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Original Article

Diagnostic value of serum pentraxin-3 in deep vein thrombosis disease

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Abstract

Aim: We investigated the diagnostic value of Pentraxin 3 (PTX-3), a marker that increases in vascular and inflammatory pathologies, in patients admitted to hospital with deep vein thrombosis clinic.
Materials and Methods: 44 patients admitted to the a tertiary medical faculty hospital and a tertiary training and research hospital, with suspect of deep vein thrombosis included in our study. Patients confirmed to have DVT by doppler ultrasonography named as DVT(+) group, and patients not confirmed to have DVT by doppler ultrasonography named as DVT (-). PTX-3 levels determined in blood samples and compared between these groups.
Results: Median levels of D-dimer in DVT(+) group was 3.92 µg/ml (1.57- 6.05), and in DVT (-) group was 1.47 µg/ml (0.97-2.37), and a statistically significant difference was found between these groups ($p<0.05$). Median levels of Pentraxin-3 in DVT(+) group was 0.42 (0.36-0.49) µg/ml, and in DVT(-) group 0.40 (0.37-0.49) µg/ml, and there was no significant difference found between these groups ($p>0.05$).
Conclusion: According to our study, PTX-3 is not a suitable diagnostic marker for the diagnosis of deep vein thrombosis. We think that the value of PTX-3 in the diagnosis of deep vein thrombosis now need to be confirmed with broader, controlled studies.

Keywords: Deep vein thrombosis (DVT), D-dimer, Diagnosis, Pentraxin 3 (PTX-3)

INTRODUCTION

Deep vein thrombosis (DVT) is a systemic disease characterized by the formation of clot anywhere in the venous system. This disease and its sequelae are among preventable diseases. Factors that increase venous stasis such as prolonged immobilization, varicose veins, obesity and atrial fibrillation; factors that increase hypercoagulability such as factor V Leiden deficiency, homocystinuria, protein C or S deficiency, pregnancy, surgery, cancer and hyperlipidaemia and factors that cause endothelial damage such as history of surgery, intravenous drug addiction, insertion of central catheter increase the incidence of deep vein thrombosis. Clinical findings and detectable symptoms are mostly insufficient in diagnosing venous thromboembolism; therefore, there may be a need for objective diagnosis [1]. Accurate diagnosis is very important in individuals with a suspicion of DVT; untreated thrombosis may cause mortal pulmonary embolism. Since the diagnosis is correct only in one fourth of the cases with suspected

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DVT, the presence of thrombus should be determined with non-invasive, rapid and inexpensive methods. Clinical examination, laboratory tests and imaging methods can be combined for this [2,3]. Pentraxin 3 (PTX-3) is an independent marker in the determination and diagnosis of prognosis and in the prediction of death due to cardiovascular diseases, mainly with its role in vascular inflammation. It has been stated that plasma PTX-3 levels increase and show a positive correlation with disease activity in ischemic heart diseases (angina pectoris, myocardial infarction) in which inflammation play an important role and in small vessel vasculitis [4,5].

Our research was carried out to investigate whether this biochemical parameter could be included in diagnostic algorithm in addition to physical examination and radiological methods in the diagnosis of deep vein thrombosis.

MATERIAL AND METHOD

In the external examination of 63-year-old male patient who was admitted to emergency service after an argument with the neighbours and who had previous heart disease, no ecchymoses, scratches or bleeding was seen. Cardiology consultation was asked because he had complaints of pain on the back and chest. In the cardiology consultation, hospitalization to coronary intensive care unit was recommended since troponin was with in normal limits and the patient had left bundle branch block. The patient did not agree to hospitalization.

In the examination at Forensic Medicine Clinic eight months after the incident, the patient stated that during the incident, he was hit hard on his back and he had pain in the chest and back after he fell on his knees, after the first intervention in the emergency service, the cardiologist told him that he needed to stay in the hospital, but he left the hospital of his free will, the doctor prescribed him Nextep and Ecopirin, he was still using these drugs, and he had used medication before due to heart disease. He still had pain on his left shoulder and neck from time to time; his examination did not show any external traumatic lesions.

