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N-TERMINAL PROHORMONE OF BRAIN NATRIURETIC PEPTIDE IN THE DIAGNOSIS AND MANAGEMENT OF PERSISTENT PULMONARY HYPERTENSION IN NEWBORNS

YENİDOĞANLARDA PERSİSTAN PULMONER HİPERTANSİYON TANISI VE YÖNETİMİNDE N-TERMİNAL PROHORMON BRAİN NATRİÜRETİK PEPTİD

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ABSTRACT

Objective: This study aimed to investigate the levels and utility of amino/N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in the diagnosis of neonatal persistent pulmonary hypertension (PPHT).

Materials and Methods: Infants born at ≥34 weeks of gestation were included in this retrospective cross-sectional study. In total, 33 newborns diagnosed with PPHT were included in the patient group and 50 healthy newborns were included in the control group. Patient and control groups were compared in terms of plasma NT-proBNP levels measured in the umbilical cord (UC) and at 72 hours of life.

Results: The NT-proBNP levels in UC and at 72 hours were significantly higher in neonates with PPHT compared to controls ($p<0.01$). For the diagnosis of PPHT, UC NT-proBNP cut-off value was >2760.5 pg/ml, sensitivity was 90.7%, and specificity was 96.6% ($p<0.01$). For NT-proBNP at 72 hours, the cut-off value was >1414 pg/ml, sensitivity was 95.9%, and specificity was 91.2% ($p<0.01$). The mean UC NT-proBNP levels were 1094.7±603 pg/ml and mean NT-proBNP levels at 72 hours were 875.7±423 pg/ml in the control group.

Conclusion: NT-proBNP levels are high during the initial days of life. They are useful in the diagnosis and follow-up of PPHT in newborns with hypoxemic respiratory failure and high fraction of inspired oxygen (FiO_2) requirement, especially in cases where transthoracic echocardiography (TTE) cannot be performed.

Keywords: NT-proBNP, persistent pulmonary hypertension, newborn, umbilical cord, echocardiography

ÖZET

Amaç: Bu çalışmada, beyin natriüretik peptidinin (NT-proBNP) amino/N-terminal prohormonunun duzeylerinin ve yenidoğan kalıcı pulmoner hipertansiyon (PPHT) tanısında kullanımının araştırılması amaçlandı.

Gereç ve Yöntem: Bu retrospektif kesitsel çalışmaya ≥34 gebelik haftasında doğan bebekler dahil edildi. Hasta grubuna PPHT tanısı konan 33 yenidoğan, kontrol grubuna ise 50 sağlıklı yenidoğan alındı. Hasta ve kontrol grupları, göbek kordonunda (UC) ve 72 saatlik yaşamda ölçülen plazma NT-proBNP seviyeleri açısından karşılaştırıldı.

Bulgular: UC'da ve 72. saatte NT-proBNP seviyeleri, kontrollere kıyasla PPHT'lu yenidoğanlarda anlamlı derecede yüksekti ($p<0,01$). PPHT tanısı için UC NT-proBNP eşik değeri >2760,5 pg/ml, duyarlılık %90,7 ve özgüllük %96,6 ($p<0,01$) idi. Yetmişikinci saatte NT-proBNP için eşik değeri >1414 pg/ml, duyarlılık %95,9 ve özgüllük %91,2 idi ($p<0,01$). Kontrol grubunda ortalama UC NT-proBNP seviyeleri 1094,7±603 pg/ml ve 72 saatte ortalama NT-proBNP seviyeleri 875,7±423 pg/ml idi.

Sonuç: NT-proBNP seviyeleri yaşamın ilk günlerinde yüksektir. Özellikle transtorasik ekokardiyografinin (TTE) yapılamadığı durumlarda, hipoksemik solunum yetmezliği ve inspire edilen oksijen fraksiyonu (FiO_2) gereksinimi yüksek olan yenidoğanlarda PPHT tanı ve takibinde faydalıdır.

