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The relation between brain natriuretıc peptide and patent ductus arteriosus in premature infants

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Summary

Aim: To compare brain natriuretic peptide level and some of the echocardiographic parameters of premature infants and to search its value for the diagnosis of patent ductus arteriosus.

Material and Method: Fifty infants born before the 34th gestational week in the neonatology clinic of Bakırkoy Obstetrics and Children's Education Hospital between March 2009 and August 2009 were inspected prospectively.

Patients with patent ductus arteriosus constituted Group 1 (n=20) and patients without patent ductus arteriosus constituted Group 2 (n=30). The diagnosis of patent ductus arteriosus was made by M-mode and Doppler echocardiography on the 7th day postnatally. Ductus diameter, left atrium aortic root diameter ratio, left ventricular end diastolic diameter, interventricular septum thickness, left ventricular posterior wall thickness, ejection fraction and fractional shortening were evaluated. The infants with hemodynamically significant patent ductus arteriosus were treated.

Brain natriuretic peptide was evaluated on the 1st, 3rd and 7th days of postnatal age in all patients and also on the 3rd day after treatment.

For statistical analysis SPSS for Windows 15.0 was used. The study was conducted after obtaining informed consent from the patients and was approved with the decision of the ethics committee (number 231, date 12-6-2009).

Results: Sex, gestational age and birth weight were similar in both grups. When brain natriuretic peptide level was compared with ductus diameter, left atrium aortic root diameter ratio and left ventricular end diastolic diameter values, the results were found to be statistically significant ($p<0.05$). When comparison was made with interventricular septum thickness, left ventricular posterior wall thickness, ejection fraction and fractional shortening values, the results were found to be statistically insignificant ($p>0.05$). Brain natriuretic peptide level decreased significantly after treatment.

Conclusions: Brain natriuretic peptide level was found be higher in infants with patent ductus arteriosus compared to infants without patent ductus arteriosus. It was shown that ductus diameter, left atrium aortic root diameter ratio and left ventricular end diastolic diameter were related with brain natriuretic peptide levels. *(Turk Arch Ped 2012; 47: 92-6)*

Key words: Patent ductus arteriosus, brain natriuretic peptide, premature infant, echocardiography, atrial natriuretic peptide, left atrium aortic root diameter ratio, left ventricular end diastolic diameter.

Introduction

Persistance of patency of ductus arteriosus which should be closed postnatally is called patent ductus arteriosus (PDA). Since patent ductus arteriosus leads to severe conditions in preterm infants, its diagnosis and treatment are important. The size of the shunt and the time it remains open determine the prognosis. Hemodynamic disorders, necrotizing enterocolitis, bronchopulmonary dysplasia, enteral feding intolerance, congestive heart failure, inability to be separated from the ventilator predispose to intraventricular bleeding (1).

Clinical findings are very important in the diagosis of patent ductus arteriosus. For definite diagnosis echocardiography is the golden standard. However, supplementary investigations can be beneficial, if clinical findings suggest PDA in centers where ECHO is unavailable. Natriuretic peptide is one of these (2,3). In recent years, use of natriuretic peptide (BNP) as a supplementary investigation in the diagnosis has increased, though not used solely in the diagnosis of PDA.

Brain natriuretic peptide is a polypeptide consisting of 32 amino acids and a hormone released from the ventricles of the heart in case of hemodynamic stress and congestive heart failure

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(4-6). BNP which is released from the ventricles as a response to increased ventricular volume load is a cardiac marker which is convenient for use for urgent diagnosis, since it is produced rapidly at high levels in cases of congestive heart failure, left ventricular dysfunction and increase of pressure and volume load in the left and right ventricles. Its half-life is approximately 20 minutes. It has an important role in the investigation of the diagnosis, screening and response to treatment in cardiac diseases in children as well as in adults (7-12).

In this study, the presence of PDA was investigated by performing ECHO on the 7th day in preterm babies born with a gestational week of 34 and it was attempted to determine the relation between BNP and the cardiac variables which are affected by volume and pressure load.