DISCUSSION

The study is a multi-centred, prospective, time-limited, cross-sectional clinical study. Permission was obtained from local Clinical Research Ethics Committee for the study protocol (2015-159). After ethics committee approval was obtained, the study was conducted in 6 months between June and December 2016 in the Emergency service and Cardiovascular surgery (CVS) outpatient clinics of a tertiary medical faculty hospital and a tertiary training and research hospital.

44 patients aged 18 and older who were admitted to the clinic with suspected DVT according to the diagnostic algorithm in the Guide published by ACEP (American College of Emergency Physicians) in 2009. The patients who did not give consent for the study, those who had missing data in the study form and those who were found to have hemolysis in the serum samples taken were excluded from the study. Of the patients who were evaluated in terms of Wells score with a clinical suspicion of DVT and who were found to have low risk, those whose D-dimer test were negative were also excluded from the study since DVT was excluded according to diagnostic algorithm. Patients diagnosed with DVT on Doppler USG constitute the DVT positive group, and patients without DVT on Doppler USG constitute the DVT negative control group. Individuals younger than 18 years of age, those who had advanced liver, kidney and heart failure, acute coronary syndrome, acute pulmonary embolism, acute cerebral stroke, acute mesenteric ischemia, peripheral artery occlusion, pregnancy, malignancy, hematological or rheumatological diseases were excluded from the study. Demographic characteristics, symptom and physical examination findings, laboratory and radiology reports of the patients to be included in the study were recorded with study forms prepared by the researchers.

Study protocol

Wells scoring

The patients who referred to the related clinics with extremity pain, redness and swelling were evaluated by clinicians in accordance with the diagnostic algorithm created by Wells scoring (Figure-1). The patients whose low risk D-dimer test was positive according to this scoring (cut-off value 0.5µg/ml) and who had higher risk degree were included in the study by performing doppler USG.

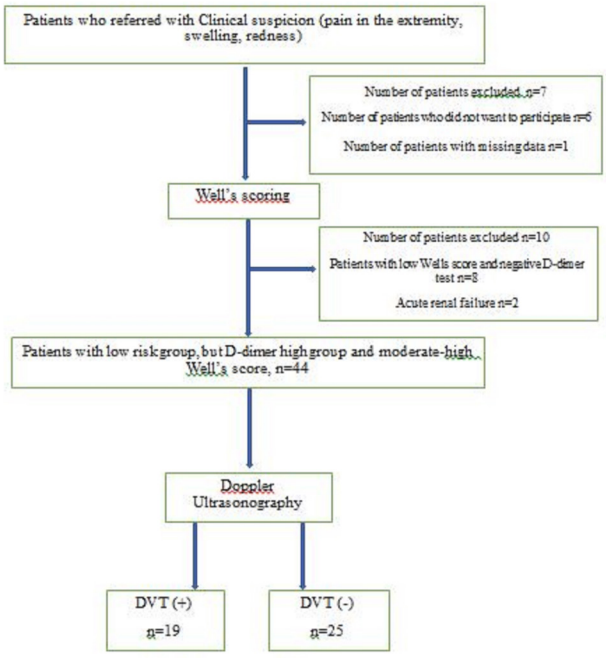

Figure 1. Study protocol

Doppler USG

The patients included in the study underwent doppler examination of the veins in the extremity with symptoms with the use of Toshiba Aplio 500 USG by radiologists. Veins with loss of compression were thrombosed and reported. While the patients who were found to be DVT positive formed the DVT + group, those who did not have DVT were included in the control group.

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Biochemical sampling

At the time of admission, approximately 5 cc of venous blood samples of the patients in both DVT and control group were taken with an injector from the brachial vein into a chemistry tube with a separator. The blood samples were kept for minutes at room temperature for coagulation. After the samples were centrifuged for 10 minutes at a speed of 1,800 × g, the resulting serum was separated and the analysis was kept at -80 C degrees. At the end of the study protocol, all samples were studied simultaneously by a researcher who was blind to the study data and patient groups.