Anahtar Kelimeler: NT-proBNP, persistan pulmoner hipertansiyon, yenidoğan, göbek kordonu, ekokardiyografi

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INTRODUCTION

Persistent pulmonary hypertension in newborns is a common critical complication of the neonatal lungs. The incidence of persistent pulmonary hypertension (PPHT) ranges between 0.4 and 6.8 per thousand liveborn term infants with an associated neurodevelopmental morbidity ranging from 30% to 35% and mortality ranging from 3% to 39% (1-5). PPHT occurs when pulmonary vascular resistance does not decrease after birth. When respiratory distress is complicated by oxygenation issues and low saturation, PPHT should be suspected. Because most diseases in newborns start with respiratory problems, PPHT is often difficult to diagnose (6, 7). PPHT is caused by a variety of factors, such as perinatal asphyxia, pneumonia, transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), pulmonary vasospasm, congenital diaphragmatic hernia (CDH), aspiration of amniotic and fluid meconium, sepsis, drugs, idiopathic, and maternal urinary tract infection during pregnancy, which is mainly manifested as pulmonary arteriolar remodeling, hyperplasia, and vasospasm (8, 9).

N-terminal prohormone of brain natriuretic peptide (NT-proBNP), the amino-terminal portion of the preprohormone, is secreted into the peripheral blood in equimolar portions to brain natriuretic peptide (BNP). BNP has a short half-life of 20 minutes and is unstable at room temperature. In contrast, NT-proBNP has a longer half-life of 60–120 minutes and is stable under a range of storage conditions (10). BNP is an endogenous natriuretic peptide hormone secreted from the cardiac ventricular myocytes in response to an increase in ventricular wall stretch volume and ventricular pressure loading. Hypoxia also affects the secretion of NT-proBNP in human cardiac myocytes. The physiologic activities of BNP include the inhibition of sympathetic activity, induction of natriuresis, diuresis, vasodilatation, and inhibition of the renin–angiotensin–aldosterone system. The net effect is a reduction of intravascular volume and ventricular preload and afterload. NT-proBNP levels are elevated soon after birth, peaking at 24 h of life, decreasing thereafter for up to four months, and remaining unaltered until the age of 15 years. NT-proBNP levels are elevated in PPHT, but their measurement is not sensitive enough to contribute to routine diagnosis (11-13).

In this study, umbilical cord (UC) NT-proBNP and postnatal 72-hour NT-proBNP levels were measured in patients with PPHT and echocardiographic examination was performed. The results were compared with the healthy control group. The usefulness of NT-proBNP in the diagnosis and follow-up of PPHT was evaluated. NT-proBNP levels were also analyzed in subgroups of patients with PPHT.

MATERIALS AND METHODS

This work is designed as a prospective study. Parental consent was obtained for all patients. Ethics committee approval was obtained retrospectively from the ethics committee of Tekirdağ Namık Kemal University Faculty of Medicine (Date: 18.06.2020, No: 46048792-050.01.04-E.).

A total of 38 neonates that were born between July 2018 and July 2020 at >34 weeks of gestation and hospitalized at the neonatal intensive care unit with PPHT were included in the study. Patients with multiple congenital anomalies (1 patient), acute renal failure (1 patient), and other structural congenital heart diseases (3 patients), except small atrial septal defect, were excluded from the study. A total of 33 patients were finally included in the patient group. Fifty newborns born at >34 weeks of gestation who were followed-up for reasons such as jaundice and/or nutritional problems and did not have neonatal sepsis or respiratory problems were included in the control group by the sequential random-access method. Data were obtained from the electronic registry system and patient files. Parameters such as gestational week, gender, birth weight, 1st and 5th minute Apgar scores, pH in umbilical cord blood gas, base excess, NT-proBNP levels in the UC and at 72 hours, transthoracic echocardiography (TTE) at postnatal six hours, vasoactive inotropic score (inotrope and pressor score), oxygenation index (OI), Downes score (DS, for respiratory failure) at postnatal 1 hour, nasal continuous positive airway pressure (CPAP), intubated mechanical ventilation (MV) time, and length of hospital stay were recorded.

NT-proBNP levels were analyzed by electrochemiluminescence immunoassay using the Elecsys-cobas e602 analyzer (Roche Diagnostics, Germany). The NT-proBNP test was studied from the umbilical cord in the first 30 minutes after birth and from the baby's venous blood (0.5 ml) at the postnatal 72nd hour (measuring range is 5-35.000 pg/ml).

