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Evaluation of Serum Levels of N-terminal Pro Brain Natriuretic Peptide and Atrial Natriuretic Peptide in Neonates with Respiratory Distress

Noor Mohammad Noori[1], Sima Savadkoohi[2], *Alireza Teimouri[3] , Fatemeh Alizadeh[4]

[1]Professor of Pediatric Cardiology, Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.
[2]Assistance Professor of Pediatric Cardiology, Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.
[3]Assistant Professor of Demography, Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.
[4]Pediatric Ward, Faculty of Medicine, Zahedan University of Medical Sciences and Health Services, Zahedan, Iran.

Abstract

Background: Acute respiratory distress (ARD) is a critical respiratory failure due to lung injury of neonates leading to the clinical appearance of poor lung compliance. The aimed of the study was to evaluate the diagnostic values in differentiating respiratory from heart diseases with using of N-terminal pro brain natriuretic peptide (*NT*-pro BNP) and Atrial natriuretic peptide (ANP) in neonates.

Material and Methods: Ninety neonates randomly collected from those who hospitalized in the neonate ward of the Ali Ebne abitalib Hospital, Zahedan, Iran. After taking blood samples ANP and NT pro Brian Natriuretic peptide using ELISA kit were measured. The separated serum was kept in -20 °C until BNP measurement. 250 µl of the patients' serum was isolated to assess pro BNP level using ELISA kit (USA). Data were analyzed using SPSS- 20 with considering of $P< 0.05$.

Results: NT pro-BNP level had the highest in cardiac patients and followed by respiratory. The level of NT pro-BNP for control neonates had the lowest. These levels had significant variation ($P<0.05$). The level of ANP had the lowest for the cardiac patients. ANP level had the lowest for the acyanotic. NT pro-BNP had the highest concentration in acyanotic patients and and had the second highest concentration in cyanotic. Respiratory diseases ranked in the third levels in concentration of pro-BNP. The level of NT pro-BNP had the lowest for controls. The analysis showed a significant difference in the level of NT pro-BNP ($P<0.05$).

Conclusion: Many studies revealed that NT pro-BNP cannot be used as a tool for differentiation between cardiac and respiratory as a cause of respiratory distress during neonate, but the results of the present study showed that it would be good biomarker.

Key Words: Atrial natriuretic peptide, Neonates, NT pro-BNP, Respiratory diseases.

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Corresponding Author:

Dr. Alireza Teimouri, Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran.
Email: Alirezateimouri260@gmail.com
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1- INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a critical respiratory failure due to lung injury of neonates (1). The annual incidence of ARDS is 13-23 people per 100,000 in the general population (2) and the prevalence of acute lung injury is 16.1% in ventilated patients (3). Pneumonia and sepsis are the most common triggers and pneumonia is presented in up to 60% of patients and may be either causes or complications of ARDS (4). The death rate varies from 25–40% in centers using up-to-date ventilator strategies and up to 58% in all centers (5, 6). One of the most common causes of respiratory distress is Congenital heart disease (CHD) in newborns when its prevalence reported 4 to 50 occurrences in the 1000 live births (7). Brain natriuretic peptide (BNP) and NT-pro-BNP are used for CHD diagnosis. (8). It has been reported that the level of BNP increasing in children with heart failure (9). Low information of BNP and NT-Pro-BNP suggest that these peptides are useful to diagnosis cardiac involvement in pediatric patients (10). BNP and NT-Pro-BNP are elevated in children with heart disease duo to ventricular pressure and volume overload. In addition, plasma BNP is correlated with shunt in left-to-right CHD and increases with Left ventricle (LV) ejection fraction decreasing and positively correlating with increasing right ventricular systolic pressures. NT-Pro-BNP is a good marker for persistent left ventricular dysfunction in children with dilated cardiomyopathy. Plasma NT pro BNP measurement can differentiate between acute heart failure and lung disease among infants with respiratory diseases and can be used to monitor response to treatment (11). BNP and NT-Pro-BNP are strongly correlated with pulmonary artery hypertension in children and predict clinical signs and hemodynamic changes (12). BNP and ANP are diagnostic markers for differentiating CHD from respiratory diseases. It has also been reported that ANP has diagnostic and therapeutic roles in animals but only diagnostic role in human. Years after discovering measures of natriuretic peptides particularly such as ANP and BNP a proper diagnostic tool in cardiology has not been received, because of hidden factors that make confusing the role of wall stress. Hypoxia is a direct and sufficient stimulus for the synthesis and release of ANP and BNP (13, 14). According to the above mentioned aspects, it is clear that differentiating the causes of respiratory distress is important in treatment. On the other hand, since studies on the diagnostic value of NT-Pro-BNP and ANP in respiratory distress are not comprehensive, we decided to evaluate the diagnostic values in distinguishing respiratory from heart diseases by using biomarkers of NT pro- Brian Natriuretic peptide and ANP in neonates.

