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Clinical Value of NT-proBNP and Lactate Parameters in Infants with Congenital Heart Defects

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Abstract

Aim: Congenital heart disease (CHD), defined as anatomic abnormalities of the heart and/or great vessels, is considered one of the most common anomalies worldwide. The aim of the study was to determine whether the NT-proBNP indicator has a diagnostic value in identifying and determining the severity of the disease, based on the analysis of this marker in patients admitted with congenital heart defects at the age of up to 1 year, and also to check whether there is a correlation between lactate and NT-proBNP among patients with congenital heart defects.

Methods: NT-proBNP values in 81 critical condition congenital anomaly patients averaged 12811.6±810.7 (445-40163), control group averaged 135.6±14.0 (78-320) among 20 patients, Pf< 0.001 which was reported to be statistically significant.

Results: In our study, NT-proBNP indicators of patients diagnosed with CHD were found to be higher in the first 28 days compared to other infant groups (1-6 months and 6-12 months). The results revealed that the difference between the CHD lactate level between the surviving and lethal groups was statistically significant (Pf< 0.001; Pu 0.017).

Conclusion: We should state that in our study, blood NT-ProBNP levels in critically ill infants with congenital heart anomalies were found to be approximately 10 times higher than in healthy infants (Pf < 0.001). At the same time, a correlation was established between the blood lactate index and the blood NT-ProBNP level.

Keywords: Congenital heart anomalies, NT-proBNP level, lactate level, mortality predictor.

Introduction

CHD is defined as an anatomical abnormality of the heart and/or great vessels resulting from intrauterine development [1]. Diagnosis of innate defects during the antenatal period or immediately after birth remains one of the current problems of medicine. Despite advances in diagnostic evolution, in modern times a large proportion of children with congenital heart defects remain undiagnosed until serious complications develop.

Congenital heart disease (CHD) is one of the most common anomalies worldwide, affecting approximately 0.8%–1.2% of live births [2, 3]. The prevalence of congenital heart defects has been extensively studied and is reported to be approximately 9.5/1000 [4].

CHD incidence and mortality rates have been found to be significantly heterogeneous across geographic regions and countries [5, 6]. Thus, it was determined that the incidence of CHD varied by region, and the results presented the frequency as varying between 1.2 and 17 per 1000 live births [7]. Although the field of cardiology and cardiovascular surgery has advanced in recent years, with mortality rates decreasing dramatically, allowing most patients to reach adulthood, congenital anomalies remain the leading cause of death and result in a reduced quality of life associated with the disease [8]. Congenital heart defects account for 3% of infant deaths. Studies have shown that with timely detection of congenital heart defects and early intervention, neonatal mortality rate

can decrease from 2–3/1000 to 0.6–0.8/1000 live births [9].

Various tests have been tested to improve the diagnosis of CHD and reduce mortality. Screening tests using pulse oximetry are used to detect critical CHD, allowing early diagnosis in infants who have not been diagnosed with the disease before birth. Meta-analyses have shown that this screening test has a specificity of 99.9%, a sensitivity of approximately 76%, and a false-positive rate of 0.14% for critical CHD [10]. Although screening is now mandatory in many high-income countries, challenges remain in implementing screening in low- and middle-income countries (LMIC) [11, 12].

CHD is classified into two main groups: 1. Asianotic CHD: Left to right shunt- VSD; ASD; PDA and Outflow obstruction - Pulmonary stenosis; aortic stenosis; aortic coarctation. 2. Cyanotic CHD: Tetrada of Fallot; Tricuspid atresia; transposition of trunk vessels; truncus arteriosus; total pulmonary venous return anomaly (TAPVR); Ebstein anomaly.

Guidelines prepared by the European Society of Cardiology (2016) recommend the use of brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) as clinical biomarkers for the diagnosis and prognosis of heart failure [13]. Compared to BNP, NT-proBNP is a more stable protein and its serum half-life is longer than that of BNP [14].