The total vasoactive inotropic score was obtained by summing daily inotrope score (dopamine [μg/kg/min]×1)+(dobutamine [μg/kg/min]×1)+(milrinone [μg/kg/min]×10) and pressor score (norepinephrine [μg/kg/min]×100)+(vasopressin [U/kg/min]×10,000)+(epinephrine [μg/kg/min]×100).

Severity of respiratory failure was evaluated using the DS within the first hour after birth. A score of 0–3 points was evaluated as mild, 4–6 points as moderate, and 7–10 points as severe respiratory failure (14). Oxygenation, in arterial blood gas analysis, the OI was calculated as mean airway pressure (cm H_2O)×FiO_2×100/PaO_2 in mmHg.

The first TTE was performed at postnatal 6 (±1) hours in all infants. Echocardiography was performed by a pediatric cardiologist in all enrolled patients using the Acuson SC 2000 ultrasound system transducer (Siemens, Germany) at a frequency bandwidth of 2.5–8 Mhz. Two-dimensional views were used to detect cardiac septal defects. For

accurate measurement of these defects, shunt direction in color flow mapping was determined. Doppler examinations were performed to assess pulmonary blood flow. PPHT was defined as hypoxemia with echocardiographic findings of elevated pulmonary artery systolic pressure (>35 mmHg), position of the intraventricular septal wall configuration (shape, size, and position to the right and left ventricles), and right-to-left shunting through a patent foramen ovale (intracardiac shunt) or patent ductus arteriosus (extracardiac shunt) or both. Pulmonary artery systolic pressure (PASP) of the newborn was measured using the tricuspid regurgitation pressure gap (TRP) method (PASP=TRP+10 mmHg). Left ventricular ejection fraction (LVEF) was calculated using the following formula: (end diastolic diameter−end systolic diameter)/(end diastolic diameter)×100. The severity of PPHT was graded as mild (pulmonary arterial systolic pressure <⅔ systemic systolic pressure), moderate (⅔-to systemic pressure), or severe (suprasystemic pressure) (15).

In the etiology of PPHT, various risk factors have been identified, including pneumonia, neonatal sepsis, pneumothorax, meconium aspiration syndrome (MAS), neonatal RDS, perinatal asphyxia, TTN, CDH, late prematurity (≥34 to <37 weeks of gestation), small for gestational age (SGA; birth weight <10% percentile for gestational week), nondiabetic large for gestational age (LGA; birth weight >90% percentile for gestational week), infant of a diabetic mother (IDM), oligohydramnios, and maternal drug use.

Statistical analysis

Pasw statistics software version 18 was used for data analysis. Data were presented as mean±standard deviation. Student's t test for quantitative independent variables was used for analyzing the differences between the two groups. Comparison between multiple subgroups was performed using one way analysis of variance. The correlation between quantitative variables was investigated using Pearson's chi-squared test. A p-value of <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve was drawn according to the relationship between NT-proBNP levels and pulmonary artery systolic pressure in the UC and at the postnatal 72nd hour.

RESULTS

There was no difference between the patient and control groups in terms of gender, gestational week, birth weight, mode of delivery, 1st minute Apgar score, maternal age, and number of pregnancies (p>0.05). PASP was higher, 5th minute Apgar score, pH, base excess and LVEF were lower in the patient group compared to the control group (p<0.05). The mean NT-proBNP levels of both measurements were found to be higher in the patient group than in the control group (p<0.01) (Table 1). The mean PASP was 28±2.3 mmHg in the control group. In the control group, mean UC NT-proBNP was 1094.7±603 pg/ml, 5th percentile was 298.5 (95% CI 248.5–547.6), 50th percentile was 986.7 (95% CI 878–1114), and 95th percentile was 2549.7 (95% CI 1712.1–3352); mean NT-proBNP at postnatal 72 hours was 875.7±423 pg/ml, 5th percentile was 346.6 (95% CI 299.7–452), 50th percentile was 789.3 (95% CI 678–939), and 95th percentile was 1589.3 (95% CI 1328.4–2521).

