Evaluation of D-dimer using VIDAS assay in the diagnosis of suspected deep vein thrombosis

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Abstract

Background: Accurate diagnosis of deep vein thrombosis minimizes the risk of thrombo-embolic complications and averts the exposure of patients without thrombosis to the risks of anticoagulant therapy. Recent studies have shown the safety of using D-dimer assay in ruling out suspected DVT.

Objective: Evaluate the usefulness of using D-dimer (VIDAS) assay compared to duplex ultrasonography in the early diagnosis of suspected DVT in Egyptian sample size.

Patients and methods: One hundred patients with suspected deep vein thrombosis have got assessment with (i) Wells' clinical probability guide for DVT diagnosis, (ii) VIDAS D-dimer essay & (iii) duplex scanning. The results of D-dimer testing & duplex scanning were evaluated & compared on the basis of patients' clinical features.

Results: The validity of D-dimer testing in diagnosing likely patients in relation to duplex ultrasound showed that D-dimer test has reached 100 % sensitivity, 91% specificity & 99% accuracy in comparison to duplex study. Alternatively for unlikely patiens; D-dimer test showed 100% sensitivity, 89% specificity & 92% accuracy in comparison to duplex study.

Conclusion: The incorporation of information gathered from Wells' clinical score, duplex scanning & D-dimer assay should be helpful in the diagnosis of suspected DVT.

Key words: Deep vein thrombosis, D-dimer assay, duplex ultrasonography.

Introduction:

The clinical assessment of patients with suspected DVT is often difficult because of the interplay between risk factors and the nonspecific nature of the physical findings. Discordance is often present between the clinical assessment and the results of objective testing as duplex scanning.

Many studies have confirmed the diagnostic sensitivity and specificity of duplex ultrasonography for proximal vein thrombosis. Sensitivity of duplex ultrasonography for proximal vein DVT is 97%; but only 73% for calf vein. The negative predictive value (NPV) for proximal vein DVT is 99%. Overall specificity is 95%.[1] Duplex ultrasonography is also helpful to differentiate venous thrombosis from hematoma, Baker cyst, abscess, and other causes of leg pain and edema. However; duplex scanning might face difficulty in diagnosis of calf DVT, venous thrombi proximal to inguinal ligament or differentiating between old and new clots in recurrent DVT.[2]

The Wells clinical prediction guide (1997) quantifies the probability of DVT in patients into high-, moderate-, or low-risk categories.[3] Combining this with the results of objective testing greatly simplifies the clinical workup of patients with suspected DVT. The Wells clinical prediction guide incorporates risk factors, clinical signs, and the presence or absence of alternative diagnoses. The parameter of Wells Clinical Score for DVT included:

- Active cancer (treatment ongoing, or within 6 mo or palliative) +1.
- Paralysis or recent plaster immobilization of the lower extremities +1.
- Recently bedridden for >3 d or major surgery <4 wk +1.
- Localized tenderness along the distribution

of the deep venous system +1.
- Entire leg swelling +1.
- Calf swelling >3 cm compared with the asymptomatic leg +1.
- Pitting edema (greater in the symptomatic leg) +1.
- Previous DVT documented +1.
- Collateral superficial veins (Non-varicose) +1.
  - High probability >3
  - Moderate probability 1 or 2
  - Low probability <0

A score of two or higher indicates that the probability of DVT is likely; a score of less than two indicates that probability of DVT is unlikely.[4]

Recent interest has focused on the use of D-dimer in the diagnostic approach to DVT. D-dimer is a specific fibrin degradation product which results from the digestion of cross-linked fibrin by plasmin. Monoclonal antibodies specific for the D-dimer fragment are used to differentiate fibrin-specific clot from non-cross-linked fibrin and from fibrinogen. These specific attributes of the D-dimer antibodies account for their high sensitivity for venous thromboembolism.[5]

Many different D-dimer assays are available, with varying sensitivities and specificities. Traditional enzyme-linked immunosorbent assays (ELISAs), although accurate, are time-consuming and not practical for use. A rapid ELISA assay (VIDAS) with high sensitivity was validated in a large European trial.[6]

The aim of the present study is to evaluate the usefulness of using D-dimer (VIDAS) assay compared to duplex ultrasonography in the diagnosis of suspected DVT in a sample of Egyptian patients.

Patients and methods:

One hundred patients with suspected deep vein thrombosis and attending the Emergency Department or Surgical Out-patient clinic at Menoufyia University Hospitals from July 2009 till July 2011 were included into the study. All patients underwent:

(i) Full clinical assessment whereby WellsÅf model of clinical probability scoring system for DVT diagnosis was considered (mentioned above).

