity assessment.

Objectives: This study aimed to estimate serum NT-proBNP levels in preterm neonates with PDA and analyze its correlation with PDA size and hemodynamic significance (hsPDA).

Methods: A hospital-based prospective observational study was conducted on 49 preterm neonates (<37 weeks gestation) admitted to the NICU at KLEH Dr. Prabhakar Kore Hospital, Belagavi, from December 2023 to December 2024. Clinical data, 2D echocardiography, and serum NT-proBNP levels were recorded. Statistical analysis was performed using R version 4.2.3, with a significance threshold of $p < 0.05$.

Results: Among the 49 neonates, 25 (51%) were male and 24 (49%) were female. The mean gestational age was 32.52 ± 3.08 weeks. PDA was hemodynamically significant (hsPDA) in 53.06% of cases. Analysis of Variance statistical method indicated significant differences in gestational age among PDA size groups (p=0.013). A moderate positive correlation was observed between PDA size and NT-proBNP levels (r=0.52, p=0.0002). Infants with hsPDA had significantly higher NT-proBNP levels (median 26,605 pg/mL) compared to those without hsPDA (median 5,976 pg/mL, p=0.036). Additionally, NT-proBNP levels were significantly elevated in neonates with heart failure (p=0.027) and those who did not survive (p=0.034).

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Conclusion: NT-proBNP levels demonstrate a significant correlation with PDA size and hemodynamic significance, supporting its role as a non-invasive biomarker for PDA assessment in preterm neonates. The findings suggest that NT-proBNP could aid in early diagnosis and clinical decision-making for PDA management, complementing echocardiographic evaluation. Further studies are warranted to establish standardized NT-proBNP cut-off values for PDA screening in neonatal care.

INTRODUCTION

Patent ductus arteriosus (PDA) is a common cardiovascular anomaly in preterm neonates, characterized by the failure of the ductus arteriosus to close after birth. This fetal blood vessel connects the pulmonary artery to the aorta, allowing oxygenated blood to bypass the lungs in utero. Normally, the ductus closes within the first few days of life as the newborn transitions to independent breathing[1]. However, in preterm infants, this closure is often delayed or incomplete, leading to hemodynamically significant PDA (hsPDA), which can result in pulmonary overcirculation, left ventricular overload, and systemic hypoperfusion. If left untreated, hsPDA is associated with complications such as bronchopulmonary dysplasia, necrotizing enterocolitis, and intraventricular hemorrhage[2].

The incidence of PDA is inversely proportional to gestational age, with lower gestational age correlating with a higher likelihood of persistent PDA[3]. Management strategies for PDA include conservative measures such as fluid restriction and positive airway pressure[4], pharmacological interventions using cyclooxygenase inhibitors (indomethacin or ibuprofen)[5], and surgical ligation in refractory cases[6]. Treatment decisions depend on the hemodynamic significance of PDA, clinical deterioration, and associated morbidities[2,7].

In recent years, biomarkers have gained attention as potential tools for diagnosing and predicting PDA severity. Inflammatory markers such as growth differentiation factor 15 (GDF-15), monocyte chemotactic protein 1 (MCP-1), platelet aggregation markers, and prostaglandin D2 synthase (PGDH) have been associated with persistent PDA, reflecting the role of inflammation in its pathogenesis. Isoprostanes (uIPs) have been identified as reliable indicators for detecting hemodynamically significant PDA (hsPDA) and assessing its progression[8].

Among cardiac biomarkers, brain natriuretic peptide (BNP) and its precursor, N-terminal pro-BNP (NT-proBNP), have been widely studied in preterm neonates with PDA. NT-proBNP is secreted by the ventricular myocardium in response to increased wall stress and volume

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overload, making it a valuable marker for cardiac dysfunction[9]. Elevated NT-proBNP levels correlate with PDA size, severity, and persistence despite pharmacological treatment. Studies have shown that NT-proBNP levels are significantly higher in symptomatic PDA (sPDA) cases compared to asymptomatic PDA (asPDA), with a strong correlation between NT-proBNP levels and ductal diameter[10,11].

Moreover, NT-proBNP has been explored as a potential predictor of PDA closure failure, with elevated levels beyond ten days postnatally indicating an increased likelihood of persistent PDA[12]. Some studies suggest that NT-proBNP levels may aid in assessing the need for pharmacological or surgical intervention, particularly when used in conjunction with echocardiographic parameters[13,14].

Given the growing interest in NT-proBNP as a non-invasive biomarker for PDA evaluation, the present study was conducted at KLE's Dr. Prabhakar Kore Hospital, Belagavi. This study aims to estimate NT-proBNP levels in preterm infants with PDA and analyze their correlation with PDA size, thereby contributing to the optimization of diagnostic and management strategies for PDA in preterm neonates.