Determination of Pentraxin-3 (PTX3) levels in human serum

PTX3 levels of the serum samples were determined by using enzyme-linked immunosorbent assay (ELISA) kit (Boster Biological Technology, Cat No: EK0861, Pleasanton, CA, USA) according to the recommendations of manufacturers.

Statistical analysis

SPSS (Statistical Package for Social Sciences for Windows) v.13,0 program was used for the statistical analysis of the study Categorical variables were expressed as number (n) and percentage (%). The difference between the categorical variables was evaluated with Chi-square test. Since the data for numerical variables did not meet the parametric conditions, they were calculated as median (25%-75%) values. Bonferroni corrected Mann Whitney U test was used to compare the medians between groups. Spearman Correlation Analysis was used to see how the other variable was affected when the value of a variable changed. $p< 0.05$ level was taken as statistically significant difference in the results.

RESULTS

A total of 44 individuals, 19 patients who had acute DVT confirmed with doppler and 25 patients who had clinical DVT but no acute thrombus in the doppler USG, were included in the study. 6 patients were excluded because they did not want to participate in the study, 1 patient was excluded because he had missing data, 7 patients were excluded because they were found to be low risk with Well's scoring and they had negative D-dimer value and 2 patients were excluded because they had acute renal failure.

Table 1 shows the demographic and clinical characteristics of the patients. When age and gender of the patients were compared, no significant difference was found between the groups ($p>0.05$). Of the vital findings, significant difference was found between groups only in systolic blood pressure and fever measurements ($p<0.05$). Table 2 shows the measurement values of D-dimer and PTX-3 biochemical parameters measured in the study. When the D-dimer and PTX3 values were compared between groups, D-dimer value was found as 3.92 µg/ml (1.57-6.05) in the DVT(+) group and as 1.47 µg/ml (0.97-2.37) in the DVT(-) group and statistically significant difference was found between the groups ($p<0.05$). However, Pentraxin-3 values were measured as 0.42 (0.36-0.49) ng/ml in the DVT(+) group and as 0.40 (0.37-0.49) ng/ml in the DVT(-) group and no statistically significant difference was found between groups ($p>0.05$). It was also found that PTX-3 levels were within normal limits in all patients included in the study.

Table 1. Comparison of demographic characteristics and vital findings of patients

Characteristics	DVT (+)	DVT (-)	p value
Age (median)	**66**	**64**	**>0.05**
Gender Male	9 (47.4%)	11 (44%)	>0.05
Female	10 (52.6%)	14 (56%)	>0.05
Comorbid diseases n (%)			
Hypertension	8 (42.1%)	13 (52%)	>0.05
Diabetes	6 (31.6%)	4 (16%)	>0.05
Coronary artery disease	2 (10.5%)	6 (24%)	>0.05
Hyperlipidaemia	1 (5.3%)	1 (4%)	>0.05
Past SVO	1 (5.3%)	4 (16%)	>0.05
Vital findings			
Systolic Pressure (mmHg)	120 (110-130)	128 (117-139.5)	<0.05
Diastolic Pressure (mmHg)	77 (70-80)	80 (76.5-84.5)	>0.05
Pulse (beat/min)	80 (67-96)	76 (66.5-88.5)	>0.05
Respiratory rate (/min)	15 (14-19)	16 (13.5-18)	>0.05
Fever (°C)	36.6 (36.4-36.9)	36.9 (36.55-37.1)	<0.05
Habits			
Smoking	8 (42.1%)	8 (32%)	>0.05
Wells score			
Low	3	4	>0.05
Moderate	9	16	>0.05
High	7	5	>0.05

*Categorical variables number (n) and percentage (%), ** The difference between categorical variables Chi-square test, SVO: cerebra vascular disease

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Table 2. Comparison of D-Dimer, Pentraxin-3 values of DVT (+) and DVT (-) patients

	DVT (+) Median (25%-75%)	DVT (-) Median (25%-7%5)	P value
D-Dimer (µg/ml)	3.92 (1.57-6.05)	1.47 (0.97-2.37)	p<0.05
PTX 3 (ng/ml)	0.42 (0.36-0.49)	0.40 (0.37-0.49)	p>0.05

