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D-dimer Testing and Acute Venous Thromboembolism

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INTRODUCTION

Venous thromboembolism (VTE) is a common disorder associated with significant morbidity and mortality. In addition to clinical judgment, the accurate diagnosis of acute VTE requires objective testing (1). Physical examination is inadequate for establishing the diagnosis of VTE. For the diagnosis of deep vein thrombosis (DVT), a careful clinical assessment combined with the results of venous ultrasonography is accurate in most cases. Ventilation-perfusion lung scans are commonly used to diagnose pulmonary embolism (PE) although approximately 70% are nondiagnostic. In most cases, further testing is required to determine whether anticoagulant therapy is appropriate. Therefore, to reduce testing and improve diagnostic accuracy, laboratory tests have been evaluated for use as adjuncts to noninvasive testing. Measurement of D-dimer is potentially one of the most useful tests.

BACKGROUND

In normal clot formation, a fibrin clot is the result of thrombin-catalyzed cleavage of soluble fibrinogen to form fibrin monomers. The resultant thrombus is a network of highly crosslinked fibrin monomers. Plasmin is the major clot lysing enzyme capable of cleaving both fibrinogen and fibrin to yield various degradation products. Plasmin lysis of cross-linked fibrin generates the D-dimer fragment (2).

Elevated D-dimer levels are found in many clinical conditions including DVT and PE (3). Therefore, the specificity for VTE is low for all D-dimer assays. However, D-dimer can be used to rule out acute VTE. This is due to the high sensitivity and corresponding negative predictive value. There are commonly used methods for detecting D-dimer levels, all of which rely on monoclonal antibodies that recognize epitopes on the D-dimer fragment: enzyme-linked immunosorbent assay (ELISA), latex agglutination (LA) and whole blood agglutination (WBA).

D-DIMER ASSAY

ELISA is considered the reference standard determination of D-dimer concentration. An antibody with a high affinity to D-dimer is coated onto a membrane or microtiter well and binds protein in the plasma. A second tagged antibody is then added and the amount of labeled substance bound is in direct proportion to the amount of D-dimer present. The conventional ELISA is not practical in the diagnosis of VTE in individual patients because it is labor intensive, results may not be available the same day, expensive and not available in most centers.

Latex agglutination (LA) assays rely on the use of monoclonal antibodies to D-dimer that are coated onto latex particles. Macroscopic agglutinates are seen when elevated D-dimer are present in the plasma sample tested. Advantages to this method are that it is inexpensive, results are quickly available, and it can be done in most settings. Unfortunately, latex agglutination lacks the sensitivity to be used as a screening assay for VTE (4). Recent modifications of this method that involve quantification of the D-dimer using an automated analyzer have been evaluated and appear to be comparable to the conventional ELISA (98-100%). Testing in a greater number of patients is needed before this method can be recommended.

The most frequently studied whole blood assay is the SimpliRED assay. This method relies on a bispecific antibody that causes visible agglutination of red cells in the presence of D-dimer. It requires one drop of whole blood and the results are

available in 2 minutes. Several reports indicate sensitivities that are similar to conventional ELISA and are being widely used in many clinical settings including the emergency room (5).

CLINICAL SIGNIFICANCE

Presence of elevated levels of cross-linked products has been demonstrated to be a marker of an incipient or ongoing thrombotic process. The D-dimer test therefore provides a measure of fibrinolytic activity in the blood. Abnormal levels are found in patients with deep venous thrombosis (DVT), disseminated intravascular coagulation (DIC), arterial thromboembolism (AT), and pulmonary embolism (PE) as well as in bleeding and post-operative patients. In addition, it has also been useful in the monitoring of thrombolytic therapy, cancer therapy and complicated myocardial infarction.

The ELISA method of D-dimer determination has a sensitivity for DVT of 90% or greater as well as a negative predictive value of 90% or greater by most studies. This suggests that a negative D-dimer level in a symptomatic patient with clinically suspected DVT provides exclusion of DVT diagnosis. D-dimer testing is most appropriate in the assessment of outpatients, since disease prevalence and comorbid conditions are less frequent than hospitalized patients increasing the value an exclusion test.

Rapid ELISA tests show promise as a practical D-dimer test with sensitivity, similar to that of conventional ELISA for patients with suspected DVT. Two studies have recently confirmed that a normal D-dimer result (SimpliRED or Instant IA rapid ELISA) in combination with a noninvasive test and/or clinical algorithm can reliably exclude DVT in outpatients. (6,7) Accuracy studies in suspected PE complement the findings in patients with suspected DVT (8).

SUMMARY

Evaluation of D-dimer has gained importance as the diagnostic applications of this assay have been elucidated. ELISA or WBA can be valuable in the appropriate clinical setting to rule out DVT or PE and ensure proper patient management. The lack of specificity of the D-dimer assay for VTE in hospitalized patients warrants interpreting positive assay results with caution.

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