DOI: 10.24938/kutfd.1142172 Kırıkkale Üniversitesi Tıp Fakültesi Dergisi 2023;25(1):48-55
Original Article *Özgün Araştırma*

THE EFFECT OF DELIVERY MODE ON NT-PROBNP LEVELS IN NEWBORNS

Doğum Şeklinin Yenidoğanlarda NT-ProBNP Düzeylerine Etkisi

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ABSTRACT

Objective: Reference values of NT-proBNP levels in newborns may vary depending on gestational age, postnatal age and Apgar scores**.** However, the effect of the mode of delivery has been less investigated, and the results are contradictory. In this study, it was aimed to compare NT-proBNP levels in healthy term newborns born through vaginal delivery and cesarean (C/S) and to investigate whether delivery method had an effect on it.

Material and Methods: Healthy newborns born in our hospital and with a gestational age of ≥38 weeks were included in the study. Cases (n=56) were grouped according to delivery type. Both groups were similar in terms of gender, gestational age, body weight and Apgar scores. NT-proBNP levels, hematological parameters, LDH and CPK levels were studied in blood samples taken in the first hours after birth. The two groups were compared in terms of these parameters and it was investigated whether there was a relationship between the parameters.

Results: NT-proBNP levels were 3145 (372-7231) pg/ml in newborns born vaginally and 783 (401-6563) pg/ml in newborns born by cesarean section ($p<0.05$). CPK, LDH levels and white blood cell counts were higher in newborns born by vaginal delivery compared to newborns born by cesarean section ($p<0.05$). In addition, a positive correlation was found between NT-proBNP values and white blood cell counts ($r=0.6$, $p=0.000$).

Conclusion: NT-proBNP levels of those born vaginally are in the range of predefined reference levels and increased 4 times compared to those born through C/S. In addition, the relationship between NT-proBNP levels and biochemical markers and white blood cell counts suggests that vaginal delivery causes physiological stress and this may be related to postpartum adaptation.

Keywords: *NT-proBNP, newborn, mode of delivery*

ÖZ

Amaç: Yenidoğanlarda NT-proBNP düzeylerinin referans değerleri gebelik yaşı, postnatal yaş ve Apgar skorlarına bağlı olarak değişebilmektedir. Ancak, doğum şeklinin NT-proBNP düzeyleri ile ilişkili olup olmadığı halen belirsizdir. Bu nedenle çalışmamızda, vajinal doğum veya sezaryen sonrası doğan sağlıklı term yenidoğanlarda NT-proBNP düzeylerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya hastanemizde doğan ve ğgestasyonel yaşı ≥38 hafta olan sağlıklı bebekler dahil edildi. Olgular (n=56) doğum şekline göre gruplandırıldı. Her iki grup cinsiyet, gebelik yaşı, vücut ağırlığı ve Apgar skorları açısından benzerdi. Doğum sonrası ilk saatlerde alınan kan örneklerinde NT-proBNP düzeyleri, hematolojik parametreler, LDH ve CPK düzeyleri çalışıldı. İki grup bu parametreler açısından karşılaştırıldı ve parametreler arasında ilişki olup olmadığı araştırıldı.

Bulgular: Vajinal yolla doğan bebeklerde NT-proBNP seviyeleri 3145 (372-7231) pg/ml ve sezaryen ile doğan bebeklerde 783 (401-6563) pg/ml idi ($p<0.05$). Vajinal yolla doğan bebeklerde sezaryen ile doğanlara göre CPK, LDH düzeyleri ve beyaz küre sayıları daha yüksekti ($p<0.05$). Ayrıca, NT-proBNP değerleri ile beyaz küre sayıları arasında pozitif korelasyon saptandı ($r=0.6$, $p=0.000$).

