Diagnostic Value of D-Dimer's Serum Level in Patients with Cerebral Venous Thrombosis

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ABSTRACT:

BACKGROUND:

Cerebral venous thrombosis (CVT) is the presence of a blood clot in the dural venous sinuses, which drain blood from the brain. D-dimer is a specific product of the degradation of fibrin clots that can reflect the activity of coagulation and the fibrinolytic system.

OBJECTIVE:

To assess the role of plasma D-dimer, as well as, the sensitivity and specificity of this assay in diagnosis of cerebral venous thrombosis.

PATIENTS AND METHODS:

This is a case-control study which included 50 adult patients diagnosed with CVT. Other 50 age- and sex-matched healthy subjects were enrolled in the study as control group. Demographic data were collected from each participant, while the clinical data of cases were collected separately. Blood samples were collected from each participant in sodium citrate tubes, and a ready commercial kit was used to measure plasma levels of D-dimer. Receiver operating characteristic (ROC) curve was employed to evaluate the diagnostic value, sensitivity and specificity of D-dimer in the discrimination of CVT healthy controls.

RESULTS:

Mean plasma level of d-dimer in CVT patients and controls were 536.7± 102.34 ng/mL and 318.4± 88.71 ng/mL respectively with a significant difference (p= 0.029). The sensitivity and specificity of the test at cut off value of 400 ng/mL were 0.88 and 0.86 respectively, indicating a very good discrimination value.

CONCLUSION:

Measurement of D-dimer can be a reliable tool for diagnosis of CVT, especially in patients with acute and subacute disease.

KEYWORDS: cerebral venous thrombosis, d-dimer, receiver operating characteristic curve

INTRODUCTION:

Cerebral venous thrombosis (CVT) is the occurrence of blood clots within venous structures of the central nervous system (CNS). Data from population-based studies have shown that the incidence among adults is 1.3–1.6 per 100,000[(1)], and the incidence is probably even higher in Asia and the Middle East, as the rates of pregnancy and infection-related cases are higher in these countries[(2)].

The diagnosis of CVT in the emergency units is challenging due mainly to non-specific signs and symptoms of the disease[(3)].

Routine laboratory tests such as chemistry panel prothrombin time, and activated partial thromboplastin time are not helpful to establish the presence of CVT although they help in the identification of associated conditions, such as anemia, or infectious conditions[(4)]. The introduction of highly sensitive, non-invasive techniques such as magnetic resonance imaging (MRI), MR venography, and computed tomography (CT) venography have significantly improved the diagnosis and led to the discovery of more cases[(5)]. However, the difficulties associated with the use of these techniques have hindered their application as general screening methods for CVT[(6)].

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D-dimer is a specific product of the degradation of fibrin clots that results from the action of 3 enzymes: thrombin, activated factor XIII, and plasmin[7]. The measurement of serum D-dimer levels was used as a diagnostic method for non-CVT such as deep venous thrombosis (DVT) and pulmonary thromboembolism. However, This assay was not fully investigated for CVT diagnosis and still a matter of debate[8].

Thus, the current study aimed to evaluate the diagnostic value of serum D-dimer in detection of CVT in a sample of Iraqi patients.

PATIENTS AND METHODS:

This is a case control study which was conducted at Al-Yarmook Teaching Hospital. The study includes adult patients who were admitted to this center with CVT from February 2018 to March 2019. Other 50 age- and sex-matched healthy subjects were enrolled as control group.

Case Definition and Study Population

The diagnosis of CVT was suspected on the basis of the symptoms, such as a combination of headache, signs of raised intracranial pressure and focal neurological abnormalities. For definitive diagnosis, CT with radiocontrast in venous phase was used. Some cases required 3-tesla MRI which has the advantage of being better at detecting damage to the brain itself as a result of the increased pressure on the obstructed veins. Cerebral angiography in accordance with the 2012 criteria of the American Heart Association/American Stroke Association was also used in some cases, and was considered as proven when there was a partial or total lack of filling of at least one dural sinus on two projections of carotid angiogram.

Patients with a history of venous thromboembolism or stroke during the 3 months prior to admission, a history of headache due to cranial trauma, uncontrolled hypertension (systolic blood pressure ≥150 mmHg at the time before procedure), significant liver disease (including known cirrhosis), platelet counts of $<100 \times 10^9$/L and those requiring ongoing anticoagulation were excluded from the study.