Material and Method

50 newborns born before tha age of 34th gestational week between March 2009 and August 2009 in İstanbul Bakırköy Women's and Children's Education and Research Hospital were included in the study. While 20 subjects constituted the study group (group 1), 30 subjects constituted the control group (group 2). Birth weights, gestational weeks and genders were compared between the two groups. PDA characteristics of the subjects in group 1 were investigated. Information about treatment was recorded. Infants whose mothers had systemic diseases including diabetes, systemic lupus erythematosus and hyperthyroidism, who received steroid in the first week postnatally, who were found to have congenital heart disease prenatally or in the first week postnatally, who had clinical and confirmed sepsis and who used inotropic agents because of resistant hypotension were excluded from the study.

When PDA was evaluated in the study group, it was separated into three groups including hemodynamically significant, clinically significant and insignificant. Hemodynamically significant PDA was defined based on left atrium/aortic root (LA/Ao) and PDA diameter. Clinically significant PDA was defined as follows: inability to be separated from the ventilator despite hemodynamically insignificant atrium/aortic root (LA/Ao) and PDA diameter measurements. Insignificant PDA was defined as absence of clinical findings related to PDA and hemodynamically insignificant measurements.

1 ml blood was obtained from all patients on the first, third and fifth days postnatally. Blood samples were centrifuged at 7000 rpm for 5 minutes in 20 minutes and kept at -20°C. After blood samples of all subjects were collected, BNP levels were measured with microelisa method using "Brain Natriuretic Peptide-32 (Human) EIA KIT" kit (Phoneix Pharmaceutıcals, INC. 330 Beach Road Burlingame, CA 94010 USA, Catalog No: EK-011-03, Lot No: 601231). BNP levels were measured again on the third day after treatment in patients who were defined to have PDA by echocardiography and immediately after the treatment cycle in patients who received a second treatment cycle and the results were recorded.

Echocardiogram was performed by a single pediatric cardiologist using "General Electric Logiq Book XP" echo device. 8C sector probe was used in all patients. ECHO was performed on the 7th day of hospitalization in all preterm infants. ECHO was repeated on the 10th day in subjects who were defined to have PDA and who received treatment. In patients who needed the second treatment cycle, ECHO was repeated at the end of the treatment.

The cardiac variables evaluated on echocardiography included interventricular septum end-diastolic diameter (IVSd), left ventricular end-diastolic diameter (LVEDd), left ventricular posterior wall end-diastolic thickness (LVPWd), interventricular septum systolic diameter (IVSs), left ventricular systolic diameter (LVSd), aortic root width (Ao) and left ventricular (LA) width. Left atrium/aortic root ratios were calculated manually. Ejection fraction (EF) and shortening fraction (SF) were calculated by the system automatically. All measurements were repeated for three times, their avarages were taken and recorded on the form.

Infants with a PDA diameter of 1.5 mm on colored doppler ECHO and a LA/Ao ratio higher than 1.4 were defined to have "hemodynamically significant PDA".

In patients who were decided to receive treatment, oral ibuprofen treatment was started. Treatment was given to 13 patients who were defined to have "hemodynamically significant PDA" and to 2 patients who were not defined to have "hemodynamically significant PDA", but who were found to have high ventilator variables clinically and who had resistant acidosis. Ibuprofen was given with a dose of 10 mg/kg/day on the first day and with a dose of 5 mg/kg/day on the second and third days orally. In patients who needed to be treated for the second time, intravenous ibuprofen was administered with the same dose as the oral treatment.

Brain natriuretic peptide level was examined related to the following variables: gender, birth weight, gestational week at te time of birth, ECHO measurements including IVSd, LVEDd, LVPWd, EF, SF, PDA diameter and La/Ao ratio. While comparing BNP measurements related to the groups normal distribution was based on the sample mean values and assumption test was applied for population mean values. For continious variables (PDA diameter, IVSd, LVEDd, LVPWd, EF, SH, La/Ao ratio) Pearson correlation coefficient which shows the proportional relation with BNP value was calculated.