Cantinotti et al. in 2015, BNP/NT-proBNP was found to be informative as an additional marker in the course of screening, diagnosis, and surgical treatment, indicating specific haemodynamics associated with congenital heart defects. The authors advocate widespread clinical use of peptides, particularly NT-proBNP (BNP as the active moiety and NT-proBNP as the inactive moiety) as substantial biomarkers in congenital heart disease [15]. The plasma half-life of NT-proBNP is 1-2 hours [16]. Cardiomyocytes located in the ventricles of the heart secrete pro-BNP, an inactive prohormone, which is converted to biologically active NT-proBNP in a 1: 1 ratio. Because proBNP is a more stable peptide, it appears in higher plasma concentrations than the actual hormone BNP [17].

Serum NT-proBNP levels have been shown to correlate with the severity of left ventricular (LV) dysfunction and functional status and can be used to help differentiate between dyspnea due to respiratory problems and heart failure [18]. The importance of NT-proBNP level in the diagnosis and assessment of heart failure has been proven. Many studies have demonstrated the important role of natriuretic peptide testing, including NT-proBNP, in heart failure management from diagnosis to monitoring, leading to recommendations for the use of these tests in clinical practice, with a high level of evidence and recommendation in most cases [13].

Lactate is a classic marker in critically patients and has been shown to be more elevated in cases of severe illness and death [19]. Hyperlactatemia is one of the main parameters in shock states due to lactate synthesis in anaerobic metabolism and is an indicator of inadequate oxygen supply [20].

In our study, we investigated and compared NT-proBNP and lactate parameters in critically infant CHD patients.

Material and metods

The purpose of our study is to find out whether this marker is diagnostically important in detecting and determining the severity of the disease, based on the analysis of NT-proBNP indicators of patients admitted with congenital heart defects under the age of 1 year, and also to check whether there is a correlation between lactate and NT-proBNP among patients with congenital heart defects. Congenital heart defects were not specified, patients with renal failure, sepsis, and children who stayed in the intensive care unit for less than 24 hours were excluded.In a study of 101 infants, children were divided into two groups: patients diagnosed with CHD (n=81) and healthy children (n=20).

Blood samples taken from arterial, central and peripheral vessels of patients were tested for NT-proBNP with Cobas E601 and Cobas E602 analyzers. NTproBNP measurement range is 10-35000 pg/ml. The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

Ethical Considerations

The principles of the Declaration of Helsinki were considered at all stages of the study. In order to carry out the research, permission was obtained from the Ethics Committee of Azerbaijan Medical University to take additional blood analysis from patients diagnosed with congenital heart defects (18.10.2024/36). Written and verbal consent was obtained from the parents of the patients participating in the study.

Statistical analyses

Statistical studies were performed using variation (t-Student-Bonferroni, U-Mann-Whitney, H- Kruskal-Wallis), discriminant (Chi-square Pearson), variance (F-Fisher) and correlation (Rho-Spearman) methods" IBM Statistics SPSS-26 programs were performed. The "0" hypothesis was rejected when $p<0.050$ [21].

Results

In our study, NT-proBNP test was performed in 55 (67.9%) of 81 infants with critical congenital heart disease in the first 28 days; 21 (25.9%) in 1-6 months; and 5 (6.2%) in 7-12 months. 69.1% of the patients were male (56) and 30.9% (25) were female (Table 1).