Data Collection

Data were collected from each patient either by direct interview or from patient's record. Clinical and demographic data include sex, age, weight and height (for calculation of body mass index), systolic and diastolic blood pressure, and coagulation function.

Risk factors for CVT including previous DVT, pulmonary embolism family history, pregnancy or puerperium, smoking, oral contraceptive, malignant disease, dehydration, infection, trauma, and surgery were also recorded.

Based on delay from symptom onset to admission, mode of onset was defined as acute (<2 days), subacute (2–14 days), or chronic (>14 days). Accordingly, only patients with acute or subacute CVT were included. After application of inclusion and exclusion criteria, 50 patients with CVT (cases) and other 50 subjects without CVT (controls) were eligible for the study.

Measuring Plasma Concentration of D-dimer

Blood samples were collected from each participant in sodium citrate tubes. A ready commercial kit (D-dimer-check -1/ Veda lab/ France) was used to measure plasma levels of human D-dimer according to the manufacturer's manual. This assay is a rapid quantitative screening test for measurement of D-dimer in a whole blood or plasma with a detection range of 250-5000 ng/mL. The cut-off value of the assay was 400 ng/mL. The result was read with a specific apparatus provided with the kit

Statistical Analysis

Numeric data were expressed as mean ± standard deviation (SD), while categorical data were expressed as frequency and percentage. Student t –test was used to compare means of D-dimer between patients with and without CVT. Receiver operating characteristic (ROC) curve was employed to evaluate the diagnostic value, sensitivity and specificity of D-dimer in the context discrimination between patients and controls. Chi square test was used to calculated the positive and negative predictive values of D-dimer in diagnosis of CVT. All statistical analyses were conducted using Statistical Package for Social Sciences (SPSS). The accepted P-value will be 0.05 or less.

RESULTS:

Demographic Baseline of the Study population

The four included demographic characteristics were compatible between CVT patients and controls. Although, there were slight more males and smokers among controls, the differences were not significant (p> 0.05) as shown in table 1.

Table 1: Demographic baseline of the study population

Variables	Patients (n=50)	Controls (n=50)	p-value
Age, years (mean±SD)	41.7±12.9	42.2±17.4	0.411
Gender			
Male Female	29(58%) 21(42%)	31(62%) 19(38%)	0.839
BMI, kg/m^2 (mean±SD)	26.19±6.1	27.34±6.6	0.392
Smoking			
Ex/current Never	13(26%) 37(74%)	15(30%) 35(70%)	0.656

BMI: body mass index

Clinical Characteristics of CVT Patients

Headache was the most frequent presentation that observed in 84% of the patients. Focal neurological signs, papilledema and seizures came next in 42%, 40% and 38% respectively. The average duration of the symptoms was 6.9 ±3.2 days (Table 2). Transverse sinus was the most frequent site where thrombosis occurred accounting for 52% of cases, followed by superior sagittal sinus (36%), while each of left lateral sinus and right lateral sinus accounted for 26% of cases.

At imaging, cerebral infarction was seen in 13(26%) of patients, while hemorrhagic lesion was observed in 7(14%). Infection was the most common risk factor associated with 16% of cases. On the other hand, malignancies and oral contraceptive were the least frequent risk factors, each was recognized in 6% of patients.

Table 3-2: Clinical characteristics of the CVT patients

Variables	Mean±SD or No(%)
Clinical presentation	
Headache Focal neurological signs Papilledema Seizures Vomiting	42(84%) 21(42%) 20(40%) 19(38%) 13(26%)
Duration of symptoms, days	6.9 ±3.2 (range 4-10)
Site of thrombosis	
Superior sagittal sinus Left lateral sinus Right lateral sinus Intracranial vein	18(36%) 13(26%) 13(26%) 11(22%)
Imaging findings	
Hemorrhagic lesion Infarction	7(14%) 13(26%)
Risk factors	
Malignancies Dehydration Infection Oral contraceptive	3(6%) 6(12%) 8(16%) 3(6%)

Plasma Levels of D-dimer

Overall, the mean plasma level of D-dimer in CVT patients and controls were 536.7± 102.34 ng/mL and 318.4± 88.71 ng/mL respectively (Figure 1). Independent t-test revealed a significant difference (t= 2.167, p= 0.029).

According to cut-off value of the assay (400 ng/mL) there were 44 CVT patients (88%) who were positive for the test compared with 7 (14%) among controls (p< 0.001).

