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Brain Natriuretic Peptide: A Predictor for Severity Respiratory Distress Syndrome in Newborns

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Background: Respiratory distress syndrome (RDS) is considered as one of the most popular prematurity-related respiratory problems and among the most prominent reasons of deaths in preterm infants.
Objectives: Brain Natriuretic Peptide (BNP) is the secret of the volume and pressure overload response of the vessels and decreases due to resistance as well as rises in systemic vessels and also in decline of pulmonary artery pressure. In the present paper, BNP is considered as a biomarker for prediction of RDS scoring.
Materials and Methods: In this case, 65 preterm infants under 37 weeks with an Apgar score more than seven and 65 healthy term infants were chosen. All of them were controlled for three days in NICU and then divided into 4 groups based on the RDS scoring and intensity, as well as chest x-ray findings; normal, mild, moderate, and severe. Serum BNP of all the infants was measured through ELISA kit and a questionnaire was filled up for each infant based on his/her demographic information and clinical findings. The collected data were analyzed by SPSS software based on the independent statistical t-test, one-sided variance analysis and X2. $P < 0.05$ was considered as the significant.
Results: The study results revealed a significant difference between the two groups regarding the pregnancy age, weight and type of delivery between cases and control groups ($P \geq 0.05$); but there was no significant difference between BNP in cases and control groups ($P \leq 0.05$). However, the comparison between the mean of pregnancy weight, pregnancy age, and BNP based on RDS frequency among the patients was significant ($P \geq 0.05$).
Conclusions: The results of this study demonstrated that serum BNP level correlates with increased RDS scoring. Therefore, it is possible to use BNP as the prediction marker for the progressive changes of RDS which occur in premature infants.

Keywords: Brain Natriuretic Peptide; Respiratory Distress Syndrome; Severity; Infant, Newborn

1. Background

"Acute respiratory distress syndrome (ARDS) is a life threatening respiratory failure owing to lung injury from a variety of precipitants". Pathologically, ARDS is categorized by alveolar capillary leakage, diffused alveolar damage and protein rich pulmonary edema, leading to the clinical appearance of poor lung compliance, severe hypoxemia, and bilateral infiltrates on the chest radiograph. Diagnostic criteria for ARDS include: A) presence of acute severe hypoxemia, B) bilateral infiltrates on chest radiography (CXR), and C) absence of raised pulmonary artery wedge pressure (1). Premature birth is one of the most critical reasons of fatality in infants which has currently increased; however, decrease in the rate of neonatal complications is not visible (2).

RDS is the most common respiratory disorder related to prematurity and one of the most widespread causes of fatality in infants (3, 4). RDS is a hyaline membrane disease in which due to preterm delivery of the infants -age of birth less than 37 weeks, production of surfactants decreases and consequently, acidosis, hypoxia, ischemia, infection and pulmonary disease mainly occur (5) then as a result, low alveolar radius, weak chest wall and decrease of the lung compliance cause pulmonary atelectasis (6). In the end, V/Q miss match, hypoventilation, hypoxia, pulmonary vasoconstriction increase and vascular damage occur which result in RDS (7-12).

Implication for health policy/practice/research/medical education:
Prematurity and RDS are health problems especially in pediatrics, which could have serious health influences. Understanding the reasons associated with initiation and continuation of this problem and the motivations for treatment tendency could contribute to designing and implementing appropriate RDS prediction programs for premature infants.

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Furthermore, a successful shift from natal to infancy requires a series of immediate changes in the cardiopulmonary system. In premature infants, alveolar vessels as well as lungs are not fully developed and they are not able to cope with the quick changes such as increased arterial O2 and gaseous transfer during the first minute of life (13). Therefore, it causes volume overload and increased pulmonary vascular resistance as well as decrease in the systematic resistance which in return result in RDS (14). Some infants sickening to RDS possess a clinically significant shunt of PDA which is left open due to hypoxia, acidosis, secondary lung pressure increase in response to contraction of pulmonary venous pressure, systemic hypotension, immaturity and local secretion of prostaglandins due to the duct dilation; so it seems as if there is a relation between duct patency, airway inflammation and brochopulmonary dysplasia (BPD) (15, 16).

