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Original Research Article

Evaluation of diagnostic value of n-terminal pro brain natriuretic peptide in pleural fluid with cardiac origin

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ABSTRACT

Background: Pleural effusion is a common finding in patients. For a long time, a light criterion is used to analysis of pleural effusion for separation of transudative from exudative fluid. Sensitivity of light criteria is very high to determine exudative pleural effusion (98%). However, the ability of these criteria for ruling out of transudative effusions is low. For this reason, this study was carried out to determine the level of NT-proBNP in pleural fluid.
Methods: A descriptive-analytic study was carried out on 21 patients with complaints of shortness of breath and diagnosis of pleural effusion. Pleural fluid was tapped in these patients and the following tests were performed: LDH, total protein, albumin, cell count, cell differentiation, cytology for malignant cells, ADA, smear for AFB, gram smear and culture.The results of all experiments were analyzed using SPSS V16.
Results: Mean age of participants was 65 years. Male and female frequencies were 52.4 and 47.6, respectively. 33.3% of patients had CHF, 28.5% TB, 19.4% malignancy, 4.76% hydatid, and the rest left without diagnosis. A pleural fluid in 66.7% of participants was exudative and in 33.3% was transudative. The levels of NT-proBNP (Pg/ml) in serum and pleural fluid of patients with CHF were 11288.42 and 11036.81, but in malignant patient were 1721.68 and 713.59, respectively, and the levels of NT-proBNP in serum and pleural fluid in TB patient were 2429.30 and 2810.08, respectively. Also, there was no significant difference between the levels of serum and pleural effusion NT-proBNP in transudative and exudative fluid but the level of NT-proBNP was significantly higher in CHF patients compared to others.
Conclusions: The results showed that the levels of NT-proBNP in serum and pleural fluid of cardiac patients are higher than other patients, but no significant difference in NT-proBNP between transudative and exudative pleural effusion.

Keywords: Pleural effusion, Transuductive, Exuductive, NT-proBNP

INTRODUCTION

Pleural cavity is covered by two screens: visceral pleural that covered lung and the parietal pleura covering the chest wall and diaphragm. Liquid and protein entered to this space in normal mode via the systemic circulation and absorbed by the lymphatic vessels of parietal pleura. Pleural pressure lower than atmospheric pressure and this cause the lungs to inflate. Because of permeable nature of mesothelial cells layer, extra fluids can enter to this low pressure and wide space. Therefore, the pleuraleffusions are common and havedifferent causes. These accumulations can caused by pleural diseases or pectoral and ventral organs. Its annual incidence is about 1.5 million in US. One third of them come from heart failure.