MATERIALS AND METHODS

This observational study was conducted in the Neonatal Intensive Care Unit (NICU) of KLEH Dr. Prabhakar Kore Charitable Hospital, Belagavi, Karnataka, over a period of one year (December 2023 to December 2024)**.** Preterm infants undergoing echocardiographic evaluation were enrolled based on predefined inclusion and exclusion criteria. Ethical approval was obtained from the institutional ethics committee (Reference no: MDC/JNMCIEC/101), and informed consent was secured from the parents after a detailed explanation of the study objectives in an understandable language.

The sample size was determined using the formula:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where Z = 1.960**,** P = 12%[15] (prevalence of preterm births in India), and d = 10% precision. The calculated sample size was 49, with an additional 10% attrition rate, bringing the total to 53 patients included in the study. The study included preterm infants born before 36 weeks of

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gestation who were admitted to the NICU and underwent echocardiographic evaluation with parental informed consent. Exclusion criteria comprised preterm infants with other congenital heart disease, neonatal sepsis, bronchopulmonary dysplasia, congenital anomalies, or bleeding tendencies. Additionally, infants whose parents refused consent were not included in the study.
The study included 49 preterm neonates. Clinical parameters such as age, sex, birth weight, and other relevant factors were recorded. 2D echocardiography was performed, and serum NT-proBNP levels were measured in the hospital laboratory. Blood samples (2 mL) were collected in plain vacutainers and analyzed using chemiluminescence immunoassay. All collected data were meticulously recorded in an Excel spreadsheet for further statistical analysis.

Statistical Analysis

Data were analyzed using R version 4.2.3. Continuous variables were summarized as mean ± standard deviation (SD). Categorical variables were presented as frequencies and percentages. Comparisons between groups were conducted using the independent t-test or Mann-Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. Correlation analysis between NT-proBNP levels and PDA size was performed using Pearson's correlation.A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 49 preterm neonates were included in the study, with a mean gestational age of 32.52 ± 3.08 weeks. The study population consisted of 28 males (57.1%) and 21 females (42.9%), with no significant difference in PDA incidence based on gender. The mean NT-proBNP level across all neonates was 17,398 ± 16,966 pg/mL.hsPDA was observed in 25 neonates (51%), and they had significantly higher NT-proBNP levels than those with non-hsPDA ($p = 0.036$)(Table 1). Infants requiring medical intervention had markedly higher NT-proBNP concentrations compared to those managed conservatively. Out of the total study population, 7 neonates (14.3%) succumbed during the study period. NT-proBNP levels were significantly elevated in non-survivors (median 34,593 pg/mL) compared to survivors (median 10,281 pg/mL, $p = 0.034$)

Among the 49 neonates, 25 (51%) had hsPDA, classified into small (24.49%), moderate (24.49%), and large (51.02%) PDA based on echocardiographic assessment. NT-proBNP levels were significantly elevated in neonates with larger PDA diameters ($r = 0.52$, $p = 0.0002$)

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DISCUSSION

The present study aimed to estimate serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in preterm neonates with patent ductus arteriosus (PDA) and evaluate its potential as a biomarker for PDA diagnosis and severity assessment. Our findings demonstrate a significant elevation of NT-proBNP levels in preterm neonates diagnosed with hemodynamically significant PDA (hsPDA) compared to those without PDA, corroborating earlier research findings.

The elevated NT-proBNP levels in hsPDA cases can be attributed to the increased cardiac volume load and myocardial stretch, as supported by previous studies[16–18]. BNP and its precursor, NT-proBNP, are secreted by ventricular myocytes in response to pressure and volume overload[19]. The persistence of PDA leads to increased pulmonary blood flow and left atrial volume overload, subsequently stimulating BNP release[1]. Our study aligns with existing literature, wherein NT-proBNP has been identified as a sensitive marker for left ventricular volume overload and PDA severity.

A notable observation in our study was the progressive decline in NT-proBNP levels following medical closure of PDA using nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and indomethacin. This decline further substantiates the role of NT-proBNP as a dynamic biomarker reflecting changes in hemodynamic status post-treatment. This finding is consistent with previous studies demonstrating that a significant reduction in NT-proBNP levels occurs post-PDA closure[12,13,20,21], suggesting its utility in monitoring treatment response.

Furthermore, our results underscore the importance of NT-proBNP in differentiating hsPDA from non-hemodynamically significant PDA (non-hsPDA). The significantly higher NT-proBNP levels in hsPDA cases, as compared to non-hsPDA neonates, highlight the peptide's potential in guiding therapeutic decisions. Similar results have been documented in studies[11,13,22–26] where NT-proBNP demonstrated high sensitivity and specificity in distinguishing hsPDA from non-hsPDA. The application of NT-proBNP as a diagnostic marker may facilitate early and targeted intervention, reducing reliance on echocardiography, which is often resource-intensive and operator-dependent.

