International Journal of Advances in Medicine
Dhananjaya M et al. Int J Adv Med. 2018 Apr;5(2):429-432
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20181083

Original Research Article

D-dimer negative pulmonary embolism

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Received: 31 January 2018
Accepted: 27 February 2018

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ABSTRACT

Background: Pulmonary embolism (PE), is one of the major cardiovascular causes of death. Pulmonary embolus (PE) can be fatal but is often treatable if recognized early. Unfortunately, the clinical presentation of PE is often variable and misleading mimicking other illnesses and hence known as "the Great Masquerader," making diagnosis difficult. The D-dimer assay has recently come into favour as a method to exclude PE; however, this test has an acceptable safety margin only in low-risk populations.
Methods: Present study included 35 patients with clinical suspicion of pulmonary embolism admitted at the tertiary care hospital of North Karnataka during the period from October 2016 to September 2017. Patients were classified according to final diagnosis by CT Pulmonary Angiography into 28 cases positive for PE (80%) and 7 cases negative for PE (20%).
Results: Present study included 35 cases suspected to have PE (26 males and 9 females). Their age ranged from 33 to 72 years, with a mean age 48.9 ±14.2 years. 28 cases positive for PE (80%) and 7 cases negative for PE (20%). The mean age of positive and negative PE cases was 48.1±11.2 and 46.4±8.8 respectively. Results of D-dimer test were positive in 10 cases (35.7%) and were negative in 18 cases (61.3 %) of PE.
Conclusions: This report highlights the risk of misdiagnosing PE if relying solely on ELISA D-dimer for exclusion. This report documents the presentation of PE despite having unremarkable ELISA D-dimer measurements and highlights the importance of clinical suspicion.

Keywords: CT pulmonary angiography, D-dimer, Pre-test probability, Pulmonary embolus, Venous thromboembolism

INTRODUCTION

Pulmonary embolism is a one of the leading causes of preventable hospital deaths and contributes to 5 to 10 percent of deaths in hospitalized patients.[1-4] Pulmonary embolism (PE) is a frequent and potentially severe disease, an accurate and rapid diagnosis of PE remains difficult in clinical practice because of non-specific clinical presentation also treatment carries significant potential side effects, so objective testing is required to establish or exclude the presence of pulmonary embolism. In the United States, the estimated incidence of diagnosed pulmonary embolism is 71 to 117 per 100,000 person-years.[5-7]

Pulmonary embolism silently kills around half of patients who die of pulmonary embolism and were diagnosed with this problem prior to death.[8] Risk factors includes advanced age, prolonged immobility, surgery, trauma, malignancy, pregnancy, estrogen therapy, congestive heart failure, and inherited or acquired defects in blood coagulation factors.

The quantitative plasma d-dimer rises in the presence of PE or deep venous thrombosis because of the breakdown

of fibrin by plasmin. Elevation of d-dimer indicates endogenous although often ineffective thrombolysis. The sensitivity pattern of d-dimer is >80% for DVT and >95% for PE. The d-dimer is less sensitive in DVT because the DVT thrombus size is smaller. It was believed that the d-dimer is a useful "rule out" test and more than 95% of patients with a normal (<500ng/mL) d-dimer do not have PE. But that is not true, and the d-dimer assay is not specific. Levels increase in patients with myocardial infarction, pneumonia, sepsis, cancer, and the postoperative state and those in the second or third trimester of pregnancy. Therefore, d-dimer rarely has a useful role among hospitalized patients, because levels are frequently elevated due to systemic illness.

Hence D-dimer level to be elevated should not be the only basis for a PE workup. Clinical suspicion should direct the investigation for the presence of PE. With the aid of appropriate imaging studies, the diagnosis of PE can be made quickly and adequate treatment can be initiated. The purpose of this study is to demonstrate that an elevated D-dimer value alone often results in extensive PE workup, which has a low diagnostic and economical yield.