Determining the cause of pleural effusion requires strategies such as taken disease history, pleural fluid analysis and potentially invasive procedure of pleural tissue biopsy.Clinical History is very importantto diagnosis of effusion caused by heart failure. However, it is not very accurate, alone and often diagnose the cause of pleural fluid is a big headache for health care providers.[1] The criteria of light is used to analysis of pleural fluid for differentiate transudative from exudative liquids. These criteria are including: protein ratio of pleural fluid to serum ≤0.5, pleural fluid lactate dehydrogenase (LDH) ratio of pleural fluid to serum ≤0.6 and LDH level of pleural fluid equal to or less than two-thirds of the maximum normal serum LDH. If all of these criteria are true the liquid is transudative and if at least one of them is not satisfied it will be exudative.[2] The sensitivity of Light criteria to specify the exudative pleural effusion is very high (98%).[3] However, the strength of the criteria for rejection of transudative effusion is low.[4] Roth et al showed that 28% of patients with pleural effusion due to heart failure, based on the criteria of Light, mistakenly placed in the exudative liquids. The problem is aggravated when this wrong classification, leading to use of costly and invasive diagnostic methods. Therefore, a non-invasive and low-cost strategy to differentiate effusion caused by heart failure would be useful.[5] To solve this problem, Burgess et al. suggested using of Serum- pleural fluid albumin gradient.[6] Romero-candeira et al suggested the serum-pleural fluid protein gradient. However, the false diagnosis rates of albumin and protein gradient methods are 10% and 16%, respectively (transudative liquids mistakenly diagnosed as exudative).[4] The levels of plasma BNP and NT-proBNP are used in the diagnosis and treatment of heart failure as suitable biomarkers. BNP is a vasoactive neurohormonal ventricular that secreted by myocytes in response to increased pressure load and heart volume. This hormone is aprohormones called Pro BNP that first is synthesized as a 108 amino acid and is divided into two parts at secretion time of pro BNP, on partthat is biologically active called BNP and the second part is disabled and called NT-proBNP. BNP causes to diuresis, vasodilation and reduction of rennin and aldosterone secretion. NT-proBNP has higher half-life compared to BNP (120 minutes vs. 20 minutes) and therefore has a higher plasma concentration. NT-proBNP is removed from plasma, possibly by renal excretion or other unknown mechanisms. BNP disappears by Natriuretic peptide clearance receptor and metabolic degradation by proteolytic enzymes.[7] In the study of Porcel et al. the NT-proBNP level in heart disease patients was significantly higher than other patients. They reported the sensitivity and specificity of this test for the diagnosis of heart failure were 91% and 93%, respectively.[8] In the study of Gegenhuber et al 48.4% of patients were transudate and 51.6% were exudate. In their study, the diagnostic accuracy of plasma BNP in diagnosis of cardiac effusion was 93%.[9] Tomcsanyi et al measured the serum and pleural NT-proBNP levels. The relatively high and significant levels of NT-proBNP were found in blood serum and pleural fluid of patients with cardiac effusion. They suggested a Cutoff point of 599-1454 ng/l to determine heart Transudates.[10] Koldtz et al reported that the cutoff point of 4000 ng/l for NT-proBNP level of pleural fluid and serum.[7] This study aimed to investigate the diagnostic accuracy N-terminal pro brain natriuretic peptide titration in pleural fluid with cardiac origin.

METHODS

This descriptive and analytical study research was carried out in Imam Khomeini Hospital in Ardabil. The study population of patients had manifestation of dyspnea and pleural effusion. The sample size was 21 patients with pleural effusion with unknown cause that referred to Imam Khomeini Hospital (Sep-2013 to Sep-2014). Inclusion criterion was diagnosis of pleural effusion and exclusion criteria included patients' reluctance to participate in the study, patients who eventually had two or more causes for pleural effusion, existence of blood fluid or infection during tap, and patients with unknown reasons for effusion. Patients with unilateral or bilateral pleural effusion that are referred by various complaints were selected. They considered as new cases and had no previous diagnosis. The chest radiography was done after taking a thorough history and physical examination. All patients were undergone to echocardiography (by one person). Then, pleural fluid was tapped and the following parameters were determined in the fluid: LDH, protein, albumin, cell differentiation and cell cytology for malignant cells, ADA, smear for AFB, and smear and culture of gram. In the case of heart disease, if any of the following cases were exists, cardiac origin for effusions were considered: LVEF≤40%, severe valve disease Grade II-III, or severe left ventricular diastolic dysfunction. Due to lack of feasibility, investigation of the drug or other accompanying disease was ignored. Blood samples and pleura were taken at the same time and after 12 hours of fasting. The samples were collected in tubes without additives. Exudative fluidswere followed with invasive procedures until the time of diagnosis and our choice for pleural biopsy was thoracoscopy biopsy. The criteria for diagnosis of malignant pleural effusion were observation of malignant cells liquid cytology, biopsy of in pleural, or lung mass biopsy. The criteria for diagnosing parapneumonic effusions were clinical or radiological diagnosis, acute parapneumonia, or positive result of bacterial culture in pleural fluid. The levels of NT-proBNP were all collected pleural fluids and serum (by Electro chemiluminescence immunoassay). The results of all analysis were analyzed with statistical software, SPSS v16 using Chi-square, T-test and descriptive methods. The significance level for all tests was 0.05. In order to uphold the principles of medical ethics information will be kept confidential and results were reported anonymously.

RESULTS

The mean age of patients in this study was 65±18.01 years. 52.4% of patients were female and 47.6% were

male. Frequency distribution of disease among participants was shown in Table 1. The most common diagnosis among patients belonged to CHF (33.3%) and the lowest frequency observed for hydatid (4.76%).