*Bonferroni corrected Mann Whitney U

DISCUSSION

No significant result was found in the clinical study in which we investigated the diagnostic value of the biochemical study called PTX-3 in the diagnosis of DVT. DVT, which is the most common type of venous thromboembolism (VTE), is a disease characterized by clot formation in deep venous system and its annual incidence in the general population has been reported as 0.1-0.2%. Pulmonary embolism, which is a clinical situation that threatens life in the acute period, is the main cause of post-thrombotic syndrome that causes permanent damage in the lower extremity in the chronic period. Despite suitable medical treatment, it causes pulmonary embolism with a rate of 10% in the early period, while it causes serious complications such as postthrombotic syndrome development with a rate of 40% in the long term. Despite the risk of serious complications, patients with DVT mostly refer with nonspecific symptoms and this causes delays in the diagnosis and treatment [6,7]. A large number of biochemical parameters such as homocysteine, haemoglobin, leukocyte, monocyte, platelet levels, CRP, protein C, protein S have been worked in the diagnosis of VTE; however, they have not found a place in diagnostic algorithm since they are not specific or they are not worked easily [8]. In a study conducted with P-selectin, which is a member of the adhesion molecules family and which is released from active thrombocytes and endothelium, sP-selectin (soluble Pselectin) levels were found to increase in acute DVT [9]. In another prospective study in literature, 2.6 times increase was found in VTE development with the increase in sP-selectin levels [10]. D-dimer, which is a biochemical marker recommended to be studied according to DVT diagnostic algorithm, has a high sensitivity in excluding D-dimer DVT diagnosis and therefore it is used not as a diagnostic criterion, but for diagnostic exclusion. For this reason, objective radiological imaging is required for DVT diagnosis. These imaging methods are conventional angiography (venography), CT-MR venography, Doppler Ultrasonography and radionuclide imaging. [11-14]. Venography is considered as the gold standard in diagnosis; however, in recent years, colourful doppler USG, which has high accuracy, which is cheap, easily applicable and non-invasive, has begun to be preferred more in line with recent technological developments [15]. Therefore, doppler USG was used in our study as the diagostic matters.

PTX-3 plays a significant role in primary inflammatory response. For this reason, it is included in diagnostic tests of many diseases, especially cardiovascular diseases, from ovarian torsion to pleural effusion [16,17]. With immunohistochemical studies showing that plasma PTX-3 amount is increased in atherosclerosis lesions, whereas it is not increased in non-atherosclerotic lesions and PTX-3 is an indicator of localized vascular immobilization and damage, investigating the relationship between clinic atherosclerotic incidents has become important. The high PTX-3 levels in patients with CT elevated myocardial infection and the higher level in patients with CT elevated myocardiac infarctions has led to investigating plasma PTX-3 levels in this patient group [18,19]. In a study by Akira et al., PTX-3 was not found to increase in patients with acute pulmonary embolism, while PTX-3 level was increased in patients who developed pulmonary hypertension secondary to embolism in the chronic period [20]. In a study by Barbui et al. on patients with essential thrombocytopenia and the risk of thrombosis was found to decrease as PTX-3 levels increased [21]. Unlike other studies in literature, no increase was found in PTX-3 Thrombotic risk. In our study, PTX-3 levels were not found to increase in DVT, which is a thrombotic event. The mechanism of why PRX-level which increased in vascular incidents and which we are expecting to increase in acute deep vein thrombosis did not increase in our study cannot be explained fully.

Limitations

A large number of patients with DVT suspicion who referred to CVS outpatient clinic and Ahi Evran Hospital Outpatient clinics could not be included in the study due to the insufficient support of the related clinics. Since a great majority of the population consisted of patients who referred to the emergency service, it was not possible to reach the desired number of cases.

CONCLUSION

According to the results of our study, PTX-3 is not a suitable biochemical marker in terms of the diagnosis of deep vein thrombosis. Clinical studies with larger sample are required to determine the place of PTX-3 in DVT diagnosis.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Ethics Permission was obtained from Karadeniz Technical Univercity Clinical Research Ethics Committee for the study protocol (2015-159).

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