Sonuç: Vajinal yolla doğan yenidoğanlarda NT-proBNP düzeylerinin sezaryen ile doğanlara göre önceden tanımlanmış referans değer aralıkları içinde olduğu ve 4 kat arttığı görülmektedir. Ayrıca, NT-proBNP düzeyleri ile biyokimyasal belirteçler ve beyaz kan hücresi sayıları arasındaki ilişki, vajinal doğumun fizyolojik strese neden olduğunu ve bunun doğum sonrası adaptasyonla ilgili olabileceğini düşündürmektedir.

Anahtar Kelimeler: *NT-proBNP, yenidoğan, doğum şekli*

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Received / Geliş Tarihi: 20.07.2022 **Accepted** / Kabul Tarihi: 16.01.2023

KÜ Tıp Fak Derg 2023;25(1):48-55
Doi: 10.24938/kutfd.1142172

INTRODUCTION

Brain natriuretic peptide (BNP) is a peptide that is secreted by cardiac myocytes and contains 32 amino acids which regulate increased blood pressure and fluid electrolyte balance (1,2). Deep postpartum hemodynamic changes, and particularly pulmonary perfusion and increased systemic afterload, are responsible for high right ventricular cardiac volume and cardiac output leading to BNP gene expression stimulation. The procedure is mainly governed by mitogen-activated protein kinases and extracellular signal-regulated kinase, which is specifically activated in response to overpressure stimulation in cardiac myocytes (3). It is especially important in the diagnosis and treatment of heart failure and is more specific and sensitive in left ventricular failure (4,5). It has also been used to identify problems of cardiac origin in pediatric patients and in a few studies with newborns its role has been investigated in the treatment or prognosis of newborns with bronchopulmonary dysplasia, sepsis and hypoxic ischemic encephalopathy as well as the identification of PDA and related problems (6-12).

Its physiological effects include vasodilation, natriuresis, diuresis, and inhibition of the renin angiotensin system. Transition from fetal life to neonatal period includes adaptation processes related to many organs and systems. Ventricular volume and pressure load increase with postpartum circulatory changes and deactivation of the placenta. Higher serum NT-proBNP levels are observed in the neonatal period compared to cord NT-proBNP levels. In the literature, it is caused by multiple pathophysiological mechanisms such as placental effect on BNP clearance (13), increased postnatal water loss, immaturity of renal function (14), and gradual functional closure of the ductus venosus and foramen ovale and closure of the ductus arteriosus in the first hours of life of term neonates (15).

Newborn studies have shown that reference values may vary depending on gestational age, postnatal age, Apgar scores, and the measurement technique used (1-4,12,16-18). It is noteworthy that the high levels immediately after birth decreases gradually. This suggests that a triggering factor at birth may cause a physiological increase. This increase may be associated with the effect of labor, which is important for postnatal adaptation, and therefore levels can be expected to vary according to the mode of delivery.

However, there are few studies investigating the effect of mode of delivery, and the results are contradictory. Therefore, the aim of this study was to compare NT-proBNP levels in healthy term newborns delivered by the vaginal route or cesarean section (C-section) to investigate whether the delivery method had any effect on the NT-proBNP level.

MATERIALS AND METHODS

The study included healthy infants with a gestational age of ≥ 38 weeks born at the Kırıkkale University Hospital. Data were obtained from the hospital records and recorded as per maternal age, number of pregnancies, prenatal diseases, infant gender, gestational age, birth weight, Apgar scores, physical examination and laboratory findings. The study was approved by the Clinical Research Ethics Committee of Kırıkkale University Medical Faculty (decision no: 02.12.2010 / 2010 / B089) and ınformed consent was obtained from the parents of infants.

Infants were excluded from the study if they had any known disease, low birth weight, intrauterine infection or anomaly, required hospitalization, were premature or had incomplete data.

Blood samples were taken in the first hours of life. A Sysmex XT 2000I device was used for the hematological measurements and a Roche Hitachi modular P-800 device was used for the biochemical measurements. After measurement of hematological parameters, the remainder of the samples were centrifuged at 7000 rpm for 5 minutes and the separated plasma was stored at -70°C until measurement. Then, NT-proBNP levels were measured in the thawed plasma samples. Complete blood count results, biochemical

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measurements and the NT-proBNP levels of the infants included in the study were recorded.