2- MATERIALS AND METHODS

2-1. Materials and Methods

This case-control study was conducted to differentiate the respiratory diseases from heart diseases using NT pro- Brian Natriuretic peptide and ANP in neonates. Ninety neonates randomly collected from those who hospitalized in the neonate ward of the Ali Ebne abitalib Hospital, Zahedan, Iran. Participants were distributed of 35 with respiratory, 35 with heart diseases collected randomly amongst all 2-3 days age hospitalized and 20 neonates for control selected randomly from those who had been referred to the hospital for checkup. Exclusion criteria were lack of parental consent or agreement, metabolic diseases, anatomical disorders, hematologic disorders, renal diseases, neonates with hyperbilirubinemia and infectious diseases. The parents of neonates informed from the aims of the study and after taking signature from them on the constant form, their neonates

entered to the study. Ethical notes were considered in all the stages of study such as sampling, collecting controls from hospital base and case collection from the neonate ward. This study approved by Medical Research Ethics Committee of Zahedan University of Medical Sciences, South West of Iran. Respiratory distress appeared with the symptoms such as rapid breathing, difficulty breathing, moaning, retraction of intercostal muscles between and under ribs and the supraesternal along with the nostrils on inspiration and eventually cyanosis in neonates. All participants were examined by preclinical tests such as chest X-ray, biochemical test, Arterial blood gas (ABG) and echocardiography. These examinations were performed by skillful pediatric cardiologist. If any one of participants had cardiac involvement coded as a congenital heart diseases (CHD). CHD patients divided in two groups as cyanotic and acyanotic- groups. The balances of patients were belonged to the respiratory diseases group based on chest X-ray findings. Blood samples were collected to measure ANP and NT-Pro-BNP concentration. Therefore, venipuncture was not performed exclusively for the purpose of this study. After taking 2 ml blood samples from both case and controls in the neonate ward by high trained nurse, the samples were centrifuged at 5 ° C with a round of 3000 g for 10 minutes. The separated serum was kept in -20 ° C until NT pro Brian Natriuretic peptide and Atrial Natriuretic Peptide were measured. Finally, with consideration to the cold chain, it was transferred to the biochemistry laboratory. Then, 250 µl of the patients' serum was isolated to assess pro BNP and ANP levels by using ELISA kit (USA). In all cases, information related to gestational age, gender, birth weight and height along with head circumference were recorded. Weight was measured by Mika Mark recumbent weighing scale made in Japan with an error factor of 10 g. Participants' height was measured with a wooden scaled table in supine position. Head circumference measured with a flexible non-stretchable measuring tape. Data were analyzed using SPSS, 20 for Windows (SPSS, Chicago, IL, USA). Categorical variables sunnarized and presented as frequency and percentages, and continuous data are presented as mean ± SD and median. Analytic test were ANOVA and Tukey follow up with considering of P less than 0.05 for significant level.