(ii) D-dimer laboratory test was done before heparin therapy using VIDAS D-dimer essay ((Bio-Merieaux SA, Marcy-Etoile, France). It usually takes 35 minutes. The cutoff value of VIDAS was 500 ng/ml where D-dimer level ≥ 500 ng/ml was considered positive for DVT.

(iii) Duplex scanning.

The results of D-dimer testing & duplex scanning were evaluated & compared on the basis of patients' clinical features.

Results:

The study was conducted on 100 patients presented with suspected DVT. Males comprised 36 patients wile females comprised 64 with mean age 46.26±13.96 (range 20-80 years). The majority of patients (96 patients) presented with suspected lower limbs? DVT (66 left lower limbs versus 30 right ones). Only 4 patients presented with suspected DVT in their left upper limbs. These findings are shown in **Table(1)**.

Table (1): Demography of studied patients (n = 100).

Males/Females	36/64 (1:1.7)
Mean age (years)	46.26 ± 13.96
Range (years)	20 - 80
Left lower limb	66
Right lower limb	30
Left upper limb	4

Seventy-six patients (76%) were considered likely to have DVT whenever applying the Wells clinical prediction guide (score ≥ 2) versus 24 patients (24%) were considered as unlikely to have DVT. The percentage distribution of probability is shown in **Table(2)**.

Table (2): The percentage distribution of probability (n = 100).

Probability	No	%
Likely	76	76
Unlikely	24	24

Duplex scanning was positive in 74 patients (68 patients have got proximal deep veins below the inguinal ligament while 6 patients have got isolated calf veins thrombosis). 26 patients were free of thrombosis on duplex study on their first presentation. On the contrary; 72 patients were positive and 28 were negative by testing with D-dimer VIDAS essay.

The impact of Wells' criteria on the findings of duplex scanning or D-dimer test was equivocal. A little difference emerges between the results of either objective test. In the likely patients; D-dimer test was positive in 66/76 (86.8%) patients. In the unlikely patients; 8/24 (33.3%) patients were positive for the test. On the other hand; Duplex was positive in 65/76 (85.5%) patients in the likely group. Furthermore; duplex was positive in 6/24 (25%) of the unlikely patients. The incorporation of D-dimer test and Wells' criteria is shown in **Table(3)**.

Table (3): D-dimer test in likely and unlikely patients (n = 100).

D-dimer	Likely (n=76)		Unlikely (n= 24)		X^2	P- value
	No	%	No	%		
+ ve	66	86.8	8	33.3	27.14	<0.001
- ve	10	13.2	16	66.7		
Mean ± SD	4.47 ± 2.68		0.97 ± 0.92		5.89*	<0.001

** Mann Whitney-U test*

The relationship between D-dimer & duplex in diagnosing suspected DVT was interesting. In the likely group (n = 76); 66 patients were positive by using D-dimer test while 65 patients were positive to duplex study. Subsequently; 10 patients were negative to D-dimer and 11 patients were negative to duplex testing. On the other hand; in the unlikely group (n = 24); 8 patients were positive to D-dimer while 6 patients were positive to duplex. Also; in the unlikely group: 60 patients were negative to D-dimer test while 18 patients were negative to duplex study. These findings were summarized in **Table(4)**.

Table (4): D-dimer versus duplex in the likely and unlikely patients.

Probability	D-dimer				Duplex			
	(+ve)		(-ve)		(+ve)		(-ve)	
	No	%	No	%	No	%	No	%
Likely (n= 76)	66	86.8	10	13.2	65	85.5	11	14.5
Unlikely(n= 24)	8	33.3	16	66.7	6	25	18	75

The validity of D-dimer testing in diagnosing likely patients in relation to duplex ultrasound showed that D-dimer test has reached 100 % sensitivity, 91% specificity & 99% accuracy in comparison to duplex study. Furthermore; the positive predictive value estimated 98%, while the negative predictive value was 100%. Alternatively for unlikely patients; D-dimer test showed 100% sensitivity, 89% specificity & 92% accuracy in comparison to duplex study. These findings were summarized in **Table(5)**.

Table (5): Validity of D-dimer versus duplex in diagnosing likely & unlikely patients.

Validity	Likely (%)	Unlikely (%)
Sensitivity	100	100
Specificity	91	89
Accuracy	99	92
PPV (Positive predictive value)	98	75
NPV (Negative predictive value)	100	100

Discussion:

Suspected deep-vein thrombosis is a common condition, with a lifetime cumulative incidence of 2-5 % .[7] Current evidence suggests that patients with clinically suspected DVT and a normal venous ultrasound result should have a repeat ultrasound examination at 1 week interval to safely exclude DVT and continue without anticoagulation.[8] The incorporation of clinical features & duplex scanning could be insufficient in approaching successful diagnosis. Recently developed tests for plasma levels of D-dimer, a fibrin degradation product, have shown high sensitivity and moderate specificity in diagnosing clinically suspected DVT. Highly sensitive tests are generally helpful in ruling out the presence of disease. The present study was conducted in order to evaluate the usefulness of using D-dimer laboratory tests in the diagnosis of suspected DVT.[9]

The demography of patients included in the study does not seem to be different from that mentioned in literatures world-wide. The males to females ratio accounts for 1:1.7. This little increase in the females' incidence can be attributed to the small sample size of the study patients. Also; DVT usually affects individuals older than 40 years.[10] In our study the mean age of patients included was 46 years (range: 20-80) years. This may be explained on the basis of the interchange of habits & subsequently risk factors among different races.