The cases were grouped according to the type of delivery and comparisons were made between the groups in respect to hematological data, LDH and CPK levels and NT-proBNP levels.

Statistical Analysis

The data were analyzed using SPSS for Windows software (version 11.5, Chicago, IL, USA). While, discrete variables were given as numbers and percentages, continuous variables were given as mean and standard deviation (mean±SD) or as median and range values. Variables with homogenous distribution were compared using the Student's t-test and variables with non-homogenous distribution were compared using the Mann Whitney U-test. To examine the relationship between two parametric continuous variables Pearson correlation was applied and for the relationship between non-parametric variables, Spearman correlation analysis. A value of $p<0.05$ was considered statistically significant.

RESULTS

The demographic characteristics of the infants included in the study are presented in Table 1.

The groups were comparable in terms of gestational age, gender, growth status and Apgar scores. Some differences were observed between the groups in respect to hematological and biochemical measurements. NT-proBNP levels were 3145 (372-7231) pg/ml in infants born vaginally and 783 (401-6563) pg/ml in infants born by C-section ($p <0.05$). The CPK and LDH levels were 483 U/L (116-1410) and 625 U/L (210-926), respectively in infants born vaginally, and 343 U/L (40-1438), and 378 U/L (219-1000), respectively, in those delivered by caesarean section ($p <0.05$) (Table 2).

Table 1: Demographic characteristics of the infants grouped by mode of delivery

	Infants born vaginally (n=28)	**Infants born via C-section (n=28)**	**P value**
Gestational age (weeks)	38.7±0.65	38.78±1.1	0.78
Gender (F/M)	18/10	16/12	0.58
Birth weight (g)	3519±358	3303±468	0.6
Height (cm)	49.5±1.59	49±2.3	0.41
Head Circumference (cm)	34.75± 0.8	34.23±1.32	0.8
Apgar at 1 minute	8.6±0.6	8.1±1.1	0.65
Apgar at 5 minutes	9.89±0.41	9.85±0.35	0.73

Table 2: The biochemical values, CRP and NT-proBNP values of the infants grouped by mode of delivery

Values Are Given As Median (Range Of Values)	**Infants born vaginally (n=28)**	**Infants born via C-section (n=28)**	**P value**
AST (U/L)	54.5 (14-361)	27.5 (7-80)	0.02
CPK (U/L)	483 (116-1410)	343 (40-1438)	0.04
LDH (U/L)	625 (210-926)	378 (219-1000)	0.007
CRP (mg/L)	0.2 (0-4.8)	0.25 (0-5.84)	0.9
NT-ProBNP(pg/ml)	3145 (372-7231)	783 (401-6563)	0.02

The mean hemoglobin values of infants born by vaginal and cesarean delivery were found to be 17.4±1.4 and 16.3±1.4 ($p=0.008$) respectively. The median white blood cell values of infants born by vaginal and cesarean delivery were found to be 19300/mm^3 and 16700/mm^3 respectively, and the difference was significant

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(p=0.04). A positive correlation was determined between NT-proBNP levels and white blood cell counts (r=0.6 and p=0.000) in the vaginally delivered group. There was no difference between the groups in terms of other hematological parameters. The biochemical values, CRP and NT-proBNP values of the infants grouped by mode of delivery are shown in Table 2. The NT-proBNP levels and white blood cell counts of the groups are shown in Figure 1 and Figure 2, respectively.

