Original Article

A Comparative Study on Sensitivity of D-Dimer with Doppler ultrasound for the Diagnosis of Deep Venous Thrombosis

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Abstract

Introduction: Deep venous thrombosis (DVT) is a coagulation disorder that is on the rise due to lifestyle changes. Patients with DVT are at risk for developing a life-threatening complication, pulmonary embolism which urges the importance of its early diagnosis. The Gold standard modality for its early diagnosis is invasive which is Venography. Other modalities like compression ultrasound and duplex imaging are noninvasive but operator-dependent and not routinely available during evening and night shift hours. D-Dimer is a simple, noninvasive, cost-effective, and easily available diagnostic test that can be helpful in diagnosis. The objective of this study is to compare the sensitivity of D-Dimers with Doppler ultrasound for the diagnosis of deep venous thrombosis.

Materials and Methods: A cross-sectional comparative (validation) study in which 65 admitted patients with a high risk of DVT on Well's criteria for clinical diagnosis were enrolled by non-probability convenience sampling from March to August 2018. Both D-Dimer and Doppler ultrasounds were performed on all suspected patients of DVT.

Results: Amongst 65 cases, 60 (92.3%) had positive Dimer results compared to 65 (100.0%) with the Doppler ultrasound. The difference between the two diagnostic modalities was statistically significant (p-value = 0.02). The sensitivity of D-dimers was 92.3% however specificity, PPV, and NPV were 0% as none of the cases was negative on ultrasound Doppler.

Conclusion: The D-dimer test is a conveniently performed, cost-effective test with a sensitivity of more than 90% in the current study and can be useful for Emergency and critical care departments.

Keywords: D-dimer, Ultrasound, Deep venous thrombosis.

Introduction

Deep venous thrombosis (DVT) is an inflammatory response in the vessel wall induced by the presence of a thrombus within a deep vein. It has a tendency to propagate in the direction of blood flow. Changes in lifestyles which include more sedentary habits, dietary intake patterns, and less water consumption affected the prevalence and now the prevalence is on the rise. Deep vein thrombosis (DVT) incidence ranges from 45 to 117 in 100,000 adults per year.[1]

DVT tends to occur more in the lower extremities, which may include proximal and distal DVT.[2] The differential diagnosis includes a variety of clinical conditions which cause unilateral leg swelling and pain. This may include trauma, a ruptured popliteal cyst, muscle rupture, or lymphedema. Clinical symptoms are also not specific to DVT, making its diagnosis a tricky situation. Symptoms of DVT include heaviness in legs, redness, and pain which may be present in other conditions too.[3]

Swelling after Phlebitis poses a challenging situation when differentiating it from deep vein thrombosis. Nerve compression, fractures, arthritis, tendinitis, arterial occlusive disorders, and muscular trauma are a number of conditions that can cause leg pains unilaterally. Edema, localized pain, and erythema are presenting features of Cellulitis. Obstruction of the veins by external compressions like by a Baker cyst, tumor, or fibrosis, or external compression of the left iliac vein and edematous conditions secondary to renal, cardiac, or hepatic failure are important conditions that need exclusion before diagnosing DVT. The condition can lead to many complications the most fatal being pulmonary embolism while recurrent DVT and post-thrombotic syndromes can also develop.[4]

Common presentations of DVT are nonspecific and thus increase the probability of missing timely diagnosis and thus management. This urges the need for combining clinical probability with diagnostic modalities like imaging and chemistry for diagnosis.[5]

Studies revealed that localized intravascular coagulation leads to increased D-dimer and low fibrinogen levels.[6] Cross-linked fibrin degrades to D-Dimer which is used in the algorithmic approach for diagnosis and management of venous thromboembolism.[7] D-Dimer indicates thrombosis and clot dissolution by plasmin.

Pulmonary Embolism is a fatal complication of DVT urges the crucial need for objective diagnosis of the condition in the presence of unreliable clinical assessment. The diagnostic algorithms direct clinical probability assessment and then use of D-Dimer test and imaging. Those with low or intermediate probability can undergo D-Dimer testing preferably but high clinical probability guides the use of imaging modality as the preferable approach.[8]

Venography and ultrasonography have several limitations however they are considered suitable for diagnosis. Venography is invasive, expensive, and not readily available or the results reproducible, whereas ultrasonography requires technical expertise, equipment, and time consumption.[9] Contrast venography was considered the gold standard but has decreased utility due to invasiveness and cost.[10] It also causes pain at the injection site, contrast-induced idiosyncratic reactions, and nephrotoxicity.[11] The results are operator-dependent non-availability in the evening and night hours. D-Dimer is a simple noninvasive test that is cost-effective and readily available. Enzyme-linked immunofluorescent immunoassays (ELFAs) and microplate enzyme-linked immunosorbent assay (ELISA) methods are so far the best found D-Dimer sensitivity methods but both are moderately specific.