Table 1: Frequency of participant based on final diagnosis.

Variable	Frequency (%)
CHF	7 (33.3)
TB	6 (28.5)
Malignancy	4 (19.4)
Hydatid	1 (4.76)
Without diagnosis	3 (14.4)

In our study, 66.7% had exudative pleural fluid and 33.3% had transudative fluid. Results of Echocardiography showed that 72% of patients had normal ejection fraction (≥40) and 28% had abnormal ejection fraction (<40). The results T-test showed that there was significantly different between protein and LDH levels of the pleural transudate and exudate fluids but this different for serum was not significant. Exudative fluid had higher protein than those of transudative fluid (Table 2).

Among the 8 patients with pleural effusion that biopsy was done for them, four person had tuberculosis, two person showed Malignancy, one person had hidatid and one person left without diagnosis. Dyspnea function class of patients was examined and 76.2% were settled in Class 3. Counting white blood cell (WBC), monocytes (MN) and polymorphoneutrophil (PMN) were showed that there wereno significant differences between WBC, MN, and PMN in two groups of exudative and exudative (Table 3).

The results of T-test showed that there was no significant different between NT-proBNP level of pleural fluid and serum in exudate and transudate liquid (Table 4).

The results of χ^2 test for NT-proBNP level of serum and pleural based ondisease diagnosis was shown in Table 5. The results showed that the surface of the material in the examined groups is statistically significant. CHF patients had significantly higher NT-proBNP levels of serum and pleural fluid compare to other patients.

NT-proBNP level of men was higher than women, but this difference was not statistically significant (Table 6).

Table 2: Protein and LDH levels of pleural fluid and serum based on type of pleural fluid.

Variable	Group	Mean±SD	P value
Serum protein	Transudative	4.88±1.02	0.253
	Exudative	5.53±1.26	
Pleural protein	Transudative	1.25±0.48	<0.001
	Exudative	3.77±1.16	
Serum LDH	Transudative	508.42±203.38	0.714
	Exudative	473.28±±191.11	
Pleural LDH	Transudative	168.71±121.08	0.011
	Exudative	405.71±204.76	

Table 3: results of T test for WBC, MN, and PMN based on type of pleural fluid.

Variable	Group	Mean±SD	P value
WBC (million/ml)	Transudative	207±151	0.380
	Exudative	3892±1070	
MN%	Transudative	74±28	0.067
	Exudative	46±34	
PMN%	Transudative	38±33	0.346
	Exudative	25±12	

Table 4: T-test results for NT-proBNP level of pleural fluid and serum in exudate and transudate liquid.

NTproBNP level (Pg/ml)	Group	Mean ±SD	P value
Serum	Transudative	11288042±11138.92	0.058
	Exudative	3458.13±6723.23	
Pleural fluid	Transudative	11036.81±12413.44	0.103
	Exudative	3572.08±6723.81	

Table 5: Results of χ^2 test for NT-proBNP level of serum and pleural based on disease diagnosis.

NT-proBNP (Pg/ml)	Group	Mean±SD	P value
Serum	TB	2429.30±1979.51	0.013
	Hydatid	11.20±0	
	Malignancy	1721.68±1103.54	
	CHF	11288.42±11138.92	
	Without diagnosis	313.36±255.59	
Pleural fluid	TB	2810.08±1086.39	0.030
	Hydatid	5±0	
	Malignancy	713.59±466.66	
	CHF	11036.81±12413.44	
	Without diagnosis	245±157.25	

Table 6: Results of NTproBNP level of pleural fluid and serum based on sex.

