Research Article / Araştırma Makalesi

The Association Between Umbilical Cord Blood and Neonatal Plasma Brain Natriuretic Peptide Levels and Mode of Delivery

Kord Kanı ve Yenidoğan Plazma Beyin Natriüretik Peptid Düzeyleri ile Doğum Şekli Arasındaki İlişki

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Abstract: Fetal-to-neonatal adaptation involves many complex mechanisms. Cardiovascular biomarkers may help to understand fetal and maternal physiology in pregnancy and during the perinatal transition period. In this present study, our aim was to assess the association between delivery type and brain natriuretic peptide (BNP) levels in healthy full-term neonates. Forty-eight neonates born by vaginal delivery (n=25) and cesarean section (n=23) were included in the study. Plasma BNP levels were measured at cord blood samples. In addition antropometric measurements and physical examination were evaluated at first day of life. BNP levels measure and clinical evaluation were repeated 3 days later after birth. The median cord and infant BNP levels were similar in vaginal and cesarean delivery. There was no difference between the median cord and infant BNP levels in vaginal deliveries [54.0 pg/ml (q1-q3: 40.0-111.5) and 66.0 pg/ml (q1-q3: 43.0-90.0) respectively, p=0.619]. However, the median infant BNP level was statistically significantly higher than the median cord BNP level [56.0 pg/ml (q1-q3: 39.0-84.0) and 75.0 pg/ml (q1-q3: 54.0-145.0), p=0.027] in cesarean deliveries. Uncomplicated vaginal deliveries were not associated with high BNP levels and thus fetal cardiac distress. Increased levels of BNP levels on the 3rd day in elective cesarean deliveries may be predictive of delayed postnatal pulmonary and cardiac adaptation.
Keywords: Brain natriuretic peptide (BNP), vaginal delivery, cesarean section, mode of delivery, newborn

Özet: Fetal-neonatal adaptasyon birçok kompleks mekanizmayı içermektedir. Kardiyovasküler biyomarkırlar perinatal geçiş dönemindeki fetal ve anne fizyolojisinin anlaşılmasına yardımcı olabilir. Bu çalışmada amacımız sağlıklı, zamanında doğmuş yenidoğanlarda doğum şekli ile beyin natriüretik peptid (BNP) düzeyleri arasındaki ilişkiyi değerlendirmektir. Çalışmaya vajinal doğum (n=25) ve sezaryen (n=23) ile doğan 48 yenidoğan dahil edilmiştir. Kordon kanı örneklerinde plazma BNP düzeyleri ölçülmüş ve ayrıca yaşamın ilk gününde yenidoğanların antropometrik ölçümleri ve fizik muayeneleri yapılmıştır. Doğumdan 3 gün sonra BNP düzeyleri ölçümü ve klinik değerlendirme tekrarlanmıştır. Medyan kord ve bebek BNP düzeyleri vajinal ve sezaryen doğumlarda benzer bulunmuştur. Vajinal doğumlarda medyan kord ve bebek BNP düzeyleri arasında fark bulunmamıştır [sırasıyla 54,0 pg/ml (q1-q3: 40,0-111,5) ve 66,0 pg/ml (q1-q3: 43,0-90,0), p=0,619]. Ancak sezaryen doğumlarda, medyan bebek BNP düzeyi, medyan kord BNP düzeyinden istatistiksel olarak anlamlı derecede yüksek bulunmuştur [56,0 pg/ml (q1-q3: 39,0-84,0) ve 75,0 pg/ml (q1-q3: 54,0-145,0), p=0,027]. Komplike olmayan vajinal doğumlar, yüksek BNP seviyeleri ve dolayısıyla fetal kalp sıkıntısı ile ilişkili bulunmamıştır. Elektif sezaryen doğumlarda 3. günde artan BNP düzeyleri postnatal pulmoner ve kardiyak adaptasyonun gecikmesinin habercisi olabilir.
Anahtar Kelimeler: Beyin natriüretik peptidi (BNP), vajinal doğum, sezaryen, doğum şekli, yenidoğan