The data obtained were statistically analyzed using "SPSS (Statistical Package for Social Sciences) for Windows 15.0" program. The numerical variables were expressed as mean±standard deviation. The results were evaluated at a confidence interval of 95% with a significance level of p=0.05.

Results

In group 1, hemodynamically significant PDA was defined in 13 patients, clinically significant PDA was defined in 2 patients and insignificant PDA was defined in 5 patients.

While group 1 consisted of 12 female and 8 male infants, group 2 was composed of 16 female and 14 male preterm infants. Gestational weeks and birth weights of the patients in group 1 and group 2 were as follows respectively: 31.2±3.13; 30.4±2.82 weeks and 1446±445 (710-2200); 1305±419 g (610-2090 g). There was no significant difference between the two groups (p = 0.187; p = 0.135).

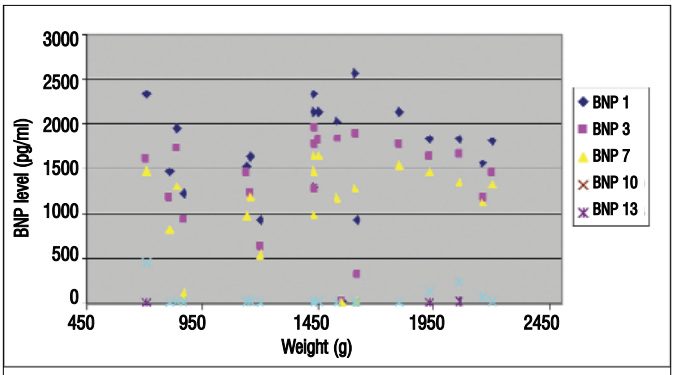
Among all patients, mean BNP level was found to be 456.93±699 pg/ml in male patients and 591.48±748 pg/ml in female patients (p= 0.257). When the groups were evaluated within themselves, no significant difference was found between male and female gender and BNP levels.

Preterm babies in group 1 were divided into two groups as ≤1500 g and >1500 g. While the mean BNP level of the patients who had a body weight of ≤1500 g was found to be 375.1±522 pg/ml, it was found to be 411±531 pg/ml in the patients who had a body weight of <1500 g. It was observed that the level of brain natriuretic peptide was not related to body weight (Graphic 1; p=0.4).

The mean PDA diameter was found to be 2.02±0.63 mm in group 1. The relation between brain natriuretic peptide and PDA diameter was determined using Pearson correlation coefficient. The coefficient calculated for 20 subjects was found to be 0,724 (p=0.0003) and it was significant. It was observed as PDA diameter increased, BNP level increased (Graphic 2). One of the most important follow-up variables in patients with hemodynamically significant PDA is LA/Ao ratio. The mean LA/Ao ratio in group 1 and 2 were found to be 1.5±0.2; 1.3±0.1, respectively. Pearson correlation coefficient between left atrium/aortic diameter and BNP level is 0.673 (p<0.0001) which is statistically significant. It was observed as left atrium/aortic diameter ratio increased, BNP level increased. In patients with patent ductus arteriosus, BNP levels increased in parallel to the increase in LA/Ao ratio, while LA/Ao ratio and BNP levels were found to be low in parallel (Graphic 3).

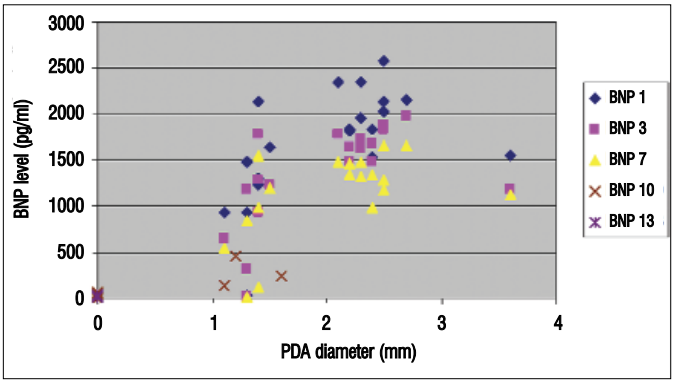
The mean left ventricular end-diastolic diameter was found to be 12.4±.9 mm and 10.3±1.8 mm in group 1 and group 2, respectively. A proportional relation was found between the left ventricular end-diastolic diameter and BNP levels and the Pearson correlation coefficient of this relation was found to be 0.771 (p<0.0001) which was statistically significant (Graphic 4). In a great proportion of the patients with increased left ventricular end-diastolic diameter, hemodynamically significant (hs) PDA was observed.

