D-dimer in the diagnostic workup of suspected pulmonary thrombo-embolism at high altitude

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ABSTRACT

BACKGROUND

Pulmonary thrombo-embolism (PTE) is relatively common in high altitude areas where radiological diagnostic facilities are usually not available. So this study was undertaken to use the results of D-dimer assay to determine the need for imaging studies in patients suspected of having PTE at high altitude.

METHOD

A total of 101 patients at an altitude of >3,000 m suspected of having PTE were evacuated. D-dimer and imaging studies were carried out to confirm the diagnosis.

RESULTS

A total of 101 patients suspected of having PTE underwent D-dimer level estimation and imaging studies for PTE. Sixty-eight of these had negative findings on D-dimer assay. All these patients with negative findings on D-dimer assay had negative findings on pulmonary imaging studies also. So this test is very sensitive with very high negative predictive value (NPV). Whereas, 17 out of 33 patients positive for D-dimer, had positive findings on imaging studies, indicating a relatively less specific test.

CONCLUSION

Clinical assessment in combination with D-dimer assay can be used for timely differentiation of PTE from other conditions such as high altitude pulmonary oedema (HAPO) especially at isolated high altitude areas/military posts, so that patients could be evacuated as early as possible by fastest means to save the precious lives and in hospital settings this test identifies patients to whom anticoagulant therapy should not be given or patients who should not be subjected to invasive imaging tests.

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Key Words: D-dimer test; PTE

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INTRODUCTION

High altitude illnesses are becoming a problem as more people enjoy the outdoors all over the world and military personnel taking part in operations at Siachen glacier and other parts of Himalayan region. Climbers staying at high altitudes for weeks have several risk factors for thrombosis. The various effects of thrombosis include pulmonary thrombo-embolism (PTE), cerebral venous thrombosis, portal/splenic vein thrombosis, and deep vein thrombosis (DVT). Out of all these conditions, PTE is an extremely common and highly lethal condition that is a leading cause of death in all age groups. A good clinician actively seeks the diagnosis as soon as any suspicion of PTE whatsoever is warranted, because prompt diagnosis and treatment can dramatically reduce the mortality rate and morbidity of the disease. Unfortunately, the diagnosis is missed more often than it is made, because PTE often causes only vague and non-specific symptoms. D-dimer test, being quite sensitive, is of immense value in the diagnosis of PTE.¹ The negative predictive value of (NPV) D-dimer is excellent as it can easily rule out PTE.² The big problem with the current state of the art is the high frequency of false positives with D-dimer. Consequently, it is important that a patient with a positive D-dimer (above the cut-off) is always followed with a confirmatory investigation that typically is performed with objective techniques such as imaging studies. However, in high altitude areas where PTE relatively is more common, the positive predictive value (PPV) of D-dimer is quite high. In this study we evaluated D-dimer measured by latex agglutination assays. Pulmonary angiography was used as the diagnostic standard in all patients.

MATERIALS AND METHOD

A total of 101 patients, staying at high altitude of >3,000 m height from sea level and with signs and symptoms of PTE such as dyspnoea, chest pain, cough, apprehension, tachycardia, tachypnoea, and fever, were tested for D-dimer using Dimer test kit (Tulip Diagnostics [P] Ltd). This kit is intended for the rapid qualitative or semi-quantitative evaluation of circulating derivatives of cross-linked fibrin degradation products (XL-FDP) in human plasma. The principle of the test is based on a rapid agglutination assay utilising latex beads coupled

with a highly specific D-dimer monoclonal antibody. The XL-FDP present in a plasma sample bind to the coated latex beads, which results in visible agglutination occurring when the concentration of D-dimer is above the threshold of detection of the assay.

Plasma samples were prepared from whole blood with sodium citrate as anticoagulant. After separation of the plasma by centrifugation, specimens were tested directly for the presence of XL-FDP by latex agglutination assay as per following procedure:

1. Place one drop of latex reagent within a well on a test card.
2. Add one drop of sample inside the same well next to the drop of latex reagent.
3. Mix the latex reagent and sample with a stirrer until the latex is uniformly distributed.
4. Rock the test card gently by hand exactly for three minutes.
5. Observe for agglutination.
6. Both positive control and negative control were included in each batch of test.

A positive test indicates that XL-FDP concentration in sample is >200 ng/mL. Pulmonary angiography was used as the diagnostic standard in all patients. Computed tomographic pulmonary angiography (CTPA) was done in every patient using Siemens somatom sensation (40 multidetector computed tomography [MDCT]) using 80 mL of iodinated contrast by bolus chase technique.

RESULTS

Total 101 patients suspected of PTE were admitted to the hospital. Mostly these patients were evacuated from $>3,000$ m of altitude. All these patients were investigated by D-dimer tests, followed by imaging studies including CT scan and CTPA to arrive at the exact diagnosis. Out of 101 patients, 33 were found positive for D-dimer qualitative test. Further, out of the 33 patients, 17 were positive for D-dimer and had positive findings on imaging studies (Figure 1) indicating a relatively less specific test.

Figure 1 Computed tomographic pulmonary angiography reveals hypodense thrombi in the right and left pulmonary arteries.