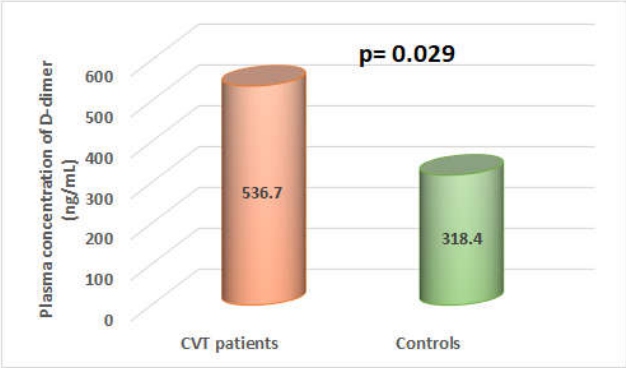

Figure 3-1: Overall plasma level of D-dimer in CVT patients and controls

Stratification of the study population according to gender revealed a wide gap between patient and control males (564.7± 114.9 ng/mL and 342.2±71.13 ng/mL respectively) with a significant difference (Figure 2). However, in females, this gap was narrower (528.4± 100.9 ng/mL in females with CVT and 367.7±92.5 ng/mL in healthy females) but still significant (p= 0.032).

In male, 3 cases out of 29 had a normal D-dimer value (10.34%) compared with 27 men out of 31 (87.1%) among controls (P<0.001). For female, 3 cases out of 31 (96.77%) showed normal level of D-dimer compared to 26 women out of 29 (89.66%) among controls (p<0.001).

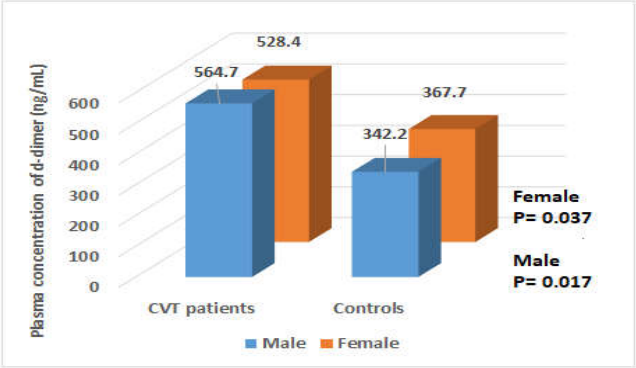

Figure 2: Plasma level of D-dimer in according to gender in CVT patients and controls

Diagnostic value of D-dimer

Figure (3) shows the result of receiver operating characteristic (ROC) curve between CVT cases and controls. The test revealed that the area under the curve (AUC) was 0.879, 95%CI=0.807-0.95, p<0.001. The sensitivity and specificity of the test at cut off value of 400 ng/mL were 0.88 and 0.86 respectively, indicating a very good discrimination value. The positive and negative predictive values of D-dimer in diagnosis of CVT was 86.27 % and 87.76% respectively.

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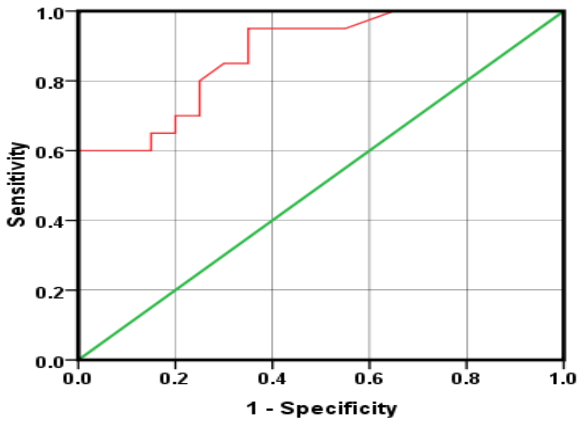

Figure 3: receiver operating characteristic curve for D-dimer in the context of discrimination CVT patients from healthy controls.

DISCUSSION:

The current results revealed a significant difference in D-dimer concentration between patients and controls. Furthermore, and according to the cut-off value of the assay, 44 patients (88%) were positive for the test compared to 14% from control group had such a result. This result is in agreement with that of Lalive *et al.*[9] who studied 54 consecutive patients with headaches suggestive of CVT. D-dimer level were tested for all patients in the emergency room before brain CT or MRI was performed. Twelve of the 54 patients in their study had CVT, 10 of these 12 patients had high D- dimer level. The other two patients with confirmed CVT and normal D-dimer level had a history of chronic headache of >30 days' duration.