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1. Introduction

Adaptation of the fetus to extra-uterine life involves many complex mechanisms. Fetal-to-neonatal maladaptation occurs in 1-2% of all newborns and may be associated with cardiopulmonary pathologies such as transient tachypnea of newborn or persistant pulmonary hypertension (1). Biomarkers can be used to assess a physiological or pathological state of an organism. Cardiovascular biomarkers are used to assess the cardiac and circulatory situation in adult medicine. These same biomarkers are also relevant in perinatal maternal and fetal physiology. Cardiovascular biomarkers can act as physiological regulators in the perinatal setting. Therefore, in the field of cardiovascular biomarkers, there is an interesting overlap between neonatology, obstetrics, and cardiology. Cardiovascular biomarkers may help to understand fetal and maternal physiology in pregnancy and during the perinatal transition period (2). Brain natriuretic peptide (BNP), which is a 32 amino acid polypeptide, modulates several biological processes by activating the natriuretic peptide receptor A (NPR-A). Cardiomyocytes in the heart ventricles in response to stretching by an increase in ventricular volume and pressure can secrete BNP as a fast and sensitive regulator that increases natriuresis, diuresis and vasodilatation and these effects result in a decreased cardiac workload (3, 4).

Studies have shown that in newborns plasma BNP and N-pro BNP levels rise rapidly during the first 2-3 days after birth, and in the following days a rapid decline is observed (5-7). Renal maturation, increased systemic vascular resistance, decreased pulmonary pressure are known as the factors that provide subsequent decline at BNP level (8).

In neonatal period BNP levels are found to be high in cases such as persistant pulmonary hypertension (PPHT) (9-11), bronchopulmonary dysplasia (BPD) (11), patent ductus arteriosus (PDA) (11, 12), perinatal asphyxia (13) and transient tachypnea of newborn (TTN) (14, 15). In addition, changes in BNP levels may reflect the short-term clinical course of critical patients in neonatal intensive care (16).

It is known that respiratory distress and the need for follow-up in intensive care unit are increasing in infants delivered by cesarean section (C/S) before spontaneous delivery starts. Postpartum respiratory distress caused by C/S may have negative results such as development of pulmonary air leaks and persistant pulmonary hypertension (17, 18). Nevertheless, even if there is no postpartum complication, pulmonary pressure decreases in newborns delivered by C/S later than the ones by vaginal delivery, so that temporary postpartum pulmonary hypertension is prolonged (19, 20).

In this study we aimed to demonstrate the association between delivery type and BNP levels in newborns by comparing the 1st day (cord) and 3rd day (infant) BNP levels of babies that had elective cesarean section and spontaneous vaginal delivery.

2. Materials and Methods

Study design

This study was carried out between July 2013 and September 2013 in the Department of Obstetrics and Gynecology of Medeniyet University Education and Research Hospital, after the approval of the decision of the Ethics Committee of Clinical Researches of the same hospital with the decision dated 25.06.2013 and number 2013/0009. All procedures in the study complied with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patient parents were informed about the study and their informed consent was obtained. Financial support for BNP measurements was provided by the project of 23.01.2014 / 33 of Medeniyet University Education and Research Hospital. The BNP measurement was performed at the Biochemistry Department of the same hospital.

Selection of participants

In the postnatal examinations, the general condition, color, activity, respiration rate, moaning, bruising, SpO2 (over 95% was accepted as normal) and cardiac auscultation findings of newborns were evaluated. The

examinations were repeated after the babies were placed next to their mother. The cases who had abnormal examination findings and needed postnatal oxygen were excluded from the study. Infants whose mothers had chronic disease, gestational diabetes mellitus, preeclampsia, premature rupture of membranes, smoking, fetal distress findings and emergency cesarean section were not included in the study. Apgar scores were recorded on the 1st and 5th minute of infants. Babies that were under eight in any case were not included into the study.

Fetal ultrasonography was used in addition to the last menstrual period which is accepted as the most reliable parameter in determining the age of pregnancy. Deliveries over the 37th gestation week were included in the study.

Data collection

In all births included in the study, immediately after the birth a double clamp was placed on the umbilical cord and 2 cc venous cord blood was taken into a tube with EDTA (Ethylenediaminetetraacetic acid) and sent to the laboratory. On the third day, the patients were called to the control and another 2cc blood was taken, put into a tube with EDTA and sent immediately to the laboratory.

The blood samples were centrifuged at 4000 rpm for 10 minutes in the laboratory to separate the plasma, were frozen and stored at -80 ° C. On the day of analysis, samples were brought to room temperature and processed on ACCESSR device by immunoassay method, using a chemiluminescent immunoassay kit (RocheDiagnostics, Grenach-Wyhlen, Germany) and the results were evaluated in terms of pg/ml.

