

Value of D-Dimers Assay in diagnosos of Pulmonary Embolism

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Introduction

Annual incidence of pulmonary embolism (PE) is 69 per 100,000 with a three-month mortality of 17.5% and untreated case mortality of 30%.^{1,2} Reason for high mortality in untreated patients seems to be inability to confirm diagnosis well in time for initiation of anticoagulant therapy. Although it is suspected clinically in about 3/1000 people every year but its diagnosis is confirmed only in about 30% of them.³ This is due to non-availability of standard diagnostic procedures in all hospitals.

More than 95% emboli arise from deep veins of the leg that are large (e.g. popliteal vein).⁴ Risk factors for deep vein thrombosis (DVT) are well known and include use of oral contraceptives, hormone replacement therapy, neoplasia and surgery.² But in about 20% there is a genetic predisposition² and in these patients PE may occur without any warning. The current gold standard for diagnosis of PE remains pulmonary angiography³ but the procedure is invasive and is not available in all hospitals. Several non-invasive procedures e.g., ventilation-perfusion imaging of lungs (V-Q Scan), ultrasonography and others have been tried but lack in specificity. These have been reviewed by Goldhaber² and Kline et al.⁵ Attention has been focussed on search for a simple test which may not be specific but is sensitive and carries a high negative predictive value, so that it can be used as a screening test to rule out the possibility of PE. This will greatly help in initiation of specific therapy in suspected patients. One such test is D-Dimers assay⁶

All thrombi and emboli are dissolved by a process of fibrinolysis. Both fibrin and fibrinogen are catabolised down to fragments D and E. However if fibrinogen has been cross-linked by activated factor XIII, as it occurs in a thrombus or embolus, then the end product also contain cross-linked D fragments

called D-Dimers.⁷⁻⁹ These are more specific for the diagnosis of thrombosis or embolism. Fibrinolytic system appears to be more rapid in dissolving emboli than thrombi and hence extremely high levels of D-Dimers are demonstrated in PE.⁴ This may be valuable in early diagnosis of PE.

This study was aimed at assessing the sensitivity, specificity, positive predictive value and negative predictive value of raised D-Dimers in patients suspected of suffering from pulmonary embolism.

Patients and Methods

A total of 43 patients were referred for investigations of PE (V-Q Scan) to Nuclear Medical Centre (NMC) of Armed Forces Institute of Pathology (AFIP), Rawalpindi. Inclusion criteria comprised two of the following in the presence of clinical symptoms and signs of PE:

- Existence of a recognised predisposing factor for DVT/PE.
- Existence of diagnosed deep vein thrombosis (DVT).
- Existence of radiological findings in chest X-ray suggestive of PE.

Reterosternal chest pain, dyspnoea, cough and haemoptysis were considered symptoms of high suspicion. Chest X-ray was obtained in all cases. All patients were subjected to Perfusion scanning of lungs which was performed after injecting 99mTC labeled macroaggregated human serum albumin. Patient was positioned under gamma camera and imaging was done after 2-5 minutes of injection. In patients where perfusion scan showed defects and there were no corresponding radiological findings, a Ventilation scan was performed. Ventilation scan was performed after administration of 99mTc labelled diethylene triamine penta acetic acid or gluconate (specific activity 5-6 mCi/ml) aerosol by

inhalation. Patient was positioned under the gamma camera and imaging was done. The two scans were then matched for the site of defect. If ventilation did not occur at the site of perfusion defect, the scan was considered "mismatched" and of high probability. If ventilation did occur at the site of perfusion, it was considered as "matched" V-Q defect and of low probability. Sub-segmental defects were considered of low probability. Ventilation was not considered if perfusion defect corresponded to radiological defect and the scan was classified as "indeterminate".