Table 1: Demographic features of the patient and control groups

Features	Patient group (n=33)	Control group (n=50)	p-value
Gender (female/male)	14/19	25/25	0.32
Gestational week (mean)	37.5±1.9	38.0±1.6	0.20
Birth weight (gr)	3079.2±714.6	3141.7±511.2	0.64
Normal vaginal delivery (%)	8 (24%)	17(34%)	0.24
Maternal age (years)	29.4±6.4	28.6±4.6	0.51
Number of pregnancies	2.3±1.2	2.4±1.4	0.64
1st minute Apgar score	6.8±2.01	7.4±1.2	0.15
5th minute Apgar score	8.0±1.2	8.6±0.7	**0.03**
UC pH	7.27±0.13	7.35±0.06	**<0.01**
UC base excess (mmol/L)	-5.79±4.24	-3.60±2.57	**0.01**
UC NT-proBNP (pg/ml) (mean)	16204.0±13459.9	1094.7±603.0	**<0.01**
NT-proBNP at 72 hours (pg/ml)(mean)	3559.5±3400.3	875.7±423	**<0.01**
PASP (mmHg)	54.6±12.5	28±2.3	**<0.01**
Ejection fraction (%)	65.2±2.5	67.84±2.8	**<0.01**

UC: umbilical cord, PASP: pulmonary artery systolic pressure, NT-proBNP: N-terminal prohormone of brain natriuretic peptide

The etiology of PPHT included neonatal pneumonia (36.4%), neonatal sepsis (30.3%), late preterm birth (30%), MAS (24.2%), IDM (18%), perinatal asphyxia 5 (15%), RDS (15%), SGA (15%), pneumothorax (12%), TTN (12%), nondiabetic LGA (9%), oligohydramnios (9%), and idiopathic factors (9%). Almost all patients had more than one risk factor (Table 2).

There was no statistical difference among the mild, moderate, and severe PPHT groups in terms of gender, gestational week, birth weight, mode of delivery, and LVEF. In the severe PPHT group, NT-proBNP in UC and at 72 hours, need for inotropic support, oxygenation index, respiratory failure score, and PASP values were higher than the other two groups ($p<0.05$). In addition, nasal CPAP/intubated MV time and lengths of hospital stays were longer in the severe PPHT group. Moreover, 1st and 5th minute Apgar scores, UC pH, and base excess were lower in the severe PPHT group, albeit not significantly ($p>0.05$). One patient in the severe PPHT group died (Table 3).

ROC analysis of UC NT-proBNP with PASP revealed the following: Area Under the Curve (AUC) 0.938, cut-off >2760.5 pg/ml, sensitivity 90.7%, and specificity 96.6% ($p<0.01$). ROC analysis of postnatal 72 hour NT-proBNP with PASP revealed the following: AUC 0.968, cut-off >1414 pg/ml, sensitivity 95.9%, and specificity 91.2% ($p<0.01$) (Table 4, Figure 1). The Pearson's correlation analysis revealed a strong positive correlation of UC NT-proBNP with PASP and oxygenation index and a moderate positive correlation with vasoactive inotropic score and Downes score. There was a moderately significant negative correlation between UC NT-proBNP and pH, 1st minute Apgar score, and base excess ($p<0.05$). NT-proBNP at postnatal 72 hours had a strong positive correlation with vasoactive inotropic score and a moderate positive correlation with PASP and oxygenation index ($p<0.05$). In addition, there was a moderate negative correlation between postnatal 72nd hour NT-proBNP and 5th minute Apgar score, UC pH and base excess ($p<0.05$) (Table 5). For PPHT, the stepwise regression model was applied in the univariate regression analysis. A significant correlation was observed between UC NT-proBNP and 1st minute Apgar score, OI, DS, VIS, PASP, and intubated MV time ($p<0.05$, explanatoriness 93.9%). In addition, a significant correlation was found between NT-proBNP at 72 hours and VIS ($p=0.01$) (Table 6).

DISCUSSION

In this study, plasma NT-proBNP levels in the patient and control groups were evaluated at two different time points. It was observed that NT-proBNP levels at both timepoints were higher in the patient group compared to the control group. Further, these levels increased as the clinical presentation of the disease became more severe.

