

THE D-DIMER TEST

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INTRODUCTION

In the body there is a finely-balanced physiological defence mechanism, haemostasis, which prevents blood loss after vascular damage. Following the sequential triggering of a coagulation cascade, fibrinogen is converted to an insoluble cross-linked fibrin. The fibrin clot prevents blood loss from the damaged vessels. At the same time, clot removal is activated (fibrinolysis) to limit the size of the clot. An excess of intravascular fibrin may be produced in some circumstances. The fibrinolytic system breaks down thrombus and insoluble cross linked fibrin is digested by a serine protease, plasmin, yielding a variety of fibrin degradation products (FDPs). Amongst these is found the D-dimer, a marker of intravascular fibrin formation.

Plasma D-dimer levels may rise in a variety of medical conditions in which fibrin production is enhanced and reactive fibrinolysis occurs (Table 1). Raised D-dimer levels have a low specificity for venous thrombosis, a poor positive predictive value, and should not be used to diagnose acute venous thrombosis. The usefulness of the D-dimer test over recent years has focussed on its negative predictive value in the exclusion of acute venous thrombosis. It was envisaged that if a negative non-invasive test could reliably exclude venous thrombosis, a patient could be spared additional radiological tests, with avoidance of inappropriate anticoagulation whilst waiting for tests and there would be a reduction in hospital admissions.

deep vein thrombosis (DVT)
pulmonary embolus (PE)
disseminated intravascular coagulation
pre-eclampsia
acute myocardial infarction
surgery
trauma
malignancy
vaso-occlusive disease
liver disease
severe sepsis
inflammation
pregnancy

Table 1 Conditions in which D-dimer levels may be raised

D-DIMER TEST: METHODS

Performance of laboratory tests may be assessed according to specificity, sensitivity, positive predictive value and negative predictive value. *High specificity* may be used to establish a

diagnosis, whereas a test with *high sensitivity* may exclude a diagnosis. The D-dimer test falls into the latter category and is most useful in its negative predictive value (NPV).

Several D-dimer methods are currently available. All the methods rely on monoclonal antibodies, which react specifically with the D-dimer fragment. The classical ELISA test (enzyme-linked immunoabsorbent assay) consistently produced the highest sensitivity (98%) and negative predictive value (98%) in assays using diagnostic imaging tests as a reference standard⁽¹⁾. It is, however, time-consuming and thus unsuitable for use in an emergency or outpatient setting, where rapid results are desired. Bedside tests were developed, including the SimpliRED test, and the IL Test D-dimer, a quantitative automated latex-enhanced immunoassay, which gave similar negative predictive results. The automated method and quantitative result of the IL test is particularly suited to busy hospital laboratories. The IL test was evaluated in 105 outpatients suspected of deep vein thrombosis in combination with venography as a reference test and found to have a high NPV and sensitivity (100% at a cut-off D-dimer level of 230ng/ml in this study)⁽²⁾. Diagnostic models, in which patients have been assessed clinically as having a high, moderate or low probability of thrombosis have been studied in combination with D-dimer tests. Scoring systems have been developed using variables and assigned scores and it has been shown that a negative D-dimer level, in conjunction with a validated low clinical probability score, may safely exclude PE and DVT in a large number of patients with suspected thrombosis^(3,4).

LIMITATIONS OF THE D-DIMER TEST

As the level of D-dimers may be raised in the comorbid conditions of hospital inpatients, the D-dimer screening test has consistently been shown to have higher negative predictive value in the outpatient population. Negative D-dimer levels are useful for the exclusion of acute venous thrombosis. If a thrombosis has occurred 10 or more days before presentation, however, the thrombus may become fibrinolytically inactive, giving a false negative result. Whilst some investigators have shown a decreased sensitivity with prolonged duration of symptoms, others have not found this correlation⁽⁵⁾. The value of negative D-dimer assays in patients with cancer is uncertain. A retrospective analysis of three prospective studies on 1068 patients, of whom 121 had cancer, concluded that the negative predictive value of the tests was significantly lower in the patients with cancer⁽⁶⁾. D-dimer levels increase during the course of normal pregnancy, which may limit the usefulness of the test, although a negative D-dimer may still be helpful in excluding thrombosis in pregnancy. Anticoagulation causes a fall in D-dimer levels by preventing intravascular fibrin formation

and therefore levels taken from patients who have been started on anticoagulation may not be reliable. Following acute venous thrombosis, studies have found that D-dimer levels return to normal three months after adequate anticoagulation. There is, however, very little information on the value of D-dimer testing in suspected recurrent thrombosis.

A THREE-MONTH ASSESSMENT OF D-DIMER TESTING AT ROYAL LANCASTER INFIRMARY (RLI)

In September 2000, D-dimer testing was introduced in Lancaster, using an automated, quantitative IL latex method on an ACL Futura machine. A prospective audit was carried out for the first three months following the introduction of testing. The aim of the audit was to establish whether there was a clear cut-off level between negative and positive results and to assess whether the results were clinically useful, as a negative predictive indicator, in the exclusion of venous thrombosis in patients presenting acutely to the admitting medical team.

From 1st September 2000 to 30th November 2000, 125 consecutive patients with suspected DVT or PE, presenting acutely to the medical admitting team at RLI, had D-dimer levels measured. One hundred and fourteen patients were seen on the medical assessment unit, seven in A&E, and four on medical wards. A local protocol was drawn up with the requirement that all patients with suspected DVT should have a clinical score, D-dimer testing and an imaging test, usually a Doppler ultrasound scan. For patients with suspected PE the protocol included a validated clinical probability score, a D-dimer level and an imaging test only if the score was 4 or more (Tables 2 and 3). There were 63 patients with suspected DVT and 62 with suspected PE.

