Short Communication

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Usefulness of Serum Brain Natriuretic Peptide Level for Screening Hemodynamically Significant Patent Ductus Arteriosus in Preterm Neonates

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Abstract

Objective: We studied usefulness of serum B-type natriuretic peptide level as a screening tool for detecting hemodynamically significant patent ductus arteriosus in the preterm neonates.

Methods: Sixty admitted preterm neonates with gestational age ≤34 weeks, birth weight ≤2500 gr, and age of >3 days have been enrolled in this study. We measured serum B-type natriuretic peptide levels at the beginning and after completion of drug therapy for ductus occlusion.

Findings: Mean±SD gestational age and weight was 31±1.9 weeks and 1680±350 gr, respectively. The peptide levels in the neonates with significant duct (n=13) were significantly higher than in those with insignificant duct (n=17) or no duct (n=30) (1667±821 pg/ml versus 667±666 and 309±171, respectively). The peptide level dropped significantly after ibuprofen administration in the neonates with significant PDA (n=13), (1667±1165 pg/ml to 429±386).

Conclusion: At a cutoff point of 450 pg/ml, B-type natriuretic peptide level had a sensitivity of 92% and specificity of 87%, the negative predictive value of 98.5%, the positive likelihood ratio of 6.92 and the negative likelihood ratio of 0.089 for detecting significant patent duct. Levels below this can eliminate the need for echocardiography.

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Key Words: Brain natriuretic peptide; Patent Ductus Arteriosus; Echocardiography; Ibuprofen

Introduction

The prevalence of patent ductus arteriosus (PDA) in preterm neonates <1750 gr is 45% while in those <1200 gr it reaches 80%[1]. Surfactant replacement therapy in the preterm neonates with respiratory distress syndrome may prevent natural PDA closure in up to 90% of the cases due to decrease in the pulmonary vascular resistance[2]. The significant left to right shunt through PDA can lead to intra-ventricular hemorrhage, necrotizing enterocolitis (NEC) and death[3]. PDA in the preterm neonates can increase the risk of bronchopulmonary dysplasia[4]. Therefore, early treatment of a hemodynamically significant PDA (hsPDA) can reduce symptoms, hospital stay, ventilator support, and the need for surgery[5,6]. The hemodynamic significance of a PDA is based on the clinical signs, chest radiography findings, and echocardiography as the gold standard method of diagnosis[7-10].

B-type natriuretic peptide (BNP) is secreted from

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the cardiac ventricles in response to volume or pressure overload[11]. Serum level of this peptide or its N-terminal propeptide are popular biomarkers for ventricular volume or pressure overload[12]. The children with a hemodynamically significant ventricular septal defect have increased BNP levels, correlating with the shunt ratio and left ventricular end diastolic volume[13,14]. Previous studies have shown that there is a good relationship between BNP level and significance of PDA[2,3,14-16].

Echocardiography is a relatively expensive tool and requires skilled echocardiographer to detect hsPDA. The objective of our study was to identify whether serum BNP level can differentiate between hsPDA and hemodynamically insignificant PDA (hiPDA). Specifically, we searched a cut-off point for diagnoss of hsPDA. If serum BNP level can differentiate hsPDA from hiPDA, it can guide treatment of PDA reducing the number of indometacine/ibrufen doses.

Subjects and Methods

We conducted this study in the neonatal intensive care unit at Motahhari Educational Hospital, Urmia University of Medical Sciences, West Azerbaijan Privince, from August 2011 to July 2012. The Ethics Committee of the University approved it. We obtained written informed consent from all parents.

Selection criteria: Preterm neonates <34 weeks of gestational age and <2500 gr birth weight on the second or the third day of life were enrolled. We administered oral ibuprofen for medical treatment of PDA. The neonates with congenital heart diseases other than PDA, documented sepsis, shortening fraction <28%, NEC, renal failure (blood urea nitrogen >30 mg/dl or serum creatinine >2 mg/dl), persistent pulmonary hypertension, Apgar score <3 in 10 minutes, multiple congenital anomalies, or under vasopressor treatment were excluded from the study[17-19].

Echocardiography: The first echocardiography was applied at the time of enrollment and the patient assigned to any of hsPDA, hiPDA, or control groups. Then a blood sample was taken for measuring BNP level. The neonates with PDA were treated by oral ibuprofen (10mg/kg on first day, and 5 mg/kg on second and third days). On the fifth day after taking the first dose of ibuprofen, the second echocardiography and blood sample were applied in those in the PDA group.

We measured shortening fraction and the left ventricular end-diastolic diameter in diastole (LVED) by echocardiography (MicroMaxx Ultrasound System, Sonosite Inc., USA) on M-Mode. The narrowest diameter of PDA was measured by the two-dimensional ductal view with the color Doppler mode. All echocardiographies were performed and interpreted by a single pediatric cardiologist blinded to the clinical and serum BNP data. hsPDA was defined according to either of the following parameters[20]:

1) Elevated left atrial to aortic root ratio (>1.3:1 or >1.5:1, depending on fluid and diuretic policy),
2) Retrograde diastolic flow in the descending aorta exceeding 30% of the antegrade flow,
3) Narrowest ductal diameter >1.4 mm.

