Original Article

The role of D-dimer in diagnosis of cerebral sinus venous thrombosis

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Abstract

Background: Cerebral sinus venous thrombosis (CSVT) is a fatal condition and should be considered in all patients with acute new onset headache. D-dimer has been shown to be a sensitive diagnostic tool in deep vein thrombosis and pulmonary thromboembolism. The purpose of this study was to investigate whether this test could be useful in the diagnosis of CSVT. **Materials and Methods:** In this prospective study, we reviewed patients referring to Nemazee hospital with presentations suggestive of CSVT. Diagnosis was established, using MRI and MRV. Serum D-dimer level was checked among 24 hours after hospital admission. **Results:** From 117 enrolled patients, 37 (31.6%) patients had CSVT. The reported D-dimer levels showed negative (< 500 ng/ml) in 21 (56.76%) and positive level in 16 (43.24 %) patients who had CSVT. Also, D-dimer was negative in 66 (82.5%) and positive in 14 (17.5%) patients who did not have CSVT. These results demonstrated a sensitivity of 43.24%, specificity of 82.5%, positive predictive value of 53.3%, and negative predictive value of 75.86%. **Conclusion:** Our study suggests that D-dimer test may guide us to approach patients who are suspected with CSVT in emergency situations with limited access to MRI/MRV, although every patient with high D-dimer level and clinical suspicion of CSVT should undergo specific brain imagines. In addition, our results showed a negative D-dimer test was not a reliable assay to completely rule out CSVT. However, we recommend further studies to confirm our results.

Keywords: D-dimer, cerebral sinus venous thrombosis, diagnosis

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Introduction

Cerebral sinus venous thrombosis (CSVT) is a fatal condition accounting for 0.5 percent of all strokes, which leads to elevation in intracranial pressure and subsequent neurological disability that presents with variable signs and symptoms: headache, seizure, hemiparesis, altered consciousness, and papilledema (1). It was first reported in 1825, a rare cause of stroke especially among young adults and children with more incidences in women due to sex-related risk factors: oral contraceptives (OCP), pregnancy or puerperium and hormonal replacement therapy.

CSVT is one of the important differential diagnoses in patients with acute new onset headache that presents with a wide range of neurological

features which makes hardships in recognition; so, it should be considered in emergency situations to make the next steps in clinical approach (1).

Magnetic resonance imaging (MRI), magnetic resonance venography (MRV) and CT venography are routine non-invasive diagnostic approach (2). But due to higher incidence in developing countries and less access to neuroimaging techniques, an available and non-expensive diagnostic method to rule out this disease is needed especially in emergency terms (3). A good choice is D-dimer blood test, a product of fibrin degradation which is helpful in diagnosis of pulmonary embolism (PE) and deep venous thrombosis (DVT), however, the usefulness of this measurement in excluding CSVT is not clear yet (4). Many studies have been done on the role of D-dimer in the diagnosis of CSVT.Although ,the negative predictive value of the D-dimer test in values less than 500 ng/ml has been demonstrated in most of conducted studies , there is still a great deal of controversy about this. Most studies show an increase in serum D-dimer levels in patients with CSVT compared to controls, but for the mean D-dimer level, patients with CSVT have different values (5-7). In order to test D-dimer, the results of different laboratory methods such as ELISA, VIDAS and STA-Lia test did not show any significant difference (8). Thus, the difference in mean D-dimer level may be due to ethnic and regional differences. Due to the low prevalence of CSVT in their geographic area and, consequently, the low sample size, and retrospective study pattern, most CSVT studies have limited research implementation. Hence, they recommend prospective studies with a larger sample size (5, 7, 9, 10).

In this prospective study, we considered the role of D-dimer in diagnose of CSVT in comparison with MRI/MRV in Nemazee Hospital referred patents with notable incidence of CSVT and larger sample size. Indeed, in spite of most recent studies which were done retrospectively on the documented cases of CSVT, our study was designed prospectively on all patients who are suspicious to CSVT aside they are had the disease or not. Therefore, we could determine sensitivity, specificity, positive and negative predictive value of the D-dimer test.

Methods

Patients. In this prospective study, we reviewed all consecutive adult patients referring to the emergency department of Nemazee Hospital, an academic center affiliated to Shiraz University of Medical Sciences, from December 2015 to December 2017 with new onset headache and presentations suggestive of CSVT. Every medical or surgical condition which causes an increase in D-dimer level was considered as exclusion criteria.