Following are the few preliminary examination steps:

a) **Physical examination** Homans' test has a limited diagnostic value but poses more danger of dislodging thrombus. Dorsiflexion of the foot causes pain in the posterior calf. It is not part of clinical probability testing.

b) Probability scoring

Wells score or criteria:

i. Cancer in active stage -- 1 point
ii. Calf swelling greater than 3 cm -- 1 point
iii. Collateral superficial veins (non varicose) -- 1 point
iv. Pitting edema (limited to symptomatic leg) -- 1 point
v. Swelling in the whole leg - 1 point
vi. Localized pain along the territory of deep venous system—1 point
vii. Paralysis, weakness, or recent immobilization of lower extremities (orthopedic procedure)—1 point
viii. Bedridden for more than 3 days, or major surgery under regional or general anesthesia in the past four weeks—1 point
ix. Alternative diagnosis as likely—minus 2 points

Interpretation: If the score is 2 or higher the diagnosis of DVT is likely and the patient will be assessed further by imaging.

The score of less than 2 – indicates deep vein thrombosis is unlikely and the patient will be assessed further by a D-Dimer test to rule out DVT

Anticoagulant treatment is advised for patients with proximal deep vein thrombosis. Controversy exists regarding the use of anticoagulants for isolated deep vein thrombosis of the calf. Anticoagulant treatment should be done for at least three to six months for patients with acute idiopathic deep-vein thrombosis. Recurrent DVTS as well as DVT provoked by conditions like malignancy or hypercoagulability also require treatment for an indefinite period. Anticoagulants halt thrombus propagation and enhance the endogenous lytic system. The standard treatment protocol is anticoagulation with heparin, followed by treatment with oral Vitamin-K antagonists.

The risk of recurrent DVT depends on the presence of provoking factors. In some patients with provoking factors, anticoagulants can be safely discontinued after some short duration however in unprovoked cases, the risk of recurrent VTE is higher.[12] Keeping in mind the evident proof of the sensitivity, cost-effectiveness, availability, and safety of the D-dimer test there is a need for a continuous effort to standardize this test in health facilities with the support of more scientific knowledge through research.

Objectives:

The diagnosis of DVT is by imaging using compression ultrasound or venography. However, due to expensive tests and increasing, negative tests requested and thus incurred delayed access to them, guided to use alternative approaches to diagnosis in suspected cases of DVT.it is desired to safely and timely exclude DVT by D-Dimer and thus reduce the need for imaging modalities.

Materials and Methods

A total of 65 patients with a high risk of DVT on Well's criteria for clinical diagnosis were enrolled in this cross-sectional study in the inpatient department of the Pakistan Institute of Medical Sciences, Islamabad, and data was collected from March to August 2018. All suspected patients of DVT were diagnosed first on D-dimer and then later confirmed on Doppler ultrasound. Pakistan Institute of Medical Sciences (PIMS), Islamabad is a tertiary care hospital with a large number of referrals of patients with clinical suspicion of DVT. To improve the standardization and use of D-dimer assays in our settings we, therefore, planned to carry out the current research study to determine the sensitivity of D-Dimers in comparison to Doppler ultrasound in the diagnosis of DVT.

Table 1: Baseline characteristics of study patients (n = 65)

		Number	*% age*
Gender	Male	25	38.5%
	Female	40	61.5%
Age	Mean + SD	42.2 + 18.3	
	Range (Min-Max)	14 -88	
Age groups (years)	10 – 29	22	33.8%
	30 – 49	21	32.3%
	50 – 69	13	20.0%
	70 and above	9	13.8%

Results

In this study, a total of 65 cases were enrolled. Out of the total cases, 25 (38.5%) were male and 40 (61.5%) were females. The mean + SD age of the patients was 42.2 + 18.3 years ranging from 14 to 88 years. Looking at age categories distribution, 22 (33.8%) were between 10 to 29 years, 21 (32.3%) were between 30-49 years, 13 (20.0%) were between 50 and 69 years while 9 (13.8%) patients were having 70 or above years of age as explained in Table 1.

Looking at the results of clinical examination and presentation of patients we see that 6 (9.2%) had active cancers. Out of the total 65 cases, 26 (40.0%) were paralyzed or immobile, and 43 (66.2%) were bedridden. On presentation, it was seen that all 100% of patients had localized tenderness and unilateral calf swelling, 61 (93.8%) had leg swelling, and 64 (98.8%) had unilateral pitting edema. Forty-seven of our study patients had non-varicose collateral superficial veins.

The information about the risk score of study patients was calculated. Out of the total 65 cases, 10 (15.4%) had a risk score of 4, 16 (24.6%) had a 5 risk score and 18 (27.7%) had a risk score of 7. Twenty-one of our study patients had a score of 7 or above. The mean + SD risk score of study patients was 5.8 + 1.1. (Table 2)

As per the study objective, the proportions of negative and positive D-dimer test results were compared with that of Doppler ultrasound results. We found out that out of 65 cases, 60 (92.3%) had positive results compared to 65 (100.0%) with the Doppler ultrasound. The negative cases with D-dimer were 5 (7.7%) compared to 0 (0.0%) with the ultrasound. The difference between D-dimer and ultrasound was statistically significant (p-value = 0.02).