Table 1 Characteristics of patients

			Mean	Std error
Gestasional week	Preterm	22 (27.2%)	37.3	0.2
	Term	59 (72.8%)		
Age range	1-28 days	55 (67.9%)	38.6	7.1
	1-6 month	21 (25.9%)		
	7-12 month	5 (6.2%)		
Gender	Male	56 (69.1%)		
	Female	25 (30.9%)		
Weight			2933,1	61,9
Delivery	Physiological	29 (35,8%)		
	Caesarean section	52 (64,2%)		
Abqar scale 1 st min	< 7 score ≥ 7 score	40 (49,4%) 41 (50,6%)	6,3	0.1
5 st min	< 7 score ≥ 7 score	19 (23,5%) 62 (76,5%)	6,8	0,1

In the healthy group, 10 out of 20 babies (50%) were born in the first 28 days; 3 (15%) between 1-6 months; and 7-12 months (35%). Of these, 5 (25%) were preterm and 15 (75%) were term babies. Of the healthy group, 17 (85%) were male and 3 (15%) were female. Mean birth weight was 2957.5 ± 107.7. Nine (45%) of the healthy children were born physiologically and 11 (55%) were born by cesarean section. The mean Abqar 1 score was 7.7±0.2 and the mean Abqar 5 score was 8±0.1.

When the reasons for these patients being admitted to intensive care were examined, it was seen that 33 (40.7%) patients were not associated with anomaly, 32 (39.5%) patients

were associated with anomaly, and 16 (19.8%) patients were suspected of anomaly. Multiple anomalies were detected in 12 (14.8%) of these patients; 4 (4.9%) of them simultaneously had gastrointestinal system anomalies, 2 (5%) had nervous system anomalies, 1 (1.2%) had metabolic diseases, and 8 (9.9%) had other anomalies (Table 2).

Table 2 Evaluation of patients according to anomaly and clinical condition

Reason for admission to intensive care	not due to anomaly	33 (40,7%)	
	related to the anomaly	32 (39,5%)	
	Suspected anomaly	16 (19,8%)	
A congenital anomaly has been identified	In the birth house	34 (42%)	
	In intensive care	47 (58%)	
According to the type of anomaly	Structural	80 (98,8%) .	
	Structural+functional	1 (1,2%)	
According to the damage number of the anomaly	Single	69 (85.2%)	
	Multipl	12 (14.8%)	
Mechanical ventilation	None	34 (42%)	4.5± 0.6 days
	Yes	47 (58%)	
Duration of parenteral nutrition			1.9±0.3 days
Surgical intervention	None	72 (88,9%)	
	Yes	9 (11,1%)	
Length of stay in intensive care		10.8± 0.9	
Conclusion	Survived	65 (80.2%)	
	Lethal	16 (19.8%)	

NT-proBNP values in 81 critical condition congenital anomaly patients averaged 12811.6±810.7 (445-40163), control group averaged 135.6±14.0 (78-320) among 20 patients, Pf < 0.001 which was reported to be statistically significant (Table 3).

Table 3 Comparison of NTproBNP patient group and control group.

Groups	Patient №	Mean	St error	Min	Max	
Control	20	135,6	14,0	78	320	Pf < 0.001
Main	81	12811,6	810,7	445	40163	

When we analyzed NT-proBNP values separately for congenital heart defect anomalies, we obtained the results shown in Table 4.

Table 4 Analysis of NT-proBNP values of congenital heart defect anomalies.

CHD	Patient №	NT-proBNP average value pg/ml	Pf	Pu
Coarctation of the aorta	7	11651,7±1705,1	< 0.001	< 0.001
Aortic stenosis	4	13295,0±1454,3	< 0.001	0.002
Aortic hypoplasia	3	10233,3±2316,8	< 0.001	0.006
ASD	48	12228,2±1056,7	< 0.001	< 0.001
AVSD	14	15816,6±2952,4	< 0.001	< 0.001
Dextrocardia	2	12136,0±7624,0	< 0.001	0.022
Ebstein anomaly	3	19643,3±5652,5	< 0.001	0.006
Fallot tetrada	10	15163,2±1368,0	< 0.001	< 0.001
Magistral damar transpozisya	8	11993,8±2147,8	< 0.001	< 0.001
PDA	14	16413,4±2497,9	< 0.001	< 0.001
Pulmonar stenoz	24	12799,8±1617,6	< 0.001	< 0.001
Taussig Big	1	40163,0	< 0.001	0.098
Single ventricle	4	15782,5±1485,5	< 0.001	0.002
VSD	42	11290,7±837,8	< 0.001	< 0.001