Four out of the 17 PTE cases also showed DVT. Pulmonary thrombo-embolism could not be detected by imaging studies in 16 patients, although these were positive by D-dimer tests. Further investigations were carried out on these patients and finally diagnosed as high altitude pulmonary oedema (HAPO) in nine cases, pneumonitis in two cases, myocardial infarction, enteric fever, disseminated intravascular coagulation (DIC), and sepsis in one case each. In one case, diagnosis could not be confirmed. All 68 patients with negative findings on D-dimer assay had negative findings on pulmonary imaging studies also. Typically these patients belonged to HAPO, therefore this test is very sensitive with very high NPV. The results of D-dimer tests and imaging studies have been shown in Table 1.

The sensitivity of this test was 100% and NPV was 100%. The specificity was 80.9% and PPV was 51.5%.

DISCUSSION

The term 'high altitude' has no precise definition. Most of the studies refer high altitude as 3,000 m and above, while extreme altitude exceeds 5,500 m from sea level.

Climbers staying at high altitudes for weeks have several risk factors for thrombosis. Red blood cell counts and haemoglobin concentrations increase to maintain oxygen transport in the hypobaric environment. In addition, despite large amount of water loss while climbing, fluid is restricted by difficulty in obtaining water.

Earlier studies on Indian soldiers at high altitude indicated a significant increase of plasma fibrinogen levels.³ Another study described changes in the coagulation factors suggesting an activation of the coagulation cascade and associated endothelial cell damage.⁴ Anand et al reported a 30 times higher risk of spontaneous vascular thrombosis on long-term stay at high altitude in Indian soldiers. Veins are common sites for such thrombotic events.⁵ Jha et al studied the clinical profile of 30 cases of stroke at high altitude and reported that long-term stay at high altitude with polycythemia vera and hypercoagulable state were associated with higher risk of stroke.⁶ Recently, Jyoti Kotwal et al carried out a prospective cohort study at a height of 3,500 m above sea level and concluded that the combination of erythrocytosis, increased platelet count, platelet activation and raised fibrinogen level combined with hypoxia

Table 1 Results of D-dimer test and imaging studies.

D-dimer	PTE positive by by imaging	PTE negative by imaging	Total
Positive cases	17	16	33
Negative cases	0	68	68
Total	17	84	101

PTE: pulmonary thrombo-embolism.

and dehydration at high altitude cause a thrombotic milieu to occur, leading to thrombosis in normal individuals or in asymptomatic cases with inherited/acquired thrombophilia.⁷ Bad weather conditions can force prolonged periods of inactivity, causing venous stasis, which may also contribute to thrombosis. When a climber has a procoagulation disorder such as protein C deficiency, fibrinolytic enzyme deficiency or antiphospholipid antibody syndrome, thrombosis can develop even at a moderate altitude. Jyoti Kotwal et al while studying 21 cases of stroke in young at high altitude found hyper homocystinaemia in three patients, protein C and protein S deficiency in one each.⁷

D-dimer is a unique degradation product produced by plasmin-mediated proteolysis of cross-linked fibrin. D-dimer is measured by latex agglutination or by an enzyme-linked immunosorbent assay (ELISA) test. These tests have been primarily used to diagnose DVT and resultant PTE. The principle is based on measuring the increase in specific plasma degradation products of fibrin, which is elevated due to the action of plasmin and other endogenous thrombolytic agents. A positive D-dimer indicates the presence of an abnormally high level of fibrin degradation products in the body and indicates that there has been significant clot (thrombus) formation and breakdown in the body, but it does not tell the location or cause. D-dimer levels are elevated not only in the setting of acute thrombosis, but also in other conditions such as pregnancy, infection and malignancy. In contrast, a negative result using a sensitive D-dimer test is useful for excluding acute DVT or PTE.⁸

In this study, specificity is on the higher side as compared to the other studies.⁹ This could be due to healthy individuals posted at high altitude and thrombo-embolism is relatively more common in high altitude areas. The troops are usually free of malignancies, liver diseases, DIC, and other conditions responsible for positive D-dimer test and these conditions are quite common in hospital settings of plain areas. As a result, the specificity of D-dimer is low in other hospitals as compared to high altitude areas among troops. Further, it has been noticed that in high altitude, most of the times the troops presenting with dyspnoea, tachycardia, and chest pain have either HAPO or PTE. In this study, mostly patients presenting with these symptoms with negative D-dimer had HAPO. It is therefore clear this simple test helps in differentiating HAPO and PTE.

The true benefits of the D-dimer assay lie in its NPV, which, in turn, translates into cost savings by eliminating the need for expensive imaging exams for negative low-risk patients. These patients are able to avoid invasive testing to rule out PTE.¹⁰ On the other hand, a positive result leads to additional testing to rule out or diagnose PTE. A variety of imaging tests, such as a leg vein ultrasonography and colour Doppler, pulmonary angiography, ventilation perfusion scan, or CT scan, may be ordered to rule out or diagnose DVT or PTE.

CONCLUSION

D-dimer assay is highly sensitive but less specific. In PTE, it is an excellent screening test with sensitivity of almost 100% and NPV of 100%. So, a negative D-dimer test can easily rule out PTE, thereby it identifies patients to whom anticoagulant therapy should not be given or patients who should not be subjected to invasive imaging tests. A positive D-dimer test is also equally important, especially in high altitude areas where majority posts are located in inaccessible remote areas and radiological facilities are not available or feasible, because it gives a sense of urgency of patient evacuation to a specialised centre for definite management by fastest means available.

Intellectual Contributions of Authors

Study concept: Col KR Rathi

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CONFLICTS OF INTEREST

None identified.

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