All patients in the present study (n =100) were evaluated for suspected DVT with duplex scanning and D-dimer assays. We have chosen VIDAS test of D-dimer assays because of rapid & accurate results. The results of both evaluations were compared to each other on the basis of patients' clinical features.

All patients were applied to the clinical probability scoring system of Wells (mentioned earlier) where 76 patients (76%) were likely to develop DVT and 24 patients (24%) were unlikely to develop DVT.

In the likely group: D-dimer was +ve in 66/76 (86.8%) patients while duplex study was +ve for DVT in 65/76 (85.5%) patients. Subsequently; D-dimer was-ve in 10/76 (13.2%) patients, while duplex was -ve for DVT in 11/76 (14.5%) patients.

The results of using D-dimer test in the likely group showed an increase in its validation in the diagnosis of DVT compared to duplex study where D-dimer has reached 100% sensitivity and 91% specificity with accuracy reaching 99%.

In unlikely group: D-dimer test was +ve in 8/24 (33.3%) patients, while duplex study was +ve in 6/24 patients (25%). Subsequently; D-dimer was -ve in 16/24 (66.7%) patients, while duplex was -ve for DVT in 18/24 (75.5%) patients.

The results of using D-dimer test in the unlikely group showed an increase in its validation in the diagnosis of DVT compared to duplex study where D-dimer has reached 100% sensitivity and 89% specificity with accuracy reaching 92%.

Data gathered from this study strongly supports the use of a D-dimer assay in the clinical algorithm of suspected DVT. A negative D-dimer assay results rules out DVT in unlikely patients with low-to-moderate risk (Wells' score <2). Also; a negative result also obviates the need for surveillance and serial testing in likely patients with moderate-to-high risk whenever associated negative ultrasonographic findings.

Furthermore; the usage of D-dimer assay

can be helpful aid whenever a negative D-dimer assay result rules out DVT in patients with low-to-moderate risk and a Wells' DVT score less than 2. All patients with a positive D-dimer assay result and all patients with a moderate-to-high risk of DVT (Wells' score > 2) require a further diagnostic study (duplex ultrasonography).

Every effort should be made in order to diagnose or rule out DVT before starting the patient with anticoagulation therapy. Duplex scanning which is the most commonly accepted world-wide test in diagnosing DVT still presents the corner stone. However; the incorporation of data gathered from Wells' clinical scoring, duplex scanning & D-dimer assay should be helpful in the diagnosis of suspected DVT.

References:

1- Taimur Hussain Babar, Muhammad Nafees, Shakil Sarwar, Naveed Ashra: Validity of color doppler ultrasonography with d-dimers in clinically suspected deep venous thrombosis of the lower limb. *Pakistan Armed Forces Medical Journal* 2010; 3: 267-272.

2- Blann AD, Lip GY: Venous thromboembolism. *BMJ* 2006; 332 (7535): 215-218.

3- Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, et al: Value of assessment of pretest probability of deep vein thrombosis in clinical management. *Lancet* 1997; 350(9094): 1795-1798.

4- Brenda K, Zierler: Ultrasonography and diagnosis of venous thrombo-embolism. *Circulation* 2004; 109: 9-14.

5- Soheir S Adam, Nigel S Key, Charles S Greenberg: D-dimer antigen: Current concepts and future prospects. *Blood* 2009; 113(13): 2878-2887.

6- Perrier A, Desmarais S, Miron MJ, de Moerloose P, Lepage R, Slosman D, et al: Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet* 1999; 353(9148): 190-195.

7- Anand SS, Wells PS, Hunt D, Brill-Edwards P, Cook D, Ginsberg JS: Does this patient have deep vein thrombosis? *JAMA* 1998; 279(14): 1094-1099.

8- Bernardi F, Prandoni P, Lensing AWA: D-dimer testing in suspected DVT. *BMJ* 1999; 317: 1037-1040.

9- Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al: Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003; 349(13): 1227-1235.

10- Froehling DA, Daniels PR, Swensen SJ: Evaluation of a quantitative D-dimer latex immunoassay for acute pulmonary embolism diagnosed by computed tomographic angiography. *Mayo Clin Proc* 2007; 82: 556-560.