Blood sample was collected in 100 mmol/l solution of trisodium citrate in the ratio of nine to one. The sample was centrifuged at 2000g for 20 minutes to obtain platelet poor plasma. Plasma was used for D-Dimers assay as soon as possible. All samples were first tested for D-Dimers qualitatively and those found positive were assayed semiquantitatively. For D-Dimers assays Minutex® D-Dimer kit manufactured by Biopool International, USA was used. Kit utilises latex particles coated with specific monoclonal antibody against D-Dimers. Instructions by the manufacturer were followed. For the purpose of this study cut-off point of D-Dimers level was taken as 500ng/ml

Results

A total of 43 patients were inducted in the study, of whom 37 were males and 6 females (male to female ratio 6:1). Their age ranged from 19 to 68 years with a median of 32 years. Of these 13 gave a history of DVT, Embolism and Cerebro Vascular Accident (CVA) in the past. Predisposing factors e.g. prolonged bed rest, fractures, surgery etc. were present in 10 patients while 20 patients were otherwise healthy young adult climbers evacuated from high altitude with clinical suspicion of PE (Table 1).

Reterosternal chest pain with dyspnoea was the most common clinical presentation followed by cough and haemoptysis (Table 2). Six patients had radiological abnormalities on chest X-ray. Fourteen (33%) patients had a normal perfusion scan and hence diagnosis of PE was excluded. V-Q scan was interpreted as "indeterminate" in 06 (13.9%) patients. Only six (13.9%) patients had mismatched multiple segmental defects strongly suggestive of PE (Figure 1). Findings in others are detailed in Table 3.

Table 1. Etiological factors (n=43).

Etiological factors	No	%
History of DVT, CVA, embolism, IHD and Liver disease with or without presence of pre-disposing factors	14	32.6
Presence of predisposing factors e.g. prolonged bed rest, fractures, malignancy etc. alongside	9	20.9
Evacuated from high altitude	20	46.5

Table 2. Clinical presentation (n=43).

Symptom/Sign	No	%
Reterosternal chest pain	33	76.7
Dyspnoea	30	69.8
Cough	22	51.2
Haemoptysis	16	37.2
Headache	07	16.3
Vomiting	17	16.3

Of 43 patients, 24 had D-Dimers levels of more than 500 ng/ml. Details are shown in Table 4. It is important to note that if D-Dimers were low, these were below 250 ng/ml and if these were high the levels were >1000 ng/ml except in two patients. Correlation between V-Q scan and D-Dimers assay results are shown in Table 5. Levels of D-

Table 3. Findings of V-Q Scan (n=43).

Finding	No	%
Normal	14	32.6
Matched multiple segmental defects (low probability)	13	30.2
Segmental perfusion defects (low probability)	6	13.9
Sub-segmental perfusion defects (low probability)	4	9.3
Intermediate scan	6	13.9

Table 4. Results of D-Dimers assay.

Assay value (ng/ml)	No	%
<500	19	44.19
500-1000	2	4.65
1000-2000	15	34.88
>2000	7	16.28

Table 5. Correlation between V-Q Scan and D-Dimers levels

V-Q Scan result	Levels		% Correlation
	<500mg/ml	>500mg/ml	
Normal	14	0	100
Matched multiple segmental defects (low probability)	2	11	84.6
Segmental perfusion defects (high probability)	0	0	100
Sub-segmental perfusion defects (low probability)	0	4	100
Intermediate scan	3	3	50

Dimers in Pulmonary embolism patients are shown in Figure 2.

There were six patients with indeterminate results on V-Q scan. Of these three had D-Dimers levels of >500 ng/ml and three had levels <250 ng/ml, these are excluded from the calculations. The sensitivity of D-Dimers in picking up PE in 37 patients was 91.3% whereas specificity was 100%. Positive and negative predictive values of D-Dimers for PE in 37 patients were 100% and 87.5% respectively

Discussion

The clinical diagnosis of PE is highly non-specific, because none of the symptoms and signs are unique for PE and may be caused by several other disorders.² On the other hand it is important to make an early diagnosis so that specific treatment can be initiated. Pulmonary angiography remains the gold standard for diagnosis⁵ but it is invasive, expensive, time consuming and not readily available. Other investigative procedures used are V-Q scan,

plethysmography and ultrasonography^{10,11} but none of these are specific. At the same time these are time consuming, require shifting of patient from intensive care and are also not available in all hospitals. Of all these procedures, V-Q scan appears better as sensitivity of normal or near normal V-Q scan is reported to be 99%.¹¹ Prospective Investigations for Pulmonary Embolism Diagnosis (PIOPED) trial¹² found that: (a) A normal V-Q scan excluded PE; (b) A combination of high clinical suspicion and high probability V-Q scan result was diagnostic of PE and (c) A combination of low clinical suspicion and low probability or negative result of V-Q scan excluded PE in 96% cases. In view of these findings, non-invasive nature and ready availability V-Q scan was taken as the diagnostic test for comparison in this study.