Computed Tomography (CT) scan was performed in all suspected cases of CSVT. The diagnosis was established using MRI (1.5 TESLA) and MRV(Three-dimensional time of flight (3D-TOFL)). Serum D-dimer level was checked at time of the patients admission and before starting anticoagulant therapy if they had CSVT; using a turbidimetric method with a normal reference range below 500 ng/ml.. If the quantitative result was less than 500 ng/ml, it was considered as negative and equal or more than that was noted positive test. Written consent was obtained before entering the study. For all subjects, a neurological examination, including evaluation of mental status, motor function, sensory modalities, cranial nerves, and ophthalmoscopy, was done by a neurologist and a questionnaire was filled out anonymously for each person (demographic data, gender, age, risk factor). The data were logged into the SPSS software and analyzed by a statistician. Descriptive data were shown as mean ± standard deviation. Independent student T test or Chi square tests were used for data analysis as appropriate. After determination of patients with real diagnosis of CSVT and results of the D-dimer tests, sensitivity, specificity, negative and positive predictive values were calculated. Cut-off point was also evaluated by ROC cure analysis. A p value <0.05 was applied to interpret all achieved data from analysis. This study was reviewed and approved by Ethics Committee of Shiraz University of Medical Sciences with a grant number 95-01-94-11609.

Results

In this observational cross-sectional study, we enrolled 117 patients (27 men, 90 women). 37 (31.6%) patients were CSVT positive and 80 were CSVT negative. Patients with negative results of MRI/MRV included 62 females and 18 males; whereas positive results were found in 27 females and 10 males. The mean age was 37.72 ± 12.256 years in the negative and 37.49 ± 10.471 in the positive group. The results are shown in Table 1. From eight evaluated pregnant women, none had CSVT (p =0.04).

Table1. Demographic and clinical data of all patients

Patients characteristics (n=117)	CSVT Yes (n=37)	CSVT No (n=80)	P value
Age (mean ±SD)	37.49±10.471	37.72±12.256	0.97
Sex (Female)	27 (30.0%)	63(70.0%)	0.36
OCP consumption	16(43.2%)	20(24.7%)	0.03
Pregnancy	0 (0.0%)	8 (9.9%)	0.04
Postpartum	5 (13.5%)	8 (9.9%)	0.38
Protein C or S deficiency	0 (0.0%)	1 (2.7%)	0.31
Previous DVT	3 (8.1%)	2 (2.5%)	0.17
Neurological manifestations			
Papilledema	1 (2.7%)	2 (2.5%)	0.68
Seizure	9 (24.3%)	8 (9.9%)	0.04
Limb weakness	7 (18.9%)	18 (22.2%)	0.44
Impaired Level of Consciousness	4 (10.8%)	5 (6.2%)	0.29
Laboratory data			
ESR (mean ± SD)	25.536±20.5	23.421±22.3793	0.383
WBC (95% CI)	10.57 (8.0914.66)	9.89 (8.37-11.95)	0.72

SD: standard deviation. CI: confidence interval.

The reported d-dimer levels of both groups are shown in Table 2. According to D-dimer results, the cut-off point of 500 ng/ml was determined. For cut-off point 0.5, Area Under the Curve (AUC) was 0.645 (p= 0.008). Accordingly, this level of value had acceptable ability to recognize the CSVT. The results yielded a sensitivity of 43.24%, specificity of 82.5%, positive predictive value of 53.3% and negative predictive value of 75.86% (Figure 1).

Table 2. D-dimer values in patients with and without CVT

D-dimer value (ng/ml)	With CSVT Number (%)	Without CSVT Number (%)	P value
Positive (>500 ng/ml)	16(43.24 %)	14(17.5%)	24 25.10 0.003
Negative (<500 ng/ml)	21(56.76%)	66(82.5%)	

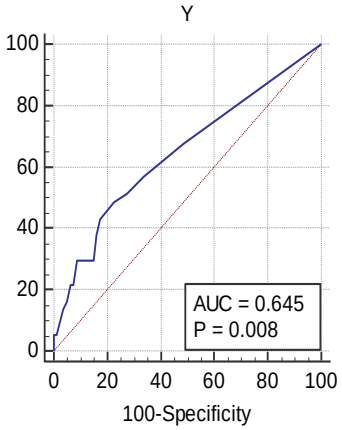

Figure 1: Comparison of the under curve surface for D-dimer

Discussion

Degradation of fibrin in the blood causes D-dimer elevation which is used in evaluating the amount of thrombin and plasmin production in blood circulation and has been considered as a long half-life , an easy, non- expensive and available diagnostic marker in thrombotic events (11). D-dimer test is helpful in excluding deep vein thromboembolism and pulmonary thromboembolism (5). Moreover, several studies have indicated that D-dimer is a beneficial diagnostic tool in patients suspicious with cerebral sinus vein thrombosis (3-5, 7, 12-15). The cut off value of 500 ng/ml is usually defined in thrombotic events and also CSVT as we used here.