Plasma NT-proBNP levels are very high during the first few days of life in healthy neonates, presumably owing to the fetal-to-neonatal transition of circulation. After this period, NT-proBNP levels decrease rapidly until the end of the 1st week of life and then decreases slowly until the end of the neonatal period (16). In our study, NT-proBNP levels of the included neonates were found to be higher than those of children and adults (17). It was observed that mean UC NT-proBNP levels decreased on the 3rd postnatal day in all groups, which was consistent with the results of a study by Zhu et al. (18). Schwachtgen et al. reported mean UC NT-proBNP levels of 818 (281–2595) pg/ml in 62 healthy infants. These results were also close to the UC NT-proBNP levels observed in our control group (19).

Table 2: Etiologies of persistent pulmonary hypertension

Causes	Mild (n=14)	Moderate (n=11)	Severe (n=8)	Total (n=33) (%)
Neonatal pneumonia	4	6	2	12 (36.4%)
Neonatal sepsis	4	3	3	10 (30.3%)
Late preterm birth (>34 week of gestation)	4	3	3	10 (30%)
Meconium aspiration syndrome	1	2	5	8 (24.2%)
Infant of a diabetic mother	3	1	2	6 (18%)
Respiratory distress syndrome	2	2	1	5 (15%)
Perinatal asphyxia	1	1	3	5 (15%)
Small for gestational age	3	1	1	5 (15%)
Transient tachypnea of the newborn	3	1	0	4 (12%)
Pneumothorax	2	1	1	4 (12%)
Nondiabetic large for gestational age	0	2	1	3 (9%)
Oligohydramnios-pulmonary hypoplasia	0	1	2	3 (9%)
Idiopathic	1	1	1	3 (9%)

Table 3: Features of patients with persistent pulmonary hypertension

	Mild (n=14) Mean±SD	Moderate (n=11) Mean±SD	Serious (n=8) Mean±SD	p value
Gender (female) (%)	7 (50%)	5 (45%)	2 (25%)	0.50
Gestational week	37.9±2.2	37.36±2	37.1±1.7	0.63
Birth weight (gm) (mean)	2983.9±631.4	3127.8±599.6	3180.0±1023.5	0.80
Vaginal delivery (%)	3 (21.4%)	3 (27.2%)	2 (25%)	0.8
Umbilical cord NT-proBNP (pg/ml)	4931.7±3412.2	21587.3±14004.9	28528.6±7288.5	**<0.01**
NT-proBNP at 72 hours (pg/ml)	2645.2±1117.6	2877.2±1817.2	6097.9±6004.4	**0.04**
Vasoactive inotropic score	21.0±13.9	47.3±23.1	124.6±86.7	**<0.01**
Oxygenation index (mean)	20.1±3.5	29.8±3.2	37.50±1.5	**<0.01**
Downes score (mean)	5.2±2.1	7.5±1.6	9.4±1.1	**<0.01**
Intubated MV time (hours)	38.4±21.5	39.3±41.4	52.1±39.8	0.73
Nasal CPAP (hours)	31.1±31.1	47.1±30.8	55.5±13.4	0.18
1st minute Apgar score	7.15±2.3	7.13±1.8	6.36±1.8	0.59
5th minute Apgar score	8.25±1.6	8.08±1.3	7.91±1.0	0.85
UC pH	7.33±0.11	7.24±0.13	7.21±0.12	0.10
UC base excess (mmol/L)	-4.8±3.3	-5.6±5.1	-7.9±4.1	0.24
PASP (mmHg)	44.4±2.3	53.4±4.4	73.7±6.9	**<0.01**
Ejection fraction	65.4±2.7	65.1±2.6	65.0±2.1	0.95
Hospital stay (days)	12.4±4.4	14.6±8.2	17.1±8.1	0.30

SD: standard deviation, CPAP: continuous positive airway pressure, MV: mechanical ventilation, UC: umbilical cord, PASP: pulmonary artery systolic pressure, NT-proBNP: N-terminal prohormone of brain natriuretic peptide

Table 4: ROC curve analysis of NT-proBNP levels measured in UC and at 72 postnatal hours with PASP in patients vs. controls

	AUC	Cutoff	p value	95% CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
UC NT-pro BNP	0.938	>2760.5	<0.01	0.877–0.999	90.7	96.6	96.5	90.7
Control NT-pro BNP	0.968	>1414	<0.01	0.933–1	95.9	91.2	91.2	94
PASP (mmHg)	1	>36.5	<0.01	1–1	100	100	100	100