Statistical Analysis

Shapiro-Wilk normality test was applied to all data. Student's t-test was used to compare means in normally distributed data. The Mann-Whitney U and the Wilcoxon tests were used to compare the non-normally distributed data. Descriptive statistics were presented as mean±standard deviation (SD) for normally distributed data, median (interquartile range, 25%-75%) for skewed-data, and as numbers and percentages for categorical data. In all analyzes the significance level was determined as $p<0.05$. All data analyzes were performed in PASW Statistics 18 (SPSS Inc.).

3. Results

In the study period, this study was completed with 25 mothers and neonates in vaginal delivery group and 23 mothers and neonates in cesarean delivery group. Spinal or epidural anesthesia was performed in all cesarean sections. Demographic and clinical parameters of vaginal and cesarean delivery groups were summarized in Table 1. Between the vaginal and cesarean delivery groups, there was no significant difference regarding the maternal age, gravidity and parity; and neonatal gender, gestational age at delivery, and birth weight.

Cord and infant BNP levels were similar in vaginal and cesarean delivery. While the median cord BNP level was 54.0 (q1-q3: 40.0-111.5) in vaginal deliveries, 56.0 (q1-q3: 39.0-84.0) was found in cesarean sections ($p=0.657$). Infant BNP level was found 66.0 (q1-q3: 43.0-90.0) in vaginal deliveries and 75.0 (q1-q3: 54.0-145.0) in cesarean deliveries ($p=0.173$). There was no difference between the cord and infant BNP levels in vaginal deliveries [54.0 (q1-q3: 40.0-111.5) and 66.0 (q1-q3: 43.0-90.0) respectively, $p=0.619$]. In cesarean deliveries, the median infant BNP level was significantly higher than the median cord BNP level [56.0 (q1-q3: 39.0-84.0) and 75.0 (q1-q3: 54.0-145.0), $p=0.027$] (Table 2). In figure 1, the boxplot chart of cord and infant BNP levels according to the mode of delivery is shown.

Accompanied by these data, the post hoc power of cord BNP analysis (vaginal delivery versus C/S) was 0.42, and of infant BNP analysis (vaginal delivery versus C/S) was 0.58 in the 95% confidence interval using the 'OpenEpi calculator' (https://www.openepi.com/Power/PowerMean.htm).

Table 1. Selected demographic characteristics and maternal-neonatal clinical parameters of vaginal and cesarean delivery groups.

	Vaginal delivery (n=25)	Cesarean delivery (n=23)	Significance
Maternal age (yr)*	27. 5 (±5.5)	30.2 (±4.8)	NS
Gravidity (n)**	1 (1-3)	3 (2-3.5)	NS
Parity (n)**	1 (1-2)	2 (2-3)	NS
Gender (Male) (n)	12	11	NS
GA at delivery (week)**	40 (39-40)	38 (38.5-39)	NS
Birth weight (g)*	3350 (±349)	3347 (±357)	NS

** Data were presented as mean (± standard deviation), ** Data were presented as median (interquartile range, 25%-75%). NS, not significat at a p value of 0.05.*

Table 2. Comparison of cord and infant BNP levels according to delivery type

	Cord BNP (pg/ml)	Infant BNP (pg/ml)	**p value
	Median (q1-q3)	Median (q1-q3)	
Vaginal delivery	54.0 (40.0-111.5)	66.0 (43.0-90.0)	0.619
Cesarean delivery	56.0 (39.0-84.0)	75.0 (54.0-145.0)	0.027
***p value**	0.657	0.173	

** Mann-Whitney U test, ** Wilcoxon test*

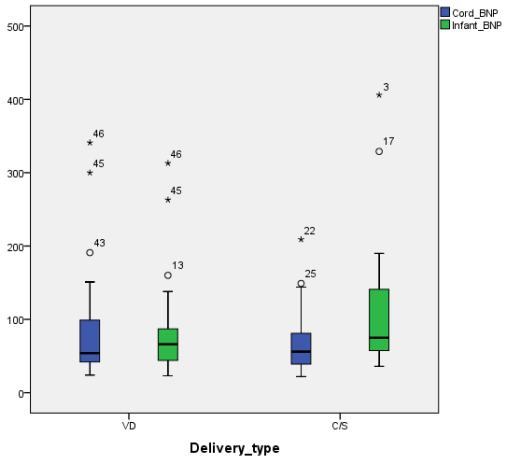

Figure 1. *The boxplot chart of cord and infant BNP levels according to the mode of delivery*