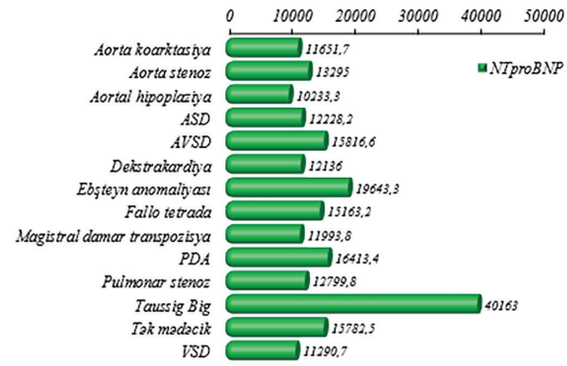

Figure 1 – text

When conducting a comparative analysis of the indicators lactat and NT-proBNP, according to the age range, the following results were noted. Also, in our study, a comparative analysis was conducted according to the age range (Table 5).

Table 5 Blood levels of lactat and NT-proBNP depending of age of infants.

	Age range	Patient №	Means	St error	Min	Max	Pf
Lactate	1-28 day	253	6,0	0,2	1	22	0,943
	1-6 month	68	5,9	0,5	1	20	
	7-12 month	11	6,3	1,1	2	14	
NT-proBNP	1-28 day	55	13398,2	1095,5	445	40163	0,442
	1-6 month	21	10951,9	1082,4	3000	18500	
	7-12 month	5	12060,0	3438,4	1000	19800	

Also, in our study conducted by Spearman's rho method, it was found that there is a correlation between lactate and NT-proBNP (rho=0.333; p=0.003) (Table 6).

Table 6 Correlation between lactate and NT-proBNP

Lactate	Correlation Coefficient	1,000	0,333
	Sig. (2-tailed)		0,003
NT-proBNP	Correlation Coefficient	0,333	1,000
	Sig. (2-tailed)	0,003	

In the patients examined in our study, the average value of the lactate index in the survived group was 5.6±0.2, and NT-proBNP was determined as 12894.9±853.3. In the lethal infant group, lactate index was 7.9 ±0.8 and NT-proBNP was 11903.8 ±2371.2. The results revealed that the difference between the CHD lactate level between the surviving and lethal groups was statistically significant (Pf< 0.001; Pu 0.017) (Table 7).

Table 7 Comparative analysis of lactate and NTproBNP values between surviving and lethal groups

Patient groups	Lactate mg/l	NT-proBNP pg/ml
Survived 65 (80.2%)	5.6 ± 0.2	12894,9 ± 853,3
Lethal 16 (19.8%)	7,9 ± 0,8 (Pf< 0.001; Pu 0,017)	11903,8 ± 2371,2 (Pf= 0,633; Pu= 0,239)

Discussion

Although it is known that the NT-proBNP test in patients with severe cardiac pathology is informative in terms of identifying the degree of heart failure, we studied the effect of this indicator on the occurrence of complications and mortality in children admitted to the intensive care unit with a diagnosis of congenital heart disease, as well as the level of lactate, reflecting tissue hypoxemia, and the correlation of its level with NT-proBNP in hypoxia caused by heart defects, and analyzed its prognostic value.