Natriuretic Peptides especially brain natriuretic peptides are neuro-hormones which are released from ventricular myocytes in response to ventricular dysfunction and wall stress. Secreted pro-hormone BNP breaks to active BNP in circulation but active BNP only remains 3 days in the room temperature. Increase of plasma BNP is seen in the first days of life and its decrease occurs in the first week. The reason for increase of BNP level after birth is unknown. It is thought that wall stretch of myocytes is the first stimulator for BNP secretion (17). BNP (brain natriuretic peptide) is a peptide with 108 amino acids which is located in the brain, but secreted through myocytes in reaction to volume and pressure overload (10). BNP has a regulatory function role for physiological changes of hypoxia, pulmonary artery, vasodilator and rennin angiotensin antagonists (18, 19) and decreases due to increase in systemic vascular resistance and pulmonary pressure (20).

It is expected to observe BNP increase in premature infants in response to hypoxia as well as having vasodilator effect following pulmonary vasoconstriction. Moreover, due to the antagonistic effect of rennin, its angiotensin will play the role of reducing intravascular volume in accordance with coping with volume and pressure overload in RDS-infected infants. Moreover, BNP plays an important role in collaboration with cells in their reaction to pulmonary hypertension. In prematurity, BNP increases partly due to elevated pulmonary artery pressure and reduction of systemic vascular resistance (20) and the sequence of these changes illustrate prematurity progress toward RDS.

2. Objectives

Because of severe and stable conditions in which based on scoring, forms of RDS usually finish off in creation of bronco pulmonary dysplasia (BPD) as well as patent ductus arteriosus (PDA) and regarding the fact that we can observe the BNP level increase based on the performed studies (21, 22, 23). Other studies showed that there is a relationship between BNP and , hemodynamic changes of pulmonary dysfunction in neonate with acute respiratory distress syndrome (19,20). Therefore, we tried to analyze BNP levels in preterm infants and its relationship with RDS severity based on scoring.

3. Materials and Methods

In this study, 65 preterm infants under the 37 weeks with Apgar score more than 7 and 65 term infants were selected as groups studies. All of them were admitted and examined in NICU department of Zabol Amir Al Momenin hospital. The eligible infants, who had no malformations, genetic diseases, heart abnormality, renal failure, and water and electrolyte imbalance, were put under close study after their parents filled up the consent form.

At birth point, 1 mL blood was drawn from the umbilical cord of all infants. Then samples were centrifuged at 5°C with a round of 3000 g for 10 minutes. The separated serum was kept in -20°C refrigerator until BNP measurement. Finally, with consideration to the cold chain, it was transferred to the Biochemistry Lab of Zabol University of Medical Sciences. Then, 250 μL of the patients' serum was isolated to assess BNP level using ELISA kit (USA). All infants were under the NICU supervision for three days. According to SCORE classified severity of RDS, they were divided into four groups, based on chest X-ray findings: normal (without abnormal chest X-ray observation), mild (mild granularity of lungs), moderate (generalized granularity of lungs with air bronchogram with preserved cardiac borders) and severe (white out lungs with loss of cardiac borders).

In all cases, information related to gestational age at birth, sex and birth weight were recorded. Weight was measured by Mika Mark recumbent weighing scale made in Japan with an error factor of 10 g. After collecting data using SPSS software as well as descriptive and analytical statistics, the independent t-test, analysis of one-side variance and X2 were performed and $P < 0.05$ was considered as a meaningful level.

4. Results

In this study, 130 infants, treated in Amir al Momenin hospital (In Neonatal Intensive Care Unite ward) Zabol, Iran, were divided into two groups; case (65 premature infants) and control (65 term infants). Among them, 77 were born via vaginal delivery (59.2%) and 53 through the Caesarean section. The mean gestational age, birth weight and serum level of BNP were 35.500 ± 2.213 weeks, 2.575 ± 0.791 kg and 19.179 ± 19.741 pg/mL, respectively.

The obtained results represented significant statistical differences based on the variables such as gestational age, birth weight, and type of delivery between the two groups ($P \leq 0.05$) (Tables 1 and 2).