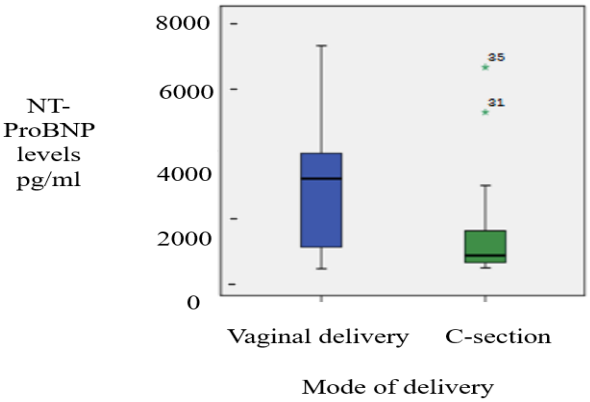

Figure 1. NT proBNP levels of the infants grouped by mode of delivery

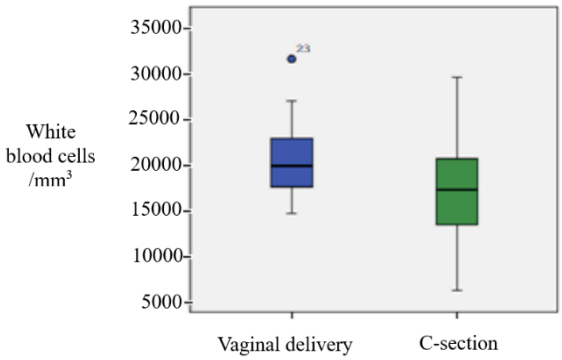

Figure 2. White blood cell counts of the infants grouped by mode of delivery

DISCUSSION

Physiological fluid loss with intercompartmental fluid exchange and diuresis results in a decrease in fluid load in the first week (19). It is thought that this change observed in the first days after birth is related to postnatal adaptation, and it develops when the left ventricular pressure increase due to PDA present at birth returns to normal with the physiological closure of PDA and leads to a decrease in NT-proBNP levels (10, 12). The decrease in plasma NT-proBNP can be attributed to the diuresis associated with renal maturation, suppression of renin-aldosterone-angiotensin I and II system activity, and postnatal increase in neonatal water loss (20,21). The gradual decrease in serum level of the biomarker continues into the first months of life and remains fairly constant from infancy to the onset of puberty (22).

Since only the levels in the first 24 hours were examined in our study, no change in consecutive values was observed. The levels in Nir's study correspond to the values in the first two days, that is, when they reach the highest values, and it was thought that the upper limit being higher than the values in our study may be related to the time of blood sampling (23).

One noteworthy point is that the NT-ProBNP levels show wide distribution in previous studies. This may be related to the variables not being homogeneous and some factors such as gestational age and Apgar scores may affect the levels (9,10). In a study by Seong it was stated that NT-proBNP levels were higher in preterms and in those with lower Apgar scores (10). However, Bar-Oz et al. stated that there was no relationship between cord blood NT-proBNP levels and Apgar scores (11).

Another factor affecting NT-ProBNP levels may be the mode of delivery. However, the results of studies investigating this relationship are contradictory. Kocylowski et al. reported that CPK levels were higher and NT-proBNP levels were lower in term infants delivered vaginally compared to a C-section group, and stated that the rise of NT-proBNP levels in the C-section is associated with volume loading (8). In contrast to this, in a prospective study which examined neonatal stress factors such as cardiac troponin, NT-pro-BNP, copeptin and C-reactive protein levels in the cord blood, no significant change was found in NT-proBNP levels according to the mode of delivery (4). Seong et al. suggested that vaginal delivery may cause fetal cardiac stress, although they could not demonstrate that vaginal delivery caused an increase in NT-proBNP levels (10).

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Therefore, the aim of the current study was to compare NT-ProBNP levels in infants of similar gestational age, birth weight, gender and Apgar scores delivered by different modes. The NT-ProBNP levels in the infants delivered by the vaginal route were determined to be 4-fold higher than those born by C-section (p=0.02), which supports the hypothesis that NT-proBNP levels are affected by the mode of delivery.