VD: vaginal delivery, C/S: cesarean section, BNP: pg/ml

4. Discussion

There is a limited number of studies investigating the relationship between the mode of delivery and serum BNP levels. In their study, Itoh H. et al. (13) compared the babies delivered by elective cesarean with the ones delivered by normal spontaneous vaginal delivery and having fetal distress findings. They found first day BNP levels of the infants delivered by vaginal delivery 19 times higher. In a similar study, the BNP levels in cord blood of preeclamptic mothers babies were found higher than healthy newborns depending on the fetal stress they experienced (21). There is no evidence that uncomplicated vaginal delivery creates fetal cardiac distress and increases cord BNP values. In a study

which conducted by Seong et al., healthy infants delivered by VD and elective C/S were compared in terms of cord amino-terminal pro-brain natriuretic peptide (N-pro BNP) levels; it has been thought that uterine contractions during normal vaginal delivery may cause fetal cardiac stress by decreasing placental and umbilical artery blood flow, but no statistically significant difference was detected, and it was concluded that vaginal delivery alone did not cause cardiac stress (22). In addition, in a study with limited participation, It was concluded that the usual birth stress maximizes NT-pro BNP levels, so it cannot be used as a marker to differentiate birth stress (23). In our study in which newborns with fetal distress were not included, we also found no statistically significant difference in cord BNP levels between vaginal and elective C/S deliveries.

BNP and NT-proBNP are of fetal origin and are higher levels in cord blood than adults (2, 23, 24). It has been shown that in the newborns plasma BNP and N-pro BNP levels showed a rapid increase during the first 2-3 days after birth; and in the following days, as a result of kidney maturation, systemic vascular resistance and decreased pulmonary pressure, BNP and N-pro BNP levels have decreased (5, 6, 8). Many newborns delivered by C/S before the onset of spontaneous delivery have many problems, especially respiratory ones such as TTN, PPHT (17, 18). Martelius et al. (25) compared the amount of pulmonary fluid by performing pulmonary ultrasonography at postnatal 1st, 3rd and 24th hours to infants delivered by elective C/S and VD. Altghough at the first hour, no statistically significant difference was found, at the third hour, C/S delivered babies had statistically significant elevation in the amount of pulmonary fluid compared to vaginally delivered babies. They marked that this difference vanished at the 24th hour. There was a positive correlation between high BNP levels and tachypnea duration in newborns diagnosed with TTN; it has been concluded that BNP value could be used as a marker to determine the severity of TTN (14, 15). Similarly, BNP levels were detected higher in the newborns with PPHT than in the control group (9). In the previous studies, elective C/S and vaginally delivered infants were compared in terms of pulmonary pressure, and transient pulmonary hypertension has been shown to be prolonged in the C/S delivered babies group (19, 20). A statistically significant pulmonary artery pressure decrease in the vaginal delivery group stopped on the 3rd day, whereas in the cesarean group it extended till the 5th day (20). High BNP levels may also be related to the type of anesthesia used during C/S, such as general versus spinal/epidural anesthesia. Large amounts of IV fluid given to mothers who receive epidural anesthesia before delivery can affect their offspring's fluid balance, leading to mild hypervolemia and higher levels of vasoactive hormones such as ANP and BNP (26). In our study, there was a statistically significant increase in 3rd day BNP value compared to cord BNP level in elective C/S deliveries. There was no statistically significant increase in vaginal births. This difference between the type of birth may be related to the delay in pulmonary and cardiac adaptation due to elective cesarean deliveries. Again, epidural anesthesia may have contributed to this increase.

There are some limitations in our study. One of these was the inability to perform echocardiography (Echo) in newborns, and that the pulmonary pressure was not measured. The correlation between high pulmonary pressure and high serum BNP levels could have been shown more clearly if Echo could be performed. However, newborns born by cesarean section with clinical signs of respiratory distress due to pulmonary maladaptation could also be included in the study as a separate subgroup. BNP levels of this subgroup of patients would help us understand the relationship between BNP, C-section, and adaptation problems after birth. The most important limitation was that the sample size was insufficient to compare BNP levels of vaginal birth and C/S, as shown by power analyses. Maybe, a statistically significant difference could be shown in larger samples.

5. Conclusion

Uncomplicated vaginal deliveries were not associated with cardiac stress. The significant increase in BNP levels observed in elective cesarean deliveries may indicate a delay in pulmonary and cardiac adaptation. Therefore, BNP may be used as a biomarker of pulmonary maladaptation. Further functional studies may lead the way to a better understanding of the pathogenesis.

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Ethics

Ethics Committee Approval: The study was approved by İstanbul Medeniyet Goztepe Training and Research Hospital Ethical Committee (Decision no:2013/0009, Date: 25.06.2013
Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.
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