There are two commonly used methods for D-Dimers assay. One is Enzyme Linked Immunosorbent Assay (ELISA) and the other latex agglutination assay. ELISA is cumbersome, time consuming, involves special equipment and is usually carried out in batches. Latex agglutination assay is readily available on an individual basis and can be performed in less than 30 minutes in most clinical laboratories. Quinn et al have compared five different latex agglutination assays against ELISA in PE and found that the results are not only comparable with each other but also with ELISA.⁶ This background formed the basis for selection of latex agglutination assay for this study.

Various investigators have suggested levels between 250 and 500 ng/ml^{1,6,13,14} as cut off points but majority agree on value of 500 ng/ml. Same level was used as cut off point in this study as well. However, it has been suggested that if D-Dimers by latex agglutination method are <500 ng/ml then the test should be repeated with ELISA because 30% of these may be positive with the latter method.¹⁴ This could not be done in this study due to non-availability of ELISA kit.

Diagnostic efficacy of D-Dimers in PE has been assessed against V-Q scan, pulmonary angiography, and other diagnostic tools.^{6,15-17} Negative predictive value for PE has been estimated between 67% (in case of decision making algorithms) and 100% with pulmonary angiography. Bounameaux et al reviewed the results of various studies calculating an average weighted sensitivity and negative predictive value of D-Dimers levels at 96.8% and 94.2% respectively.¹⁸ Corresponding values in this study are 91.3% and 87.5%.

Six patients with indeterminate V-Q scans remained a diagnostic dilemma in this study

because three of them had D-Dimers levels >500 ng/ml and three had <250 ng/ml. The clinical suspicion was high in all these patients. ELISA could not be performed to confirm the finding.

We conclude that D-Dimers assay, by latex agglutination method, is a handy and most cost effective tool in excluding the diagnosis of PE in vast majority of cases. If carried out on patients with high clinical suspicion of PE its negative predictive value is further improved.

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test-related radiation. *Radiat Environ Biophys.* 1998;37:209-14.

Abstract

Objective: To determine the value of D-Dimers assay in the diagnosis of Pulmonary Embolism (PE) at Armed Forces Institute of Pathology, Rawalpindi, Pakistan from January to November 2000.

Methods: Forty three consecutive patients clinically suspected of suffering from pulmonary embolism and referred to Armed Forces Institute of Pathology for Ventilation-Perfusion scan of lungs were inducted in the study. A detailed history was taken and clinical examination was performed. All patients were then subjected to Perfusion and/or Ventilation scan, which was taken as the standard for the diagnosis of PE. Blood samples were collected from all patients in trisodium citrate. Platelet poor plasma obtained from the samples was tested for D-Dimers semi-quantitatively using latex agglutination method.

Results: Out of 43 patients 14(32.6%) had completely normal ventilation-perfusion scan hence the diagnosis of PE was excluded. In 6 (13.9%) patients the results were considered indeterminate. Abnormalities suggestive of pulmonary embolism were detected in 23 (53.5%) patients. D-Dimers were less than the cut off value of 500 ng/ml in 19 (44.2%) patients, whereas in 24 (55.8%) the levels were more than 500 ng/ml. When compared with the results of ventilation-perfusion scan the sensitivity of D-Dimers was 91.3% and specificity was 100%. Positive predictive value of the test was 100% whereas negative predictive value was 87.5%.

Conclusion: D-Dimers assay combined with high clinical evidence is a cost effective, readily available test which can safely exclude the diagnosis of pulmonary embolism in majority of the cases (JPMA 54:348;2004).