3- RESULTS

Three groups of participants were patients with respiratory disease, patients with cardiac involvement and healthy neonates. Mean age of participants was 2.490 ± 0.503 such that, for the patients with respiratory, cardiac diseases and controls were 2.343±0.482, 2.600±0.497 and 2.550±0.510 days respectively. **Tables.1 and 2,** shows descriptive statistics of anthropometric measurements, neonates' age and gestational age, among the participants. From the tables it would be observed the mean and standard deviation (SD) for variables in the study. Mean gestational age of respiratory diseases, cognitional heart defect and control were 31.66±0.52, 37.257±0.351 and 37.6±0.407 weeks with median of 32, 38 and 38 weeks respectively. Range of deviation for gestational age were (26-37), (28-39) and (32-39) week in the order given. **Table.2,** shown frequency and relative percent of some categorical variables for the participants. This table showed that female participants were 42.22%. Mothers with natural delivery were 44.44%. **Table.3** shows the results of variance for the quantitative variables in patients with respiratory diseases, among cardiac and control groups. NT-Pro-BNP had the highest value in cardiac patients (459.415±58.716) and followed by respiratory patients (380.918±208.311), the level of NT-Pro-BNP for control

neonates had the lowest. These levels had significant variation (F= 10.057, P=0.001). The level of ANP had the lowest level for the cardiac patients (583.914±285.645) with the P>0.05 in which showed this difference is not significant. Mean weight (P=0.001), mean height (P=0.013) and mean head circumference (P=0.001) showed significant differences. In respect to the (**Table.4)** NT-Pro-BNP levels in respiratory patients were different from the levels of NT-Pro-BNP in cardiac patients (P=0.047) and controls (P=0.049). The levels of NT-Pro-BNP in cardiac patients and control were difference significantly (P=0.001). In the cases of weight, height and head circumference, the **Table.3** showed that patients with respiratory diseases had lower weight, height and head circumference compared to cardiac patients and controls. The results of ANOVA test for respiratory diseases, cyanotic, acyanotic and control groups have been shown in the (**Table.5**). NT-Pro-BNP had the highest concentration in acyanotic patients (474.542±75.596) and followed by cyanotic (450.476±45.726) when respiratory diseases had (380.918±208.311). This level of NT-Pro-BNP for control neonates had the lowest. The analysis showed a significant differences in the level of NT-Pro-BNP (F=6.732, P=0.001). ANP level had the lowest for the acyanotic patients that didn't observe differences with the others groups. Mean weight (P=0.001), mean height (P=0.006) and mean head circumference (P=0.002) showed significant differences. The results of multiple tests showed the NT-Pro-BNP levels were significant for control vs. acyanotic and control vs. cyanotic (**Table.6**).

Table 1: Descriptive statistics about Anthropometric measurements, neonates' age and gestational age of participants

Variable	Number	Mean	SD
Neonate age(day)	90	2.4889	0.502
gestational age(week)	90	35.156	3.756
Neonate Weight(gr)	90	2423.667	725.518
Neonate Height(cm)	90	46.194	6.716
Neonate Head circumference(cm)	90	33.168	5.320

Table2: Countable variables' frequency of participants

Variables	Categories	number	%
Birth order	1	47	52.22
	2	25	27.78
	3	7	7.78
	4	5	5.56
	5	5	5.56
	10	1	1.11
Gender	male	52	57.78
	female	38	42.22
Type of delivery	normal	40	44.44
	Cesarean	50	55.56
Diagnosis	Respiratory diseases	35	38.89
	Acyanotic	13	14.44
	cyanotic	22	24.44
	control	20	22.22

Table 3: Results of analysis variance for three Respiratory diseases, cardiac and control groups