Blood sampling for BNP: After the first echocardiography, 2 ml blood sample was taken and collected in K-EDTA tubes and sent to laboratory within 24 hours. After centrifuging at 3500 rpm for 10 minutes, serum was stored at -20 °C until analysis by the triage BNP kit. The second sample was taken five days after treatment with ibuprofen. This test is a reliable method for the rapid measurement of BNP in the patients with heart failure[21].

Statistical Analysis: We used SPSS version 18 and the MedCalc version 12 softwares for statistical analyses. The data were expressed as mean±SD for the continuous variables and as a number and percentage for the categorical variables by the collected echocardiographic data. The groups were compared by ANOVA, Post hoc (Dunnett & Tukey), and Kruskal-Wallis tests for the continuous variables and t independent and Mann-Whitney tests to compare BNP levels before and after taking ibuprofen. The Box and Whiskers Plot of BNP levels was used to represent the distribution in these three groups. Receiver operator characteristics (ROC) curves were constructed for the different serum levels of BNP cut-off values to determine the best sensitivity and specificity and area under the curve. The statistical significance was set as $P<0.05$.

Table 1: Characteristics of the study groups with PDA in Preterm Neonates

Variables	Control (n=30)	hiPDA (n=17)	hsPDA (n=13)
Age (days)	2.93	2.82	3
Weight (gr)	1702	1765	1530
Gestational Age (weeks)	31.2	31.1	3.04
B-type natriuretic peptide (pg/ml)	309	667	1667

PDA: Patent Ductus Arteriosus; hiPDA/ hsPDA: Hemodynamically insignificant/significant PDA

Findings

Basic characteristics: Sixty preterm neonates including 36 males and 24 females have been enrolled. The gestational age was 31±1.9 weeks, the birth weight 1680±350 gr, and the postnatal age 2.9±0.28 days. There was no difference among these groups regarding age, weight, gestational age and gender (Table 1).

Serum BNP data: The serum levels of BNP in hsPDA neonates (n=13) was significantly higher than in hiPDA patients (n=17) and those in the control group (n=30) (Table 1). There was a significant difference between serum BNP levels before and after oral ibuprofen in hiPDA (n=17, 667±606 vs 198±106) and hsPDA (n=13, 1667±1164 and vs 429±386).

Value of BNP in diagnosing hsPDA: We calculated sensitivities, specificities, negative and positive predictive values and positive and negative likelihood ratios along with 95% confidence intervals of the serum BNP levels in diagnosing hsPDA using various cut-off points. The area under the curve was maximum (0.962, 95% CI 0.854 to 0.997) at a cut-off point value of 450 pg/ml with a sensitivity of 92.3%, specificity of 86.7%, positive predictive value 55%, negative predictive value 98.5%, positive likelihood ratio of 6.92 and negative likelihood ratio of 0.089.

Discussion

Based on our findings, the serum level of BNP can reliably differentiate hsPDA from hiPDA and no PDA state in preterm neonates. Serum levels of BNP <450 pg/ml has a high negative predictive value and in this case, echocardiography can be avoided. In addition, serum level of BNP can differentiate hsPDA from hiPDA, avoiding unnecessary interventions. Probability of the presence of hsPDA is high at the serum level of BNP >450 pg/ml because of positive likelihood ratio of 6.92. Therefore, in case of a high level of serum BNP an echocardiography is indicated to differentiate PDA from other cardiac structural anomalies and left ventricular dysfunction. If the serum level of BNP is <450 pg/ml, the probability of the presence of hsPDA is low according to the negative likelihood ratio of 0.089, and echocardiographic examination may be unnecessary. After successful treatment and closure of PDA, the serum level of BNP dropped dramatically to the level of no PDA state and this makes the serum level of BNP a valuable tool for the therapeutic monitoring. This can reduce the number of echocardiograms and eliminates the concern about recurrent or persistent PDA after the treatment.

The higher level of serum BNP in preterm neonates with hsPDA was shown in many studies including those of Choi et al, Sanjeev et al, and Czernik et al[2,16,22-24]. The best cutoff point in the latter study was 550 pg/ml with sensitivity and the specificity of 83% and 86%, respectively[2,16,22].

Decrease of the serum BNP level after the closure of hsPDA is compatible with the results of Sarjeev et al, and Bagnoli et al[1,16].

Conclusion

Plsma BNP level was proved to be a good predictor for ductal intervention. In infants with PDA diagnosed by echocardiography and serum BNP levels >450 pg/ml, intervention is required. Decrease of the serum level of BNP to its normal level indicates a successful treatment.

Authors' Contribution

Concept / Design: A.J. Khosroshahi, A. Kianfar
Acquisition of Data: A.J. Khosroshahi, A. Kianfar
Data Analysis / Interpretation: A.J. Khosroshahi, A. Kianfar, K. Sayadpour Zanjani
Manuscript Preparation: B. Mohammadpour Aharanjani, K. Sayadpour Zanjani
Critical Revision of the Manuscript: K. Sayadpour Zanjani
All authors approved final version of the paper.

Conflict of Interest: None

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