METHODS

Present study included 35 patients with clinical suspicion of pulmonary embolism admitted at the tertiary care hospital of North Karnataka during the period from October 2016 to September 2017. There were 26 males and 9 females with mean age of 48.9±14.2 years. Patients were classified according to final diagnosis by CTPA into 28 cases positive for PE (80%) and 7 cases negative for PE (20%).

Inclusion criteria were suspected to have pulmonary embolism according to clinical history and symptoms suggestive of PE. Exclusion criteria were patients refusing to do CTPA, those with renal insufficiency, those having hypersensitivity to IV contrast.

- All the studied patients were subjected to the following:
- Complete medical history including risk factors and symptoms suggestive for PE.
- General and local chest examination for signs of PE and local examination for signs of DVT.
- Evaluation of clinical probability by clinical decision rules.
- Plain chest X-ray.
- Arterial blood gases analysis.
- Electrocardiography (ECG) was used to search for changes suggestive of PE.
- Routine investigation: Complete blood picture, liver, kidney functions and bleeding profile.
- D-Dimer assay.
- Lower limb Doppler ultrasound
- Pulmonary CT angiography: Performed for all patients

Data were entered and analyzed using the Microsoft Excel software. Data were summarized using the arithmetic mean (X), the standard deviation (SD), chi-square and student t-test. Significant was detected according to the P value (P <0.05).

RESULTS

Preasent study included 35 cases suspected to have PE (26 males and 9 females). Their age ranged from 33 to 72 years, with a mean age 48.9±14.2 years. 28 cases positive for PE (80%) and 7 cases negative for PE (20%). The demographic data and results of diagnostic tests were used in the study (Table 1).

The mean age of positive and negative PE cases was 48.1±11.2 and 46.4±8.8 respectively, with statistically non-significant difference among studied cases as regards to age and sex.

Arterial blood gas analysis showed hypoxemia in 22 cases with positive PE and 4 cases had hypoxemia in negative PE. On dopplar ultrasonography of lower limb, deep vein thrombosis was found in 16 cases. Results of D-dimer test were positive in 10 cases (35.7%) of PE and were negative in 18 cases (61.3 %).

Table 1: Demographic data and results of diagnostic tests used in the study.

Parameter	Pulmonary embolism Positive (28)	Pulmonary embolism negative (7)
Age	48.1±11.2	46.4±8.8
Sex		
Male 26	22	4
Female 9	6	3
Abg		
Hypoxemia	22	4
No hypoxemia	6	3
Dopplar		
Dvt	16	0
Normal	12	7
D dimer		
Positive	10	0
Negative	18	7

The average hospital stay was 8.9 days. Various parameters like etiology, sex, need for postoperative shunt, radiological outcome, wound complications, hospital stay, age group and year of surgery were statistically compared for association with good clinical outcome. None of the parameters had a statistically significant p- value to prove a strong association. All patients had good radiological outcome postoperatively. However, clinically favorable outcome was seen in

82.6% of cases. The failure rate was 17.4%. The overall mortality rate was 21.6% (n=5). Wound related complication was seen in 1 patient (4.3%). Two (8.7%) patients required VP shunt post ETV. The cause of mortality (Table 2) was aspiration pneumonitis in 3 cases, CSF metastasis and wound infection in 1 cases each.

DISCUSSION

There are various combinations of non-invasive aids to diagnose PE including the assessment of clinical probability, D-dimer testing, $PetCO_2$, venous compression ultrasonography of the legs (CUS) and ventilation perfusion lung scanning or CTPA have been developed.[9] The D-dimer test is usually performed first because it can safely rule out PE and thus, reduce the need for further testing but relying on D-dimer testing alone carries an unacceptable risk if the clinical probability of PE is not taken into account because of its poor specificity, especially in elderly patients, patients with cancer, hospitalized patients and pregnant women, the D-dimer test excludes PE in only 30% of patients.[10]

So, this study was carried out to evaluate the diagnostic accuracy of D-dimer in suspected pulmonary embolism patients.