Improvements in diagnosis now estimate that 1.35 million children are diagnosed with CHD each year [22]. CHD is clinically classified into three main categories: 1) Life-threatening CHD - structural heart defects in which cardiovascular collapse is possible and is at risk if not treated early. Critical CHD is divided into 3 parts according to the injury: 1.Obstructive lesions of the right heart (dependent pulmonary circulation): pulmonary athesia complete ventricular wall; Critical pulmonary stenosis; combined with pulmonary atresia in tetrada of fallot; tricuspid atresia; severe Ebstein anomaly. 2. Obstructive damage of the left heart (depending on the flow-systemic circulation): Hypoplastic left heart syndrome; Critical aortic stenosis; Coarctation of the aorta; Interrupted aortic arch. 3. Mixed injuries: Truncus transposition; Total pulmonary venous return anomaly; Truncus arteriosus.

2. Clinically significant CHD - early intervention is needed in the case of structural heart defects due to the impact on heart function and the development of heart failure as a result. This group includes large ventricular septal defect (VSD), complete atrioventricular septal defect (AVSD), large atrial septal defect (ASD), and tetralogy of Fallot with good pulmonary artery anatomy (TOF).

3. Clinically insignificant CHD - anatomically defined heart defects, but functionally and clinically insignificant. These include small ventral septal defect (VSD), atrial septal defect (ASD), mild pulmonary artery stenosis (PS), diseases that can be detected only by echocardiography and require no treatment [9, 23]. We did not include patients with clinically insignificant CHD in our study.

Etiological studies reveal the cause of CHD in approximately 15% of infants with congenital heart defects [24]. In 2017, CHD caused at least 260,000 deaths, 180,000 of which were among infants [25].

BNP level may be a prognostic criterion in patients admitted to cardiac intensive care units and may indicate the presence of LV volume and pressure overload in the presence of shunts and ay identify overt cardiac disease in acute care settings [26]. Harris SL et al. study, NT-proBNP was determined as an informative biomarker in predicting HsPDA and it was found that ventilation, hypoxia and hemoglobin levels did not affect NT-proBNP, but creatinine level showed a positive correlation [27]. Jourdain P. et al. study revealed that serum NT-proBNP levels predict mortality risk and that monitoring the level of this peptide in treated CHF patients reduces the risk of CHF-related death and length of hospital stay [28].

High end-diastolic pressure and increased ventricular wall stress are the main triggers that stimulate BNP synthesis [29]. BNP is a peptide hormone that regulates circulating blood volume and arterial pressure by stimulating diuresis and natriuresis, inhibiting renin and aldosterone synthesis, and causing vasodilatation [30]. BNP acts on many organs and increases sodium excretion, stimulates urine output, causes vasodilation, and inhibits the renin-angiotensin-aldosterone system and sympathetic nerves. NT-proBNP levels increase due to abnormally high intraventricular pressure during heart failure and this level is positively correlated with the degree of heart failure [31].

In newborns, the concentration of NT-proBNP has a maximum value at birth and decreases almost 2 times in the first week of life. Measurement of NT-proBNP concentration can be used in neonates at risk of CHD and HF in the neonatal period [32].

NT-proBNP values decrease from 400 ng/L in the first 3 months of childhood to 138 ng/L in girls and 65 ng/L in boys by the age of 18. Values decrease rapidly, especially during adolescence [33]. In our study, NT-proBNP indicators of patients diagnosed with CHD were found to be higher in the first 28 days compared to other infant groups (1-6 months and 6-12 months).

In pediatric age, BNP/NT-proBNP plasma concentration values may be influenced by many factors [15]. Higher BNP/NT-proBNP values have been reported in infants with the following characteristics: maternal type 1 diabetes, premature birth, intrauterine growth retardation, cesarean delivery after uterine contraction, twins, and mothers with prenatal stress conditions, etc. [34].

Serum NT-proBNP levels can be used to help distinguish between dyspnea due to respiratory failure and heart failure and have been found to increase with the severity of left ventricular (LV) dysfunction [35]. On average, plasma BNP/NT-proBNP concentrations are highest during the first 4 days of life and then decline rapidly during the first week with a slower, progressive decline during the first month of life [36]. High NT-proBNP and BNP values are observed in infants with hemodynamically significant patent ductus arteriosus (hsPDA) and other CHD, in patients with pulmonary hypertension [37], bronchopulmonary dysplasia [38], retinopathy [39], inflammation or sepsis [40], and in premature infants [41].