Hiltunen *et al.*[10] conducted a retrospective study including 71 patients from Helsinki University Central Hospital with confirmed CVT. D-dimer was measured before the treatment. The study revealed that 62 patients out 71 had elevated D-dimer (87.32%). However, the authors did not include control subjects in their study.

In a meta-analysis including 1134 patients with suspected or confirmed CVT, Dentali *et al.*[11] reported that 10/155 cases (18.18%) had normal D-dimer level. Another systematic review and meta-analysis study including 636 patients with confirmed CVT showed that 591 (92.92%) of those had an elevated level of D-dimer.

Many other previous studies also reported that none of patients with a recent CVT (> 3 weeks duration) had normal D-dimer[12,13] which is in accordance with present results.

On the other hand, the current result did not agree with that obtained by, Al-Hashel *et al.*[14] in Kuwait who reviewed 65 CVT patient records in a retrospective study. The D-dimer was found to be elevated in 42 patients (64.4%) and was normal in 23 patients (35.4%).

This variation in the results can be attributed to many factors. Firstly, and most importantly is the time duration after the thrombosis event.

It was shown that D-dimer level returns to its normal value within three months after the thrombosis event[15]. Thus, it is of crucial importance to collect the samples within 3 weeks of thrombosis onset which was applied in the current study. The second factor is variation in the baseline characteristics of the patients and the prevalence of thrombotic risk factors. It is well known that older ages, high BMI and using of oral contraceptive are risk factors for thrombosis and can considerably affecting the results of D-dimer[16].

Thus, according to the present study, and most previous studies, the measurement of plasma D-dimer is a very useful tool for the diagnosis of CVT.

The current study showed that healthy females showed slightly higher concentration of D-dimer than healthy males, but affected males had slightly higher D-dimer thane affected females. These results are with agreement with that obtained by Hashami *et al.*[17] in which the authors investigated 16 male and 13 female Iranian patients and found that females had lower concentration of D-dimer compared to males.

This variation between the two sexes (healthy or diseased) is attributed to many factors that may affect the coagulation, the most important of which are pregnancy and using of oral contraceptive in females, smoking habit in males and age and body mass index in both sexes[16].

The other most interesting finding in the current study was the very good sensitivity (0.88) and specificity (0.86) of D-dimer test in diagnosis of CVT. International studies revealed different sensitivity, specificity and predictive values for this test in diagnosing CVT. Hiltunen *et al.*[10] reported close results to the current study (sensitivity= 87.3% and negative predictive value= 95%). In a study conducted by Kosinski, *et al.*[18], 34 out of 35 patients with CVST had high D-dimer levels giving a negative predictive value of 99.6%, specificity of 91.2%, and a positive predictive value of 55.7%. Gouda and Sabry[19] found that the sensitivity of D-dimer test was 85.7% and the specificity was 85.5%. Higher values were reported in other studies. Meng[20] who showed that the sensitivity (94.1%), specificity (97.5%), positive predicting value (86.5%) and negative predicting value (98.9%) of d-dimer. Alons *et al.*[21] reported 97.8% sensitivity and 99.8% negative predictive value.

The factors that most commonly influence the sensitivity and specificity of the test is the time at which blood samples are collected. In this regard, the longer the time duration between sample collection and thrombotic event, the less sensitivity and specificity the test has. Another factor which may affect the efficiency of the test is the method for detection. The current study used cassette method which is known to have less sensitivity and specificity compared with enzyme linked immune sorbent assay. This explains the relatively low sensitivity and specificity compared with some other international studies. However, the cassette method is very easy and less expensive. Finally, other demographic characteristics such age, BMI index, sex of the patients and smoking status can influence the efficiency of the test. Therefore, these characteristic should be comparable between patients and controls, this principle was applied in the current study. Other strength point of the current study is that it is a prospective study and involved controls which makes the results more reliable.

Collectively, these data suggest that measurement of D-dimer can be a useful tool for diagnosis of CVT, especially in patients with acute and subacute disease. The screening cassette assay is a reliable easy non-expensive procedure for quantitative measurement of D-dimer in plasma.

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Ethical Clearance:

This study was proved by Institutional Review Board (IRB) by the Iraqi Board for Medical Specializations

Conflict of Interest

The author declares that they have no competing interests.

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