Table 1. The Mean of Pregnancy age, Birth Weight and BNP in the Case and Observer Groups

Criterion	Observer Group		Case Group		P Value
	Deviation	Mean	Deviation	Mean	
Pregnancy age, wk	1.2897	38.1538	2.202	32.846	P = 0.001
Birth weight, kg	0.6296	3.1362	0.4750	2.0143	P = 0.001
BNP level, pg/mL	0.5034	1.700	153.797	36.6585	P = 0.069

Table 2. Redundancy Distribution of Delivery Type in the Case and Observer Groups

Delivery	Observe Group, No. (%)	Case Group, No. (%)	P Value
Natural	53 (81.5)	24 (36.9)	0.001
Caesarian	12 (18.5)	41 (63.1)	
Total	65 (100)	65 (100)	-

The highest frequency distributions of RDS in the patients were 38.5% for mild, 30.8% for moderate and 13.8% for severe which are shown in Table 3. The comparison between frequency of delivery based on RDS frequency among the patients didn't show any significant statistical difference ($P > 0.05$) but mean birth weight, gestational age and BNP based on RDS severity between the patients had significant statistical differences ($p \leq 0.05$) whereas the comparison based on frequency of delivery, birth weight, gestational age and BNP in the control group according to RDS frequency between the patients was not significantly statistically different ($P \geq 0.05$) (Tables 4 and 5).

Table 3. RDS Redundancy Frequency in Studied Patients

RDS	No. (%)
Natural	9 (13.8)
Mild	25 (38.5)
Moderate	20 (30.8)
Severe	11 (16.9)
Total	65 (100)

Table 4. Frequency of Delivery Type in Case and Observer Groups Based on RDS Frequency

Group	Pregnancy type	RDS					P Value
		Natural	Mild	Average	Severe	Total	
Case	natural	4 (16.7)	11 (45.8)	8 (33.3)	1 (4.2)	24 (100)	0.213
	caesarean	5 (12.2)	14 (34.1)	12 (29.3)	10 (24.4)	41 (100)	
	Total	9 (13.8)	25 (38.5)	20 (30.8)	11 (16.9)	65 (100)	
Observer	natural	6 (11.3)	21 (39.6)	15 (28.3)	11 (20.8)	53 (100)	0.053
	caesarean	3 (25)	4 (33.3)	5 (41.7)	0 (0)	12 (100)	
	Total	9 (13.8)	25 (38.5)	20 (30.8)	11 (16.9)	65 (100)	

Table 5. Mean of Weight, Pregnancy Age and BNP Between Case and Observation Group Based on RDS Frequency

Group	RDS Level	Natural, Mean ± SD	Mild, Mean ± SD	Average, Mean ± SD	Severe, Mean ± SD	P Value
Case	pregnancy weight, kg	2.5 ± 0.254	2.182 ± 0.309	1.981 ±0.333	1.295 ± 0.313	P = 0.001
	pregnancy age, wk	34.222 ± 0.666	33.76 ± 1.30	33.05 ± 1.848	29.272 ± 1.489	P = 0.001
	BNP, pg/mL	9.677 ± 25.246	2.84 ± 4.783	10.295 ± 21.116	183.527 ± 348.338	P = 0.005
Observation group	pregnancy weight, kg	0.812 ± 2.822	0.578± 3.124	0.711± 3.295	0.327± 3.131	P = 0.324
	pregnancy age, wk	37.888 ± 0.781	37.920 ± 1.077	38.350 ± 1.598	38.545 ± 0.439	P = 0.452
	BNP, pg/mL	1.577 ± 0.411	1.788 ± 0.568	1.750 ± 0.515	1.509 ± 0.356	P = 0.388

5. Discussion

During the two current decades, due to inappropriate diets, we have encountered an increase in preeclampsia, infection, and some other similar diseases. Later, following the evolution of cardio-pulmonary system and as a result of abnormal respiratory function during progression from natal to neonatal, they progress to the respiratory distress syndrome (13) and just before any proper treatment, they are unable to retrieve their lives. Therefore, it is necessary to recognize markers for early detection of RDS.

On the other hand, BNP is a biomarker with various levels due to low pressure systems, pressure loss caused

by placental volume and super pressure in a systematic pulmonary overload. Several studies have already jagged to the BNP increase in RDS. The result of current research analyses showed that serum BNP level elevates in mature and premature infants and their relationship is based on RDS scoring. Moreover, revealed a meaningful relationship between gestational age, birth weight, BNP and severity of RDS. Therefore, serum BNP level increases with the decrease in gestational age and birth weight, and this elevation depends on the severity of RDS.