The cut-off value for the D-dimer test was 275ng/ml. Levels below this were negative. Forty-five of the total 125 patients (suspected DVT and PE) had a D-dimer test, a clinical score and an objective assessment of thrombosis (an ultrasound scan, lung scan or venogram).

In the case of patients with DVT, there was not strict adherence to the protocol and scans had not been requested in 48% of cases.

For suspected PE, the protocol was followed more closely, with incomplete information in 30% of cases.

RESULTS

Suspected DVT

Of the 63 patients with suspected DVT, 58% were male and 42% female.

The age range was 19-90 years old with 50% of patients over 70 years old and 5% under 30 years old.

Thirty-three patients (52%) fulfilled all three criteria on the protocol (clinical score, imaging test, D-dimer).

Ten patients had D-dimer levels below the cut-off value of 275ng/ml (range 6-224ng/ml).

All had a negative ultrasound scan or venogram. Seven of

From 01.9.00-30.11.00 D-dimer should be requested on all cases of suspected DVT.

Clinical scoring system should be used to predict the probability of DVT:

- active cancer
- paralysis or immobilisation of legs
- bedridden for >3 days
- localised tenderness along deep vein system
- entire leg swollen
- calf swelling compared to unaffected leg
- pitting oedema
- collateral superficial veins

Score one point for each. Deduct two points for alternative diagnosis.

Low probability = 0

Intermediate probability = 1 or 2

High probability = 3 or more

Order an imaging test, usually a Doppler USS

Table 2 Protocol for D-dimer testing in suspected DVT

Score the probability of PE clinically

Seven variables:

clinical symptoms of DVT	3
no alternative diagnosis	3
heart rate >100	1.5
immobilisation or surgery within previous four weeks	1.5
previous DVT/PR	1.5
haemoptysis	1
malignancy	1

If score <4, request D-dimer test

If negative, PE is excluded

For scores of 4 or more, do not request D-dimer but order imaging test, usually a V/Q scan

Table 3 Protocol for D-dimer testing in suspected PE

these had a clinical score of 1, three had a score of 3 or above.

Twenty-three patients had high levels of D-dimer (range 535-6380ng/ml). Sixty-nine percent of these patients had a positive scan or venogram. Therefore, out of the 63 patients suspected of having DVT, we found 16 proven cases (25%). Information was inadequate on 30/63, ie 48% of cases. There were no false negative D-dimer results in the ten patients who had had both D-dimer levels and an imaging test.

Suspected PE

There were 62 consecutive patients. If the clinical probability score was less than 4, based on a clinical scoring system by Wells *et al*⁽¹⁾, a D-dimer test was requested and if negative, PE was excluded. For clinical scores of 4 or more, PE was likely and an imaging test, rather than a D-dimer test, was appropriate.

Of the 62 patients 74% were male and 26% female. Fifty percent were under 50 years old and 26% were under 30 years old. Thirty-two patients had a chest x-ray, 11 had a lung scan and one patient had an ultrasound scan of the leg.

Thirty-two patients with low D-dimers (range 2-246ng/ml) had a chest x-ray, 29 of which were normal. The four abnormal chest x-rays showed lymphangitis (1), patchy atelectasis (1), carcinoma bronchus (1) and pleural effusion.

Two patients had low D-dimer levels (56ng/ml and 69ng/ml) and negative scans. Of 10 patients with high D-

dimers (range 411-3463ng/ml), six had a high probability of PE on lung scan, one had an indeterminate lung scan, one had low probability of PE, one was reported as normal and one as probable infection.

CONCLUSION

A total of 45 patients had a D-dimer test in addition to an ultrasound scan, venogram or lung scan, and therefore radiological evidence of the presence or absence of thrombosis.

- The 12 patients with a low D-dimer score (range 6-224ng/ml) all had a negative venogram or scan.
- There were no false negative results (100% negative predictive value) in this small study.
- There was a clear cut-off level between positive and negative results.
- Of the 33 patients with a high D-dimer score (range 535-6380ng/ml), 66.6% had a positive venogram or scan. The remainder had a negative scan for thrombosis.

In our small study, the negative predictive value of D-dimer in conjunction with a low clinical score, would have been useful in excluding acute venous thrombosis in 35% of the total patients. These patients could have been spared hospital admission. The negative D-dimers correlated well with negative scans or venograms but the numbers of evaluable patients with objective imaging tests for thrombosis were low and the results were not statistically significant.

DISCUSSION

The diagnosis of acute venous thrombosis is clinically challenging. Clinical diagnosis alone is unreliable and many cases are asymptomatic. Both clinical judgement and objective testing are required for accurate diagnosis. Standard radiological investigations are time-consuming and may have limited availability. The patient usually requires hospital admission whilst waiting for imaging tests, and may be commenced on anticoagulant therapy, with its risks, until the result is known. The D-dimer test is rapid and readily available. It can exclude a diagnosis of acute thrombosis, minimise the risk of inappropriate anticoagulation, reduce

hospital admissions and radiological tests. The negative predictive value of the D-dimer test is particularly suited to acutely presenting outpatients rather than sick hospital inpatients who may have raised D-dimers in association with comorbid conditions. Our local study assessed management of a potential 'outpatient' population by applying a standardised protocol to patients who had been referred acutely to the medical admitting team, from the community. Sick medical inpatients and inpatients from other specialities, including the surgical, orthopaedic and obstetric departments, were not included.

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