Variables	Groups	Mean	SD	95% CI for Mean		P-value
				LB	UB	
NT-Pro-BNP	Respiratory diseases	380.918	208.311	309.361	452.476	0.001
	Cardiac	459.415	58.716	439.245	479.585	
	control	289.477	34.724	273.226	305.728	
	Total	391.124	149.494	359.813	422.435	
Age(day)	Respiratory diseases	2.343	0.482	2.178	2.509	0.083
	Cardiac	2.600	0.497	2.429	2.771	
	Control	2.550	0.510	2.311	2.789	
	Total	2.489	0.503	2.384	2.594	
ANP	Respiratory diseases	807.857	580.775	608.354	1007.360	0.132
	Cardiac	583.914	285.645	485.792	682.037	
	control	653.050	501.364	418.404	887.696	
	Total	686.367	473.150	587.267	785.466	
Weight(gr)	Respiratory diseases	1802.286	543.848	1615.467	1989.104	0.001
	Cardiac	2747.143	604.024	2539.653	2954.632	
	control	2945.000	305.606	2801.972	3088.028	
	Total	2423.667	725.518	2271.710	2575.623	
Height(cm)	Respiratory diseases	43.800	5.656	41.857	45.743	0.013
	Cardiac	46.957	5.536	45.055	48.859	
	control	49.050	8.888	44.890	53.210	
	Total	46.194	6.716	44.788	47.601	
Head Circumference (cm)	Respiratory diseases	30.574	5.432	28.708	32.440	0.001
	Cardiac	34.357	4.133	32.937	35.777	
	control	35.625	5.279	33.154	38.096	
	Total	33.168	5.320	32.054	34.282	
Hemoglobin(gr/dl)	Respiratory diseases	16.785	16.465	10.947	22.623	0.512
	Cardiac	19.649	21.390	12.301	26.996	
	control	14.260	2.460	13.109	15.411	
	Total	17.350	16.860	13.778	20.922	

LB: lower bound; UB: Upper bound.

Table4: Results of tukey test for RD, Cardiac and Control groups for significant variables

Variables	(I) Diseases	(J) Diseases	(I-J) Mean difference	P-value
NT-Pro-BNP	Respiratory diseases	cardiac	-78.497	0.047
		control	91.441	0.049
	cardiac	control	169.938	0.001
Weight(gr)	Respiratory diseases	cardiac	-944.857	0.001
		control	-1142.714	0.001
	cardiac	control	-197.857	0.379
Height(cm)	Respiratory diseases	cardiac	-3.157	0.108
		control	-5.250	0.013
	cardiac	control	-2.093	0.483

Head Circumference(cm)	Respiratory diseases	cardiac	-3.783	0.005
		control	-5.051	0.001
	cardiac	control	-1.268	0.631

Table5: Results of analysis variance for RD, Cyanotic, Acyanotic and control groups

Variables	Groups	Mean	SD	95% CI for Mean		P-value
				LB	UB	
NT-Pro-BNP	Respiratory diseases	380.918	208.311	309.361	452.476	0.000
	Acyanotic	474.542	75.596	428.859	520.224	
	Cyanotic	450.476	45.726	430.203	470.750	
	Control	289.477	34.724	273.226	305.728	
	Total	391.124	149.494	359.813	422.435	
Age(day)	Respiratory diseases	2.3429	.48159	2.1774	2.5083	.086
	Acyanotic	2.4615	.51887	2.1480	2.7751	
	Cyanotic	2.6818	.47673	2.4704	2.8932	
	Control	2.5500	.51042	2.3111	2.7889	
	Total	2.4889	.50268	2.3836	2.5942	
ANP	Respiratory diseases	807.857	580.775	608.354	1007.360	0.188
	Acyanotic	494.154	102.887	431.980	556.328	
	Cyanotic	636.955	343.684	484.573	789.336	
	Control	653.050	501.364	418.404	887.696	
	Total	686.367	473.150	587.267	785.466	
Weight (gr)	Respiratory diseases	1802.286	543.848	1615.467	1989.104	0.000
	Acyanotic	2519.231	772.857	2052.198	2986.263	
	Cyanotic	2881.818	445.225	2684.417	3079.220	
	Control	2945.000	305.606	2801.972	3088.028	
	Total	2423.667	725.518	2271.710	2575.623	
Height (cm)	Respiratory diseases	43.800	5.656	41.857	45.743	0.006
	Acyanotic	44.192	7.319	39.770	48.615	
	Cyanotic	48.591	3.390	47.088	50.094	
	Control	49.050	8.888	44.890	53.210	
	Total	46.194	6.716	44.788	47.601	
Head Circumference (cm)	Respiratory diseases	30.574	5.432	28.708	32.440	0.002
	Acyanotic	33.962	4.901	31.000	36.923	
	Cyanotic	34.591	3.712	32.945	36.237	
	Control	35.625	5.279	33.154	38.096	
	Total	33.168	5.320	32.054	34.282	
Hemoglobin (gr/dl)	Respiratory diseases	16.7848	16.46474	10.9467	22.6230	0.405
	Acyanotic	14.9769	2.58977	13.4119	16.5419	
	Cyanotic	22.4091	26.74723	10.5500	34.2681	
	Control	14.2600	2.46030	13.1085	15.4115	
	Total	17.3500	16.86041	13.7776	20.9224	