Table 2: Distribution of clinical presentation of study patients (n = 65)

	Number	*%age*
Active cancers	6	9.2%
Paralysis or immobilization	26	40.0%
Bedridden	43	66.2%
Localized tenderness	65	100.0%
Entire leg swelling	61	93.8%
Unilateral calf swelling	65	100.0%
Unilateral pitting edema	64	98.5%
Non varicose collateral superficial veins	47	72.3%
Alternative diagnosis	1	1.5%

The sensitivity of D-dimers in diagnosing DVT was 92.3% in our study. The rates of specificity, PPV, and NPV were 0% as none of the cases was negative on ultrasound Doppler.

Discussion

The role of D-Dimer in the diagnosis of DVT needs clarity.[16] The sensitivity of D-dimer remains an active interest for research as the incidence ranges from 48 to 182 per 100000.[10,11] In the current study we validated the accuracy of D-dimers as a sensitive tool for the diagnosis of deep venous thrombosis. As proven before, in our study D-dimers have been found highly sensitive (92.3%) and accurate for the diagnosis of DVT keeping Doppler ultrasound as a comparative standard. The information about the clinical risk score of study patients showed that 10 patients (15.4%) had a risk score of 4, 16 (24.6%) had a 5 risk score and 18 (27.7%) had a risk score of 7. Twenty-one of the study patients had a score of 7 or above. The mean + SD risk score of study patients was 5.8 + 1.1. Evidence shows that ELFA, microplate ELISA, and latex quantitative assay have comparably high sensitivity, but a lower specificity as compared to whole blood D-dimer, latex semi-quantitative, and latex qualitative assays. A systemic review of 184 studies revealed that microplate ELISA, ELFA, and latex quantitative assay for D-Dimer had significantly high sensitivities which were 97%, 95%, and 95% respectively.[13] These rates are comparable to our study findings where we found a sensitivity of 92.3%.

Though the sensitivities are high with different D-dimer assays, the specificity of the test is not clear. Some studies gave results where specificity for D-Dimer by latex qualitative, whole blood, and latex semi-qualitative were 99%, 69%, and 66% respectively.[13]

Deep venous thrombosis can present at any age. The data shows that in developed countries, it presents in mid to late ages above 40 or 50 years. However, in developing countries, it varies and presents in all ages. A study done by Ota S and colleagues revealed the average age of patients was 55.9 years. These findings are comparable to our study's results where we saw the average age of our study patients as 42 years and almost 62% of them were from female strata.

Another study performed on both D-dimer and clinical probability for exclusion of recurrent deep venous thrombosis found risk factors of thrombosis. The presentation of their patients was as 4% cancers, 2% limb immobilization, 5% immobilization, 7% varicose veins, 6% thrombophilia, and 1% local trauma 29. In our study the clinical presentation of patients was as 9% having active cancers, 40% having immobility, localized tenderness in 100%, unilateral calf swelling and pitting edema in almost 100% of cases, and non-varicose collateral superficial veins in 72% of the cases. The differences in the proportions of these clinical signs and symptoms between ours and the above-mentioned study could be due to different outcomes and designs.

D-dimer tests may give false negative results for the following reasons:

i) A monoclonal antibody is used by the D-Dimer test, against the epitope on the D-dimer fragments which is not there on the fibrin, fibrinogen, and non-crosslinked fragments of fibrin. The reactivity of different D-dimer monoclonal antibodies to these different molecular weight species is different, causing variable results with different tests in the same patient.

ii) The size of the thrombus is less in isolated calf vein DVT in comparison to extensive proximal DVT so calf vein DVT will have lower plasma D-dimer concentrations.[14]

Another study by Neale D and colleagues showed that D-dimer is easy to use and can be done within ten minutes with high sensitivity of 94.1%.[15]

A study further established that a negative D-dimer test alone is a useful test for ruling out acute recurrent DVT.[16] D-dimer is less time-consuming, easy to perform and cost-effective, and more suitable for recurrent DVT. It is useful for the safe exclusion of DVT.[17]

For the management of deep venous thrombosis and timely management of fatal pulmonary embolism, early diagnosis of DVT is crucial. D-dimer is sensitive however the specificity is variable and dependable on

the patient demographics as well. False positive results are common in admitted patients, particularly in aged patients having infections or cancers, or post-surgical conditions. This guide raises the cut-off value of D-dimer assays for use in this elderly population group. There is a need for a strategy to formulate the cut-off values for different age groups so that the reliability on D-dimer could be achieved accurately and to rationalize the use of imaging and other techniques which will thus save finances, time, and hassle.

Conclusion

The D-dimer test is easily available and can be done in a short time with a sensitivity of more than 90% in the current study. In emergency departments and other medical units of critical nature, this test is very suitable.

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