In this study, there was no significant relationship between BNP level of premature and mature infants. In the study of Ralph L. da Graca et al. BNP level changes occurred during prematurity, and also the amount of BNP was greater in premature infants compared to the mature ones (24). In another study by S. Mannarino et al. the amount of BNP was tested in the umbilical cord of term and preterm infants. Also a greater increase was observed in BNP level of preterm infants in comparison with the term cases (25). In another study, Remzi Kardag et al. demonstrated relationships between intracellular pressure and natriuretic peptide, in the plasma of patients with hypothyroidism conditions. Therefore, the plasma level of BNP increased in reaction to hypoxia (11). In fact, in prematurity, an increase in manifestation of cardiac output and hypertrophy occurs, as a result of hypoxia.

On the other hand, due it's the lung maturation inability, it is impossible to manage the vascular O2 pressure besides volume and pressure overload. Regarding BNP secretion in response to these obstacles, patient can experience an increase in BNP serum level. The discrepancy between the results probably refers to the fact that in the current study, more than half of the premature infants were infected by mild and moderate RDS (38.5% mild and 30.8% moderate) who were not under severe hypoxia conditions. As a whole, no meaningful change was observed in BNP serum level of the control group.

In the current study, there is an interwoven relationship between BNP level and RDS scoring. In a study by Gustavo Rocha et al. there was a relationship between BNP serum levels in premature infants with respiratory distress syndrome (RDS) (25). In another study by Joseph et al. increase in BNP serum level was demonstrated as a marker for recognition of BPD in prematurity. Also they reported a relation between BNP and RDS frequency in prematurity infants (26). In another study, Ainori Morichi et al. explained that serum BNP level is useful for predicting cardiac dysfunction at the birth time. Also they found a relationship between Gestational Age and BNP serum level and as a result, observed an increased BNP serum level in "Small for Gestational Age" infants (27). It shows that an increase in prematurity frequency can decrease the production of surfactant and the lungs compliance. On the other hand, as renal vascular contraction and vascular damage increase, RDS becomes more severe. In the end, in response to higher renal vascular contraction and its vasodilator effect, BNP is secreted.

In fact, higher serum BNP level demonstrated more severe RDS. Moreover, in these infants, due to prematurity, we observed the high release of FiO2 and BARO/VALU TROMA factors followed by the release of inflamed cytokines and chomocyns which determinate damage of the epithelial and endothelial cells and comsequently the decrease in the synthesis of surfactant and the production of RDS. As cytokines play a role in BNP monitoring (28), in prematurity, their increase elevates the BNP level which shows RDS frequency. In the present study, reduction of birth age was associated with the increment of serum BNP level. In another study, Afif EL-Khuffash et al. showed that there is reverse relationship between birth age and serum BNP level in preterm infants (29). Therefore, in case of lower Gestational Age, lungs maturity weakens, and eventually, higher pulmonary pressure diminished systematic vascular resistance and elevated serum BNP level occur.

Moreover, in this study we have investigated on the relationship between birth weight and BNP level and the obtained results represent a reverse relation between these two factors. The probable cause is that infants with lower weight have higher tendency toward higher hypoxia (18) and subsequently in the ones with lower birth weight, BNP level increases. Natriuretic peptides play an important role in the regulation of extracellular fluid volume. In the study of Aydemir et al. serum BNP level increased in neonates with transient tachypnea of the newborn compared to controls. Also, they demonstrated that BNP plasma level measurement can be beneficial for predicting the probable persistent tachypnea in infants and the mechanical ventilation requirements (30). The result of our study is also in agreement with the study by Aydemir et al. (30) which demonstrated that serum BNP level has correlation with increased RDS scoring. Therefore BNP is a prediction marker for progressive changes toward RDS and increase of serum BNP level illustrates RDS severity in premature infants.

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Authors' Contribution

Iraj Shahramian and Noormohammad Noori designed the study; Abasali Ramezani performed the statistical analysis, and wrote the manuscript. Elham Sharafi and Mehran Hesaraki assisted with data collection and data entry. All authors read and approved the final manuscript.

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There is no conflict of interest.

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