Table 6: Results of tukey test for RD, Cyanotic, Acyanotic and Control groups

Variables	(I) Diseases	(J) Diseases	(I-J) Mean difference	P-value
NTPro-BNP	Respiratory diseases	Acyanotic	-93.623	0.159
		cyanotic	-69.558	0.249
		control	91.441	0.088
	Acyanotic	cyanotic	24.065	0.958
		control	185.065	0.002
	Cyanotic	control	160.999	0.001
Weight (gr)	Respiratory diseases	Acyanotic	-716.945	0.001
		cyanotic	-1079.532	0.001
		control	-1142.714	0.001
	Acyanotic	cyanotic	-362.587	0.197
		control	-425.769	0.105
	Cyanotic	control	-63.182	0.979
Height (cm)	Respiratory diseases	Acyanotic	-0.392	0.998
		cyanotic	-4.791	0.034
		control	-5.250	0.021
	Acyanotic	cyanotic	-4.399	0.204
		control	-4.858	0.147
	Cyanotic	control	-0.459	0.995
Head Circumference (cm)	Respiratory diseases	Acyanotic	-3.387	0.160
		cyanotic	-4.017	0.019
		control	-5.051	0.003
	Acyanotic	cyanotic	-0.629	0.984
		control	-1.663	0.782
	Cyanotic	control	-1.034	0.906

4- DISCUSSION

In the present study three groups of participants were respiratory, cardiac and healthy neonates. Mean gestational age for respiratory neonates was 31.66±0.52 weeks when it was 37.257±0.351 weeks for heart neonates. Cardiac patients had the highest level of NT-Pro-BNP and followed by respiratory patients and the controls had the lowest level. The level of ANP had the lowest level for the cardiac patients in which did not show significant differences. NT-Pro-BNP had the highest value for acyanotic patients and followed by cyanotics. The analysis showed a significant difference in the level of NT-Pro-BNP in four groups of participants as cyanotic, acyanotic, respiratory and control group. Demonstrated that the levels of ANP, BNP and NT-Pro-BNP increasing immediately after birth and decreasing in the first week (15). In a study by Onal et al., the levels of ANP reduced in newborns patients than healthy newborns, 4 and 72 hours after starting Transient tachypnea neonates (TTN). They also observed that in neonates with TTN the level of ANP reducing compared to control. In our finding we didn't observed any significant differences between the groups in which it is dissimilar with Onal results (13). Olli reported that ANP had diagnostic and therapeutic roles in animals but it only had diagnostic role in humans.