The correlation analysis in our study indicated a strong positive association between NT-proBNP levels and echocardiographic markers of PDA severity, including ductal diameter and left atrial-to-aortic (LA/Ao) ratio. This association reinforces NT-proBNP's role as a reliable

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surrogate marker for echocardiographic assessment of PDA severity, consistent with prior findings in neonatal research[10].

However, certain limitations must be acknowledged. First, the study was conducted in a single tertiary care center, potentially limiting generalizability. Additionally, variations in NT-proBNP levels due to gestational age, perinatal stress, and renal function were not extensively accounted for, which may influence its diagnostic accuracy. Future multicentric studies with larger sample sizes and stratification based on gestational age may provide more robust conclusions.

CONCLUSION

NT-proBNP levels serve as a non-invasive biomarker for evaluating PDA severity in preterm neonates. Higher NT-proBNP concentrations correlate significantly with hsPDA, indicating its potential role in early risk stratification and clinical management.Our study reinforces the utility of NT-proBNP as a reliable biomarker for PDA diagnosis and severity assessment in preterm neonates. The strong correlation between NT-proBNP levels and echocardiographic parameters highlights its potential role in guiding early diagnosis and therapeutic decision-making.

REFERENCES

1. Gillam-Krakauer M, Mahajan K. Patent Ductus Arteriosus. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 30]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK430758/

2. Hamrick SEG, Sallmon H, Rose AT, Porras D, Shelton EL, Reese J, et al. Patent Ductus Arteriosus of the Preterm Infant. Pediatrics [Internet]. 2020 [cited 2024 Mar 26];146(5):e20201209. doi:10.1542/peds.2020-1209

3. Dice JE, Bhatia J. Patent Ductus Arteriosus: An Overview. The Journal of Pediatric Pharmacology and Therapeutics [Internet]. 2007 [cited 2024 Mar 26];12(3):138–46. doi:10.5863/1551-6776-12.3.138

4. Evans P, O'Reilly D, Flyer JN, Soll R, Mitra S. Indomethacin for symptomatic patent ductus arteriosus in preterm infants. Cochrane Neonatal Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2021 [cited 2024 Mar 26];2021(1). doi:10.1002/14651858.CD013133.pub2

5. Jasani B, Weisz DE, Reese J, Jain A. Combination pharmacotherapy for patent ductus arteriosus: Rationale and evidence. Seminars in Perinatology [Internet]. 2023 [cited 2025 Mar 29];47(2):151720. doi:10.1016/j.semperi.2023.151720

6. Tort M, Ceviz M, Sevil F, Becit N. Surgical Treatment for Patent Ductus Arteriosus: Our Experience of 12 Years. Cureus [Internet]. 2021 [cited 2024 Mar 26]; doi:10.7759/cureus.14731

ISSN: 0975-3583,0976-2833 VOL16, ISSUE 03, 2025

7. Nemri AMHA. Patent ductus arteriosus in preterm infant: Basic pathology and when to treat. Sudan J Paediatr. 2014;14(1):25–30.

8. Wei Y-J, Hsu R, Lin Y-C, Wong T-W, Kan C-D, Wang J-N. The Association of Patent Ductus Arteriosus with Inflammation: A Narrative Review of the Role of Inflammatory Biomarkers and Treatment Strategy in Premature Infants. IJMS [Internet]. 2022 [cited 2024 Mar 26];23(22):13877. doi:10.3390/ijms232213877

9. Cao, Jia, Zhu. BNP and NT-proBNP as Diagnostic Biomarkers for Cardiac Dysfunction in Both Clinical and Forensic Medicine. IJMS [Internet]. 2019 [cited 2024 Jan 25];20(8):1820. doi:10.3390/ijms20081820

10. Shi Y, Ji J, Wang C. Exploring the NT-proBNP expression in Premature Infants with Patent Ductus Arteriosus (PDA) by Echocardiography. Pak J Med Sci [Internet]. 2021 [cited 2024 Mar 26];37(6-WIT). doi:10.12669/pjms.37.6-WIT.4853

11. Buddhe S, Dhuper S, Kim R, Weichbrod L, Mahdi E, Shah N, et al. NT-proBNP levels improve the ability of predicting a hemodynamically significant patent ductus arteriosus in very low-birth-weight infants. J Clin Neonatol [Internet]. 2012 [cited 2024 Jun 10];1(2):82. doi:10.4103/2249-4847.96758

12. Potsiurko S, Dobryanskyy D, Sekretar L. Predictive value of blood N-terminal pro-brain natriuretic peptide concentrations for early patent ductus closure in very preterm infants. Journal of the Saudi Heart Association [Internet]. 2021 [cited 2024 Mar 26];32(4):462--470. doi:10.37616/2212-5043.1230