IVSd, LVPWd, EF, SF levels were found to be 3±0.6 mm, 2.8±0.5 mm; 3.4±0.5 mm, 3.0±0.8 mm; 71.9±3.8; 74±5.9; 38.1±2.9; 37.1±4.8 in group 1 and group 2, respectively and no statistically significant relation was found with BNP levels (p= 0.26; p= 0.17; p= 0.15; p= 0.5).

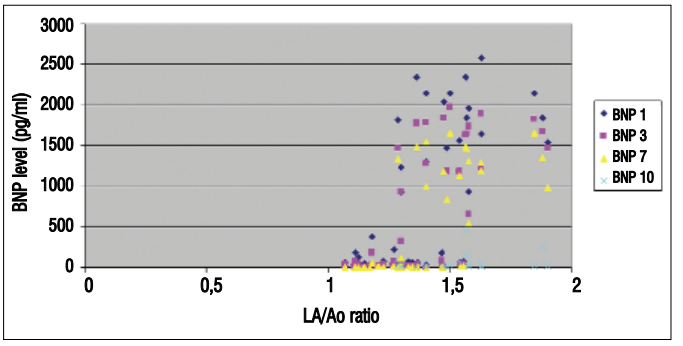


*BNP1: BNP obtained on the first day, BNP 3: BNP obtained on the third day, BNP 7: BNP obtained on the 7th day, BNP 10: BNP obtained on the 10th day, BNP 13: BNP obtained on the 13th day

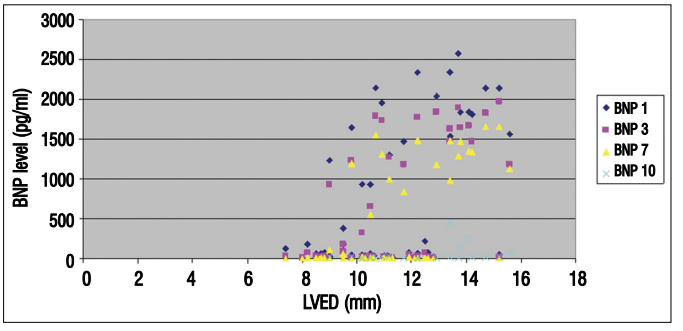
Graphic 1. The relation of BNP levels with weight



Graphic 2. The relation between BNP levels and PDA diameter



Graphic 3. The relation between BNP levels and left atrium/aortic diameter



Graphic 4. The relation between BNP levels and LVEDd

While BNP levels just before treatment were found to be 987.4±573.5 pg/ml in group 1 patients, post-treatment BNP levels were found to be 62.6±110.6 pg/ml. A significant decrease was found in BNP levels on the third day after treatment (p<0.0001).

Discussion

When BNP levels of the male and female babies in the whole study group were compared, no statistically significant difference was found (p=0.257). In the studies previously performed in newborns and children, gender difference was not investigated. In the study performed by Clerico et al. (13), BNP levels of healthy women (12.2±10.2 pg/ml) were compared with BNP levels of healthy men (7.7±7.1 pg/ml) and BNP levels of the women were found to be significantly higher. This result was attributed to female sex hormones.

No relation was found between gestational age and BNP levels in the patients included in our study (p=0.187). In the literature, Graca et al.(14) measured BNP levels in 19 patients in their study and found no relation between gestational age and BNP levels. Our finding was compatible with the literature. When the relation between birth weights and BNP levels were investigated, the difference between the patient group and the control group was insignificant (p=0.135).