ROC: receiver operating characteristic, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, UC: umbilical cord, PASP: pulmonary artery systolic pressure, AUC: area under the curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

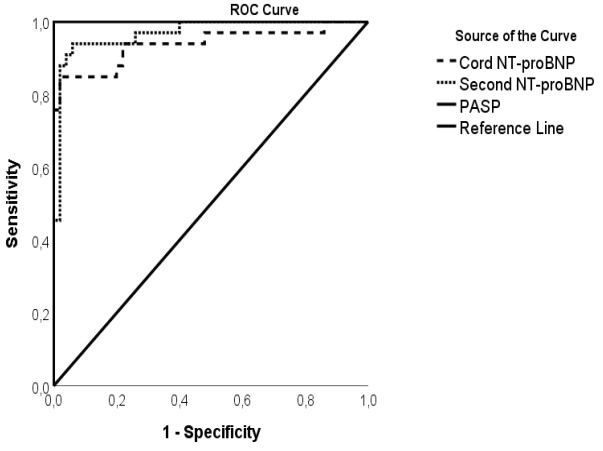

Figure 1: Receiver operating characteristic curve analysis according to the relationship between NT-proBNP levels in the umbilical cord and at postnatal 72 hours and pulmonary artery systolic pressure.

There is no apparent lung pathology involved in idiopathic PPHT. Secondary causes may be detected in three-quarters of the cases. In our study, the most common etiology of PPHT was infection (sepsis and/or pneumonia), late preterm birth, MAS, IDM, perinatal asphyxia, RDS, and SGA. There were three patients (9%) in the idiopathic group. The identified risk factors were similar to those of a study by Steurer and Bhattacharya (20, 21).

In the present study, gender, gestational week, maternal age, number of pregnancies, and mode of delivery had no effect on NT-proBNP levels (p>0.05). Similarly, Mannarino et al. reported that gender, maternal age, gestational week, and mode of delivery did not affect BNP levels in 36 preterm and 34 full-term infants (22). Seong et al. reported UC NT-proBNP levels of 766.2±536.9 pg/ml in 84 healthy newborns and demonstrated that low Apgar scores and pH were associated with increased NT-proBNP levels (23). In our study, the mean UC NT-proBNP levels in the

Table 5: Pearson's correlation analysis of NT-proBNP levels in the umbilical cord and at postnatal 72 hours

	UC NT-proBNP		NT-proBNP at postnatal 72 hours	
	r	p	r	p
Pulmonary artery systolic pressure	0.75	**<0.01**	0.54	**<0.01**
Vasoactive inotropic score	0.58	**<0.01**	0.84	**<0.01**
Oxygenation index	0.75	**<0.01**	0.40	**0.02**
Downes score	0.54	**<0.01**	0.33	**0.05**
1st minute Apgar score	-0.36	**0.04**	-0.29	**0.10**
5th minute Apgar score	-0.25	**0.16**	-0.35	**0.04**
Cord pH	-0.52	**<0.01**	-0.37	**0.03**
Cord base excess	-0.41	**<0.01**	-0.37	**0.03**

Table 6: Stepwise regression model analysis in the PPHT group

NT-proBNP	Model	Unstandardized beta	p-value	95% confidence interval
Umbilical cord	Vasoactive inotropic score	98.962	**0.02**	14.1–183.8
	1st minute Apgar score	-3753.574	**<0.01**	-4768.1– -2738.9
	Oxygenation index	616.517	**0.01**	176.7–1056.3
	Pulmonary artery systolic pressure	443.168	**0.01**	105–781.3
	Intubated mechanical ventilation time (hours)	59.37	**0.03**	111.8–6.86
Control	Vasoactive inotropic score	21.042	**0.01**	5.56–37.61

control group were slightly higher than those reported by Seong et al. This may be attributed to the presence of late preterm infants in our study group, individual differences in postnatal adaptation, and/or study methodology.