13. Cucerea M, Marian R, Simon M, Anciuc-Crauciuc M, Racean A, Toth A, et al. Serum Biomarkers in Patent Ductus Arteriosus in Preterm Infants: A Narrative Review. Biomedicines [Internet]. 2025 [cited 2025 Mar 29];13(3):670. doi:10.3390/biomedicines13030670

14. Gudmundsdottir A, Bartocci M, Picard O, Ekström J, Chakhunashvili A, Bohlin K, et al. Early N-Terminal Pro B-Type Natriuretic Peptide (NTproBNP) Plasma Values and Associations with Patent Ductus Arteriosus Closure and Treatment—An Echocardiography Study of Extremely Preterm Infants. JCM [Internet]. 2022 [cited 2025 Mar 29];11(3):667. doi:10.3390/jcm11030667

15. Jana A. Correlates of low birth weight and preterm birth in India. Weobong B, editor. PLoS ONE [Internet]. 2023 [cited 2024 Mar 26];18(8):e0287919. doi:10.1371/journal.pone.0287919

16. Xie H, Huo Y, Chen Q, Hou X. Application of B-Type Natriuretic Peptide in Neonatal Diseases. Front Pediatr [Internet]. 2021 [cited 2024 Jun 1];9:767173. doi:10.3389/fped.2021.767173

17. Mouzarou A, Hadjigeorgiou N, Melanarkiti D, Plakomyti TE. The Role of NT-proBNP Levels in the Diagnosis of Hypertensive Heart Disease. Diagnostics [Internet]. 2025 [cited 2025 Mar 29];15(1):113. doi:10.3390/diagnostics15010113

18. Wärja M, Laveborn E, Ott M, Jonsson AP, Stegmayr B. NT-pro-BNP as marker for cardiac strain that may be caused by high-output arteriovenous shunting in a haemodialysis patient. A case report. BMC Nephrol [Internet]. 2020 [cited 2025 Mar 30];21(1):544. doi:10.1186/s12882-020-02195-9

ISSN: 0975-3583,0976-2833 VOL16, ISSUE 03, 2025

19. Kuwahara K. The natriuretic peptide system in heart failure: Diagnostic and therapeutic implications. Pharmacology & Therapeutics [Internet]. 2021 [cited 2025 Mar 30];227:107863. doi:10.1016/j.pharmthera.2021.107863

20. Kusmira D, Nova R, Bakri A. NT-proBNP level and left ventricle diameters before and after transcatheter closure of PDA and VSD. PI [Internet]. 2018 [cited 2025 Mar 30];58(5):213–20. doi:10.14238/pi58.5.2018.213-20

21. Mahfouz RA, Alzaiat A, Gad M. Association of aortic stiffness to brain natriuretic peptide in children before and after device closure of patent ductus arteriosus. Journal of the Saudi Heart Association [Internet]. 2015 [cited 2025 Mar 30];27(1):23–30. doi:10.1016/j.jsha.2014.06.001

22. Bagnoli F, Rossetti A, Casucci M, Mori A. Aminoterminal B-type natriuretic peptide (NT-proBNP) in the therapy of patent ductus arteriosus. Minerva Pediatr. 2010;62(3 Suppl 1):67–70.

23. Gokulakrishnan G, Kulkarni M, He S, Leeflang MM, Cabrera AG, Fernandes CJ, et al. Brain natriuretic peptide and N-terminal brain natriuretic peptide for the diagnosis of haemodynamically significant patent ductus arteriosus in preterm neonates. Cochrane Neonatal Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2022 [cited 2024 Mar 26];2022(12). doi:10.1002/14651858.CD013129.pub2

24. Sakhuja R, Januzzi JL. NT-proBNP – A New test for Diagnosis, Prognosis and Management of Congestive Heart Failure. US Cardiol [Internet]. 2004 [cited 2025 Mar 30];1(1):148–9. doi:10.15420/usc.2004.1.1.148

25. Rodriguez-Blanco S, Oulego-Erroz I, Gautreaux-Minaya S, Perez-Muñuzuri A, Couce-Pico ML. Early NT-proBNP levels as a screening tool for the detection of hemodynamically significant patent ductus arteriosus during the first week of life in very low birth weight infants. J Perinatol [Internet]. 2018 [cited 2024 Jun 12];38(7):881–8. doi:10.1038/s41372-018-0123-x

26. Permyakova AV, Porodikov A, Kuchumov AG, Biyanov A, Arutunyan V, Furman EG, et al. Discriminant Analysis of Main Prognostic Factors Associated with Hemodynamically Significant PDA: Apgar Score, Silverman–Anderson Score, and NT-Pro-BNP Level. JCM [Internet]. 2021 [cited 2024 Jun 12];10(16):3729. doi:10.3390/jcm10163729