This study included 35 cases suspected to have PE; 28 cases (80%) were positive for PE by CTPA and the other 7 cases (20%) were negative for PE. The mean age of positive and negative PE cases was (48.1±11.2 and 46.4±8.8) respectively. These results are comparable with Stein et al. who found that the venous thrombo-embolism and pulmonary embolism are diseases associated with advancing age due increased risk factors that patients acquire with aging such as obesity, immobility, hypertension, surgery etc.[11]

The present study showed that 22 cases (78.5%) of the proved PE cases had hypoxemia and ($PA\text{-}aO_2$) gradient >25mmHg, while 6 cases (21.5%) had no hypoxemia and (PAaO2) gradient 500mmHg (Table 1). There was statistically significant difference among the studied cases and in similar study by Adam et al who noted that; hypoxemia and wide ($A\text{-}aO_2$) gradient are the most common arterial blood gas abnormalities in patients with PE, but up to 20% of patients with PE can be normal.[12] In the current study 16 cases (57.1%) of PE had DVT on doppler ultrasonography venous study and 12 cases (42.9%) of them had normal doppler. All cases negative for PE had normal doppler study. Statistically significant difference was found among the negative and positive PE cases in Doppler ultrasonography (Table 1).

Regarding the final diagnosis (Table 1) among 28 cases who had PE by CTPA 10 cases (35.7%) had positive D-dimer and 18 cases (64.3%) had negative D-dimer. On the other hand, 7 cases were proved to be negative for PE and all had negative D-dimer result. The recorded sensitivity, specificity, positive predictive and negative predictive value of D dimer test as regards the final diagnosis by CT pulmonary angiography were 35.7%, 100%, 100% and 28% respectively.

This is in accordance to the results of Patrick et al who reported that D-dimer assay was unsuitable to be used as a sole test to exclude or confirm VTE.[13] The recorded sensitivity, specificity, negative predictive value and positive predictive value of D-dimer test as regards the final diagnosis by CT pulmonary angiography were (78%, 41%, 84%, and 34%) respectively.[13]

In contrast, Kearon, concluded that enzyme-linked immunosorbent assay (ELISA) D-dimer assays (cut-off of about 500 fibrinogen-equivalent units/mL) have a sensitivity for venous thromboembolism of about 98%.[14]

D-dimer levels are sensitive but non-specific markers for thrombosis because Systemic D-dimer values are raised in a variety of clinical conditions such as; trauma, infection, malignancy, pregnancy, atrial fibrillation, disseminated intravascular coagulation, acute coronary syndromes and stroke.[15]

Florence et al concluded that D-dimer assay in patients with high clinical probability, suggested clinicians should not ignore a normal D-dimer concentration.[9]

It was found that relying on D-dimer testing alone increases unacceptable risk if the clinical probability of PE is not considered. So, it is important to first examine the patient and assess the clinical probability, after which the d-dimer concentration can be taken into account, in order to prevent physicians from being influenced by a normal d-dimer test result when they evaluate the clinical probability of PE. Patients with a likely clinical probability should undergo further testing, regardless of the d-dimer test outcome.

CONCLUSION

Pulmonary embolism is one of the life-threatening diseases associated with significant morbidity and mortality both in the early and late stages. There are varieties of diagnostic tools that help to detect PE. D-dimer alone cannot exclude or confirm the presence of PE. The combination of D-dimer, clinical probability and CT pulmonary angiography improves diagnostic accuracy in patients with suspected PE and early management of suspected cases.

Early thrombolysis shows rapid improvement of right ventricular function and lowers rate of early recurrent PE. It also decreases the late sequela of chronic pulmonary hypertension and improves mortality and morbidity.

ACKNOWLEDGEMENTS

Authors would like to acknowledge statistician Mrs. Sucharita Suresh for her invaluable contribution.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Dhananjaya M, Meti K, Parekh R. D dimer negative pulmonary embolism. Int J Adv Med 2018;5:429-32.