In the present study, increased UC NT-proBNP levels were negatively correlated with 1st minute Apgar scores and pH. Further, increased NT-proBNP levels at 72 hours were negatively correlated with 5th minute Apgar scores and pH. These findings indicated difficulties in respiratory adaptation in the perinatal period. In cases with severe MAS and severe asphyxia, a 5th minute Apgar score of <5 has been shown to be six times more associated with mortality (14). In a study by Neves, NT-proBNP was found to be associated with MV time, length of stay in the intensive care unit, need for inotropic support, and low cardiac output syndrome (24). In our study, infants with high PASP and UC NT-proBNP levels had higher inotrope scores, higher oxygen requirement, longer periods of intubated MV time, and lower 1st minute Apgar scores. Further, NT-proBNP levels at 72 hours were higher in patients requiring inotropic support.

NT-proBNP levels are closely correlated with cardiac shunt volume, increasing with decreasing LVEF, and are positively correlated with increasing PASP (25). In our study, patients with the highest levels of pulmonary artery pressure had worse clinical presentation and higher NT-proBNP levels. LVEF was lower in the patient group compared to the control group, but no significant correlation was found between NT-proBNP levels and LVEF. Increased pressure in blood vessels and/or myocardial hypoxia induce the synthesis and secretion of BNP. A previous study on 28 newborns with respiratory distress showed that NT-proBNP was much higher in the severe respiratory failure subgroup (26). In the present study, NT-proBNP levels, respiratory failure scores, and inotropic support and oxygen requirements were higher in the severe PPHT group. In addition, MV time and length of hospital stay were longer in the severe PPHT group. There were no statistical differences between the mild PPHT and moderate PPHT groups. It has been reported that PPHT accompanied by pulmonary hypoplasia results in a worse treatment response, with a mortality rate of 16.4% (4). In our study, inhaled nitric oxide (INO) therapy was used in two patients with severe PPHT. One of our three patients with oligohydramnios/pulmonary hypoplasia did not respond to INO and/or other treatments and died.

Downes score is used to evaluate respiratory failure in preterm/term infants. Rusmawati et al. showed that the sensitivity and specificity of DS were high in 88 newborns

with hypoxemic respiratory failure (14). In the present study, the clinical presentation was more severe and oxygen and inotropic support requirements were higher in patients with high DS and NT-proBNP levels.

Oxygenation index is used to determine INO and extracorporeal membrane oxygenation (ECMO) requirements in newborns with hypoxemic respiratory failure such as persistent pulmonary hypertension (9). Heindel et al. found a correlation between the severity of left ventricular dysfunction and pulmonary hypertension and elevated NT-proBNP levels at postnatal 48 hours and the need for ECMO in 44 patients with CDH. They also reported a significant correlation between elevated NT-proBNP levels at postnatal 6 hours and inotrope score (27). It has been shown that a repeated increase in NT-proBNP levels during the reduction of INO dose for PPHT treatment is associated with an increase in pulmonary vasoconstriction (7). Since INO could be used in only two patients in our study, the relationship between NT-proBNP and INO treatment response was not evaluated.

It has been shown that the rate of early deaths or ECMO requirement was higher when the NT-proBNP levels at postnatal 6 hours were ≥4682.5 pg/ml in patients with CDH-induced PPHT (27). In the present study, the threshold values for NT-proBNP levels were found to be lower due to the etiological differences in our patient group and the different blood test time. In 46 patients with perinatal asphyxia and myocardial injury, the cutoff for NT-proBNP levels was 3612.5 pg/ml (AUC 0.80), with sensitivity of 83.3% and specificity of 80.5% (25).

The strength of the study was that the diagnostic value of NT-proBNP measurement at two different time points and its relationship with the clinical follow-up of the disease were investigated in newborns with PPHT and healthy newborns.

The limitations of the study were that the number of patients was small, it was single-center, the best time to measure NT-proBNP levels was not known, different echocardiographic evaluation methods were not used, and there were no long-term morbidity results.

CONCLUSION

NT-proBNP levels are quite high in the first days of life. NT-proBNP can be a useful biomarker in the diagnosis and follow-up of PPHT when used with other parameters such as respiratory failure and high FiO_2 requirement.

Informed Consent: Written consent was obtained from the participants.

Ethics Committee Approval: This study was approved by the Tekirdag Namik Kemal University, Non-Invasive Clinical Research Ethics Committee (Date: 18.06.2020, No: 46048792-050.01.04-E.).

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