In our study, the number of patients born prematurely was 22 (27.2%) (17 of these patients in the first 28 days, 5 patients among between 1 and 6 months and 7 of them died.

Among infants diagnosed with CHD, NT-proBNP has the highest value in Taussig BIG, followed by Ebstein's anomaly and AVSD. In our study, in patients marked as PDA, along with PDA, anomalies such as trunk vessel transposition, coarctation of the aorta, ASD, VSD, etc. were found. 12 of the patients were born on time ≥ 37 weeks, the other two were born at 36 gestational weeks, and other heart defects were found along with PDA.

NT-proBNP levels <400 ng/l have a low probability of heart failure, with a negative predictive value of ~90%. However, with heart failure levels >450 ng/l, a positive predictive value of ~90% is possible [42].

In the study conducted by Ayşe Sulu and her colleagues, unlike the studies conducted in adults, the benefit of using NT-ProBNP levels in the diagnosis of heart disease in children could not be demonstrated. Therefore, randomized prospective studies are recommended to demonstrate the value of Pro-BNP in distinguishing cardiac disorders from non-cardiac diseases in children [43].

Walsh et al. found that preoperative N-terminal-pro-brain natriuretic was a predictor of mean PICU days, but they did not consider any other biochemical markers such as troponin or lactate. In a study conducted by Xiao-Jun Deng et al., blood lactate and NT-proBNP were shown to be suitable for use as a prognostic device for ventilatory support [44]. In our study, NT-proBNP was checked in 47 (58%) MVs, and it was observed that the average ventilation was 4.5 ± 0.6 days.

In our study, when we compared the blood lactate level indicators between the surviving and deceased patients, we found that the lactate level increased statistically significantly in the second group (Pf< 0.001; Pu 0.017). This result makes it suitable to use the blood lactate level as a predictor in critically patients with congenital heart anomalies. At the same time in our study, it was found that there is a correlation between NT-proBNP values and lactate values.

Studies have shown that higher NT-proBNP values prolong ICU stay [45]. In our practice, the length of stay in the intensive care unit of patients whose blood NT-proBNP levels were controlled was 10.8 ± 0.9 days.

Our study did not reveal a statistically significant difference in blood NT-proBNP levels between the group of patients with fatal heart defects and those with surviving heart defects. On the one hand, this raises the question whether blood NT-proBNP levels can be a predictor of mortality in a group of critically patients with congenital anomalies, and requires randomized studies in a larger group of patients to have a final opinion in this group of critically patients. A striking result in our study is that the statistical deviation index in the group of patients who died was 2.8 times higher than the index in the group of patients who survived. This also shows that the blood NT-proBNP level in some patients in the group of dead patients is slightly elevated, which can be explained by the limited compensatory capacity in those patients in a critical situation. Thus, it is known that BNP is synthesized by cardiomyocytes due to increased pressure in the heart cavity. More than 16 patients who died in our study group had a critical decrease in arterial pressure during the initial examination, and these patients received inotropic support to normalize blood pressure.

Conclusion

In conclusion, we should state that in our study, blood NT-proBNP levels in critically ill infants with congenital heart anomalies were found to be approximately 10 times higher than in healthy infants (Pf < 0.001). However, the difference of this indicator between the group of patients who survived and the group of patients who died is not statistically significant and has a significant high deviation in the second group. This result requires larger-scale randomized studies to investigate the possibility of using NT-proBNP level in blood as a mortality indicator in critically ill infants with heart defects. On the other hand, in our study, it was confirmed that the blood lactate index increased statistically significantly in patients who died compared to the group of patients who survived. At the same time, a positive correlation was established between the blood lactate index and the blood NT-proBNP level.

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