In our study, BNP level of 20 patients with PDA were found to be 914.4±461.4 pg/ml, while BNP level of the control group was found to be 39.4±41.6 pg/ml. The difference was statistically significant (p<0,0001). When the literature was screened, it was found that BNP levels were assessed on the second day after birth in 67 preterm babies in a study performed by Czernik et al. (15). 24 of these babies were defined to have PDA (study group) and 42 babies had no PDA (control group). The difference between the BNP levels of the two groups was significant similar to our study. In another study performed by Sabjeev S. et al. (3), a total of 29 preterm babies with a birth weight of ≤1500 g and gestational age of ≤34 weeks were followed up prospectively. In case of clinical suspicion of patent ductus arteriosus, the patients in whom ECHO was performed were divided into two groups: a) patients with hemodynamically significant PDA (hsPDA) which needed treatment b) patients with hemodynamically insignificant PDA with a small ductus diameter or patients without PDA. In these patients in whom echocardiogram was performed, BNP was measured in three hours. BNP was measured again in patients with PDA who did not receive treatment and in patients with PDA who did receive treatment 48-72 hours after the end of treatment and ECHO was repeated in these patients. Consequently, BNP levels were found to be significantly higher in patients with hsPDa (n=4) compared to the patients hemodynamically insignificant PDA and patients without PDA (508.5±618.2 and 59.5±69.9 pg/ml higher, respectively). A marked difference was found between pre-treatment and post-treatment BNP values. In this study, pre-treatment and post-treatment BNP values were found to be significantly different similar to the the study performed by Sanjeev S et al. (3). Oghuvbu et al. (2) reported in their study that PDA diameter should be 1,6 mm and above for a diagnosis of hemodynamic PDA and as PDA diameter increased, BNP level increased. El-Khuffash et al. (5) reported that BNP level was affected by PDA diameter and LA/Ao ratio after the 12th hour after birth and with the increase in both of these values BNP increased significantly in the review they published about BNP in preterm babies. These results in the literature are compatible with our study.

Increase in left atrial diameter and in LA/AO ratio as the amount of the shunt increases in patients with patent ductus arteriosus has been used to show that the shunt of PDA is large. LA/Ao ratio was found to be 1.5±0.2 in 20 patients who were found to have PDA among 50 patients included in the study and BNP levels were found to be high in parallel. LA/Ao ratio and BNP levels were found to be low in the control group who had no PDA. There was a significant difference between the two groups (p<0.0001). De Garca et al. (14) used PDA diameter, diastolic flow in the descendent aorta and LA/Ao ratio in the group defined to have clinically significant PDA in the study they performed in 19 preterm babies. In this classification, it was shown that BNP levels were compatible with increase in PDA diameter and LA/Ao ratio. Similarly, Sanjeev et al. (3) used LA/Ao ratio when making the definition of hsPDA, considered a LA/Ao ratio of ≥1.4 as hsPD and reported BNP level was markedly high in patients with hsPDS.

In patients with PDA, left ventricular load changes according to the blood crossing the PDA. Therefore, it is known that LVED increases in patients with hemodynamically significant PDA. In our study, LVEDd and BNP levels were compared. BNP levels in group 1 and group 2 were measured to be 914.7±461.4 pg/ml and 39.4±41.6 pg/ml, respectively. It was found as LVED increased, BNP level increased and the increase was statistically significant (p<0.0001).

Kunii et al. (16) showed BNP level increased significantly with the increase in LVED volume in their study in which they evaluated the relation between BNP and Qp/Qs, LVED volume, RVED volume and peak righ ventricle/left ventricle pressure ratio hemodynamically.

In 50 patients who were included in the study, other cardiac variables including IVSd, LVPWd, EF and SF values were measured and no significant difference was found between the study group and the control group, when all these values were compared with BNP level.

Conclusively, BNP level was found to be higher in preterm babies with PDA compared to the ones without PDA and was shown to be related to LA/Ao, ductus diameter and LVEDd as well as to clinical and hemodynamical PDA markers which show left ventricular loading.

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Conflict of interest: None declared.

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