The roles of the natriuretic peptide system are either as a diagnostic tool or as a guideline to treat cardiac diseases. Accordance with Olli and our findings it seems that respiratory distress and congenital heart diseases has a strong role to release ANP and BNP in infants with hypoxia and volume overload in which produced wall stress. Cardiac wall stress produced due to intravascular overload that stimulates the synthesis and release of ANP. Hypoxia is a direct and sufficient stimulus for the synthesis and release of ANP and BNP (14). A strong correlation between plasma levels of atrial natriuretic peptide and Patent ductus arteriosus (PDA) has been observed in preterm infants (16). This finding was confirmed by other studies (17) and our finding. Edema of the lungs is one of the most serious complications of cardiac and renal failure. Also, acute hypoxia or inflammatory agents increases vascular permeability and contribute to forms of non-cardiogenic pulmonary edema such as acute respiratory distress or edema provoked by infections of the lung or sepsis (18).

Dissimilarity with our study comes from the subjects under the studies. Some facts about therapeutically role of ANP have been reported in several clinical studies. Intravenous ANP infusion will improve pulmonary gas exchange and the lung injury score in patients with acute lung injury during mechanical ventilation with positive end-expiratory pressure; and will diminish pulmonary edema and pulmonary vascular permeability in intensive care patients without heart disease. In cardiac failure the anti- edematou actions of ANP could be derived from systemic natriuretic actions and improved cardiac function due to left ventricular unloading (19,20). But we aimed to assess the role of diagnosis in human for ANP in respiratory distress and CHD. Markovic-Sovtic considered NT-Pro-BNP from umbilical cord blood sampling in the assessment of respiratory distress in term neonates. They observed that NT-Pro-BNP concentration was higher but not significant in cardiac patients compared with respiratory. We received to the same results that cardiac patients had higher level of NT-pro BNP compared to respiratory patients and controls when our study conducted from vein blood sample on neonates with age ranged from 2 to 3 days. In the present study the level of NT-pro BNP had significant differences. Markovic- Sovtic concluded that neonates with respiratory have significantly higher NT-Pro-BNP compared to their healthy counterparts (21).

Shahramian (1) and Ko (22) reported that BNP level could be considered as a useful technique for detection of cardiovascular problems in newborn with respiratory diseases during the first few days after birth. Although the present study performed on NT-Pro-BNP in order to differentiate between cardiac involvement and respiratory disease in neonates, we received to the same conclusion regardless of type of biomarkers. Kara et al. performed a study and resulted lower levels of serum NT-Pro-BNP in TTN compared with controls but non-significant. Kara measured the levels of serum NT-Pro-BNP in term neonates with transient tachypnea, but our study carried out on neonates with respiratory and cardiac diseases in which the levels of serum NT-Pro-BNP was higher in patients than controls. The results of these two studies are dissimilar (23). Lechner concluded that NT-Pro-BNP levels in the umbilical cord blood of neonates with CHD were significantly elevated at labor compared with healthy neonates. Lechner also reported that NT-Pro-BNP levels in patients with CHD increased significantly after the second day. We also observed that the levels of NT-Pro-BNP was higher in patients compared their counterparts (24). Nir findings and our results confirm

that NT-Pro-BNP could be as an important biomarker for heart disease in children. The levels of NT-Pro-BNP are the highest in the first days of life and decreased by age (25).

5- CONCLUSION

The results of the present study regardless of ANP revealed that NT-Pro-BNP had higher concentration in patients with CHD compared to the patients with respiratory diseases and controls. The analysis also explored that in two type of CHD (acyanotic and cyanotic), NT-Pro-BNP had higher levels in acyanotic followed by cyanotic compared to respiratory diseases and controls. Although some of studies have reported that NT-Pro-BNP cannot be used as a tool for differentiation between cardiac and respiratory diseases during neonate, but the results of the present study showed that NT-Pro-BNP can be a good biomarkers to differentiate respiratory diseases from cardiac diseases. For having significant results, it would be needed more comprehensive studies with higher sample size.

6- CONFLICT OF INTEREST: None.

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