In a large study involving more than 10000 infants who were exclusively breastfed, two different nomograms showing weight loss according to the mode of delivery were created with measurements made from the 6th postnatal hour. As can be seen from the nomograms, weight loss is less in infants born vaginally from the first measurements, suggesting that the volume load may be higher in infants born by vaginal route (25). Based on these findings, it can be speculated that increased NT-ProBNP levels may be associated with increased volume load in infants born vaginally. According to the results of previous studies, the differences may be related to the infants included in the study, the accompanying problems of the mothers during pregnancy or the prenatal fluids, as well as the feeding patterns of the infants, the place and time of blood collection, and the study method. In our study, mothers with accompanying problems during pregnancy were excluded and no difference was observed between the prenatal fluid intakes. However, our study has some limitations. The type of anesthesia applied to the mothers during delivery, whether fluid loading was performed, the feeding patterns of the babies, the amount of fluid they took and the weight loss in the first days of life could not be recorded.

In the infants born with vaginal delivery, AST, CPK and LDH levels, which are biochemical parameters reflecting perinatal hypoxic-ischemic exposure were also determined to be increased. The effect of contractions in the uterus on cardiac functions during normal delivery is not fully known. During delivery, a decrease in uterine artery and placental blood flow is observed. Some researchers have reported that adrenaline and noradrenaline are released due to pain and stress and blood flow decreases in the uterine smooth muscles (26). In addition, it has been stated that there is an increase in fetal cardiac preload during contractions, in an effort to compensate for hypoxic stress caused by decreased blood flow at birth. In a study by Lin et al. it was reported that serum CPK, CK-MB and NT-proBNP levels showed a positive correlation in asphytic infants and the NT-proBNP level was important for the early recognition of myocardial damage (28). However, the infants in our study group comprised healthy infants with normal Apgar scores. Therefore, the increase in the levels of biochemical parameters does not seem to be related with the hypoxic-ischemic process.

Moreover, the white blood cell counts of those born via the vaginal route were higher than those born by C-section (p=0.04), and there was a moderate correlation between white blood cell counts and NT-proBNP levels in the same group (r=0.6 p=0.000). Rosemary et al. also showed that cord blood white blood cell counts were higher in healthy term infants born via vaginal delivery (28). The increased leukocyte count in term infants was reported to be in response to stress at birth and this was not observed in those born via elective C-section (29). This difference is thought to be caused by increased steroid and catecholamine release. In a study by Chirico et al. white blood cell counts and cortisol levels were examined in the first 12 hours after birth, and the white blood cell counts in both the cord blood and peripheral blood were found to be significantly higher in those born by the vaginal route (30). In addition, serum cortisol levels were higher in the same group and a significant relationship was found between cortisol and leukocyte, neutrophil and lymphocyte counts. The effect of cortisol on the neutrophil count is that it increases neutrophil release from the bone marrow and decreases clearance from the circulation. In addition, prolonged stress during labor causes mobilization of leukocytes in the pool by causing the release of endogenous cytokines (30,31). In a study by Herson et al. infants born via C-section were

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divided into two groups according to whether or not there had been any labour (32). The white blood cell count was shown to be higher in those born via C-section following labour compared to those born via elective C-section.

In conclusion, the mode of delivery is an important variable affecting postnatal adaptation. The results of this study demonstrated that NT-proBNP levels, in addition to markers and white blood cell counts which support perinatal hypoxia, suggest that this stress may be physiological since the NT-proBNP levels were within the reference range. An increase in NT-proBNP levels in those born vaginally may be associated with increased intrauterine pressure during contractions during active labor, intervillous perfusion and temporary interruption of placental gas exchange, or increased volume load. There is a need for further larger studies to investigate the type of diet, the amount of fluid taken, diuresis and daily weight loss, which are markers of postnatal fluid balance, to be able to show this relationship more clearly.

Conflict of Interest: The author has no conflict of interest to declare.

Support and Acknowledgment: There is no funding source.

Researchers' Contribution Rate Statement:

Concept/Design: IK; Analysis/Interpretation: DA; Data Collection: IK; Writer: IK; Critical Review: DA; Approver : DA

Ethics Committee Approval: The ethics committee approval of the study was obtained from the Kırıkkale University Clinical Research Ethics Committee (Date:02.12.202010 / Decision no: 2010/B089)

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