NT-proBNP (Pg/ml)	Gender	Mean±SD	P value
Serum	Man	7089.83±3264.53	0.632
	Female	5139.50±3087.35	
Pleural fluid	Man	7184.65±3615.46	0.630
	Female	5038.21±3412.12	

DISCUSSION

In this study, 33.3% of patients with CHF, 19.4 percent of malignancy, 28.47% of TB, 14.17% and 4.66% of hydatid without detection. The frequencies of disease in similar researches were very different. For example, Kolditz et al. study was conducted on 93 patients, 27% had heart failure, 43% malignant effusions, 16% parapneumonic and 14% other effusions.[7] Han et al studied 240 patients and showed that 98 patients had effusions of cardiac, 16 patientshepatic hydrothorax, 38 patients with malignant effusions, 40 cases Mycobacteria effusion and 64 patients parapneumonic.[11] Study of Porcel et al. was conducted on 90 patients with pleural effusion and 91 patients with cardiac Noncardiac, 10 patients with hepatic hydrothorax, 40 patients with malignant effusion, 15 patients with parapneumonic, 11 patients with pleural TB and 15 patients with other causesof exudative.[12] Long et al. studied 80 patients was performed on 20 patients with cardiac effusion, 20 patients with pleural post-CABG, 20 patients with malignant effusion and 20 with parapneumonic.[13] 66.7% had exudative pleural effusions and 33.3% had transducative effusions. Among the patients that were under biopsy, the most common diagnosis was tuberculosis. In the study of Tomcsányi et al. all 14 patients had exudative pleural effusion.[10] From 64 studied patients by Gegenhuber et al. 31 patients had transudate and 33 person hadexudate pleural effusions.[9] These data confirmed our result the rate of exudative pleural effusion was higher, but the rates of transudate and exudate were different in various study. Yorgancioglu et al reported that 38 cases of patients with pleural effusion were exudative and 7 cases were transdutive.[14] The highest level of NT-proBNP in serum and pleural were observed in CHF patients (11288.42 and 11036.18 Pg/ml, respectively). Followed by TB (2810.08), malignant (713.59), others (245), and hidatid. There was no significant difference between NT-proBNP of serum and pleural fluid of exdutive and transdutive effusion. This result is in agreement with the study of Koltz et al. that reported the NT-proBNP level of pleural fluid and serum was higher in the cardiac origin effusion.[7] Our results also confirmed their cutoff point for diagnosis of cardiac origin effusion (4000 Pg/ml). In the study of Pour Piranfar et al. NT-proBNP plasma levels in patients with heart failure was 421 Pg/ml.[15] Tomcsányi et al observed that the levels of NT-proBNP in patients with CHF, Pg/ml 8236 and exudative patients 276 Pg/ml (p=0.0006) and the pleural NT-proBNP in patients with CHF, 9692 Pg/ml and exudative patients 157 Pg/ml (p=0.0001).[10] Porcel et al. reported that NT-proBNP levels in heart patients 6931was Pg/ml, in patients with hepatic hydrothorax 551 Pg/ml, malignant effusions 347 pg/ml, TB 101 Pg/ml, parapneumonic effusion 514 Pg/ml and pulmonary embolism 346, therefore, the NT-proBNP level in heart patients was significantly higher than others.[8] This research is in accordance with our study, but in recent study the amount of NT-proBNP in the TB patients was higher than malignant effusions. In the study of Liao et al. the level of NT-proBNP in patients with CHF (5390 Pg/ml) was also higher than other patients (P<0.001).[16] Kolditz et al found that levels of NT-proBNP in patients with pleural effusion heart and Noncardiac patients were 10427 and 947 Pg/mL, respectively (P<0.001) the corresponding levels for serum were 10791 and 989 (P<0.001).[7] In these reports the level of serum and pleural effusion in CHF patients were higher than that of cutoff point reported by Kolditz et al, but Han et al. obtained lower NT-proBNP level for patients with pleural effusion and heart complication (3310 Pg/ml) but this value was higher in heart patients was than others (p<0.001).[7,11] Some other researchers also confirmed that that serum and pleural levels of NT-

proBNP in patients with heart failure and exudative pleural effusion, significantly higher than other patients. Seyhan et al, Porcel et al and Bayram et al, long et al and Abdalla et al.[12,13,17-19] Regarding to high cost of NT-proBNP evaluation kits and limitation of funding for thesis the sample size of the study was lower than of some other researches.

CONCLUSION

The results showed that the serum and pleural NT-proBNP in cardiac origin effusion is than any other disease, but no significant difference was observed between NT-proBNP with transudative and exudative pleural fluid. Measurement of pleural fluid or serum NT-proBNP is a confident method for diagnosing cardiac and non cardiac effusions.

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