In our study, the D-dimer level was positive only in 43.24% of 37 CSVT positive patients. This shows D-dimer is not a sensitive tool for diagnosing cerebral sinus vein thrombosis, so a normal D-dimer level in our study could not exclude CSVT in patients with symptoms suggested disease. In a similar study conducted on 73 patients with positive CSVT, normal D-dimer levels were found in 7 patients (10%) (16). In a study done in Egypt, D-dimer value more than 500 ng/ml was reported in 85.7% (18 of 23) of CVST positive patients (5). Also, in another prospective study with 343 patients, a positive D-dimer level (defined as a level >500 ng/mL) was found in 34 of 35 CSVT positive patients and 27 of 308 patients without CVT. This result produced a sensitivity of 97.1%, which confirms a clinically helpful role of D-dimer in diagnosing CSVT (13). According to American Heart Association/American Stroke Association a normal D-dimer level may be considered to help identify the patients with low probability of CSVT, but if there is a strong clinical suspicion of CSVT, a normal D-dimer level should not preclude further evaluation (17). Our results showed that the D-dimer was negative (< 500 ng/ml) in 66 out of 80 patients who did not have CSVT. This means that D-dimer test has a negative predictive value of 75.86%; thus, a value under 500 ng/mL makes presence of CSVT unusual, similar to some recent studies. Kosinski reported a higher negative predictive value of 99.6% in favor of having no CSVT when D-dimers were negative (< 500 ng/ml). It suggested that if duration of symptoms is more than 2 weeks, normal d-dimer is not useful for exclusion of CSVT (13).

No pregnant women had CSVT. We think that it could be related to low threshold of our emergency staff and physicians to prove the disease in this group of patients as soon as possible. Hence, they may evaluate them more than the others.

According to our findings, D-dimer specificity is 82.5%, in cases referred to the emergency department with neurological symptoms. It pointed into notion that this test is a good diagnostic tool for the detection of CSVT because of its high specificity. On the other hand, when there is a suspicion of thrombosis in the central nervous system, positive result could be more helpful. Whereas, peripheral thrombosis (deep vein thrombosis and pulmonary embolism) in which sensitivity of D-dimer is high, negative result seems to be more useful. We think this difference in sensitivity and specificity of D-dimer in central and peripheral parts of the body may be due to many causes for elevated D-dimer in the periphery and out of central nervous system (17), but in the central portion of the body there are not so heterogenic causes.

In agreement with our findings, Alons et al. in 2015 reported a high D-dimer specificity (84.9%) with 636 consecutive patients (4).In other study, Meng et al. found a specificity of 97.5% with 233 patients and they suggested that using D-dimer as a screening approach is a good way to define which patients are candidates for urgent MRI/MRV (14). Therefore, D-dimer value seems to be helpful for ruling out CSVT in patients presenting with acute headache in emergency situation, especially in developing countries that have limited access to expensive diagnostic tools like MRI/MRV. Although previous studies confirmed the utility of D-dimer marker in diagnosing patients without CSVT, they recommended that it was not a reliable assay to completely exclude CSVT, particularly in patients with recent isolated headache (5, 16).

We found 21 out of 37 CSVT positive patients with negative D-dimer. Multiple factors may account for these false negative results. First, D-dimer values reduce with time from the onset of symptoms, which indicated that patients who have subacute or chronic features were more prone to have normal d-dimer levels. Second, the level of CSVT involvement may correlate with D-dimer levels, which suggests that patients with lesser clot spread may have false negative D-dimer test results. Finally, several assays are available to measure the blood levels of D-dimer with variable test performance (13, 17).

In conclusion, the sensitivity of D-dimer marker was 43.24% and its specificity was 82.5% in this study. Therefore, it seems that a negative D-dimer test is a good clinical tool because it makes cerebral sinus vein thrombosis unlikely to happen.

Conclusion

Our study suggests that D-dimer test may guide us to approach patients who are suspected with CSVT in emergency situations with limited access to MRI/MRV, although every patient with high D-dimer level and clinical suspicion of CSVT should also undergo specific brain imagines.

In addition, our results showed a negative D-dimer test was not a reliable assay to completely rule out CSVT. However, we recommend further studies with larger number of patients to confirm our results.

Conflicts of Interest

No conflicts of interest were declared in relation to this article.

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