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Quantitative D-dimer: Ruling out Venous Thrombosis

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Introduction

As the U.S. population ages, the medical and economic impact of venous thromboembolism (VTE) is expected to increase. The most common manifestations of VTE are deep vein thrombosis (DVT) and pulmonary embolism (PE).[1,2,3] The initial diagnosis of VTE is often subjective, relying on "clinical impression," and is then followed by more objective and expensive testing. The use of an inexpensive screening test to eliminate the diagnosis of VTE can result in significant savings in healthcare costs. Quantitative D-dimer is an inexpensive test now available for exclusion of VTE.

Physiology

The D-dimer is a specific fragment of a fibrin clot. Covalent cross-linking of polymerized fibrin monomers by activated Factor XIII stabilizes the fibrin clot. D-dimers are generated by plasmin lysis of this cross-linked fibrin.[4] Under normal physiological conditions, the coagulation process is balanced by activation of fibrinolysis, which leads to dissolution of the clot and release of soluble fragments, including D-dimers, into the plasma. Therefore, the presence of D-dimers indicates degradation of fibrin specifically and serves as an indirect indicator of thrombotic activity.

Rationale for Use

The D-dimer assay is used in several diagnostic settings as a marker of an incipient or ongoing thrombotic process. Semi-quantitative assays help confirm ongoing systemic coagulation seen in disseminated intravascular coagulation (DIC), which is associated with very elevated D-dimer levels.[5] This type of assay should not be used to differentiate the presence or absence of VTE.

Only quantitative assays can be used to exclude DVT and PE. It has been demonstrated that quantitative D-dimer assays have sufficient specificity and clinical sensitivity to have negative predictive value for VTE.[5] If the level of D-dimer in the blood is not elevated, then no thrombotic process is ongoing and VTE is not present. However, if the quantitative D-dimer level is elevated, a clotting process is occurring, which may be due to VTE, but also may be due to other clinical conditions (DIC, trauma, post surgery, pregnancy, cancer, etc.).

The ability to use quantitative D-dimer as a negative predictor is based on the premise that the formation of a thrombus involves both coagulation and fibrinolytic activation. Although the presence of D-dimer fragments suggests that a coagulation-fibrinolytic process is taking place, the test's lack of specificity does not allow one to definitively conclude that a thrombus has formed.

Clinical D-dimer Assays

There are many different D-dimer assays currently available on the market. All of these assays rely on monoclonal antibodies. The original assay is semi-quantitative and utilizes visual macroscopic latex agglutination (used in DIC diagnosis).[5] The most sensitive quantitative D-dimer assay is based on the ELISA format, but these are time consuming and require specialized equipment and training. The most practical quantitative assays are the latex-enhanced photometric assays that are turbidimetric or colorimetric. These assays utilize latex particles coated with human monoclonal antibodies to the D-dimer antigen. They can be performed in the laboratory or at the bedside and still maintain the needed

sensitivity. Turnaround times are rapid, facilitating their use as an emergency test.[6,7]

D-dimer Laboratory Guidelines

The most difficult aspect of establishing the D-dimer assay for the exclusion of VTE is determining the cut-off value. Each laboratory must establish their own cut-off value and cannot rely on the manufacturers' recommended value or another laboratory's value. The main criteria for establishing the cut-off is that it must have 100% negative predictive value.[8,9] The following steps need to be taken:

1. Perform validation, verifying the intra- and inter-assay variability.
2. Establish normal range using a minimum of 30 normal subjects.
3. Determine D-dimer levels on at least 20 suspected VTE patients (diagnosis based on imaging results). Use ROC graph to establish cut-off.
4. Re-evaluate/adjust cut-off after evaluation of more patients (100 patients ideal).
5. Re-evaluate annually and if the methodology changes.

Establish Clinical Guidelines

Once the quantitative D-dimer has been validated with an established cut-off, the assay can be used as a negative predictor of VTE. Guidelines for the use of D-dimer should be developed with input from the clinical staff to develop criteria to be used as a negative predictor. Two major points should be incorporated into the procedure for the use of D-dimer assay.[9]

1. Use the D-dimer with caution on inpatients since numerous disease processes and invasive procedures can elevate D-dimer levels in the absence of VTE.
2. Do not use the D-dimer assay in patients on anticoagulant therapy (heparin or coumarin). Anticoagulants can decrease D-dimers and possibly generate a falsely low value, below the established cut- off.

Since the range of detection necessary for assays for DIC and exclusion of VTE are significantly different, it is generally recommended that a facility provide two D-dimer assays.

Summary

The determination of quantitative D-dimer levels is both a diagnostic and a cost-saving tool to rule out VTE. The assay can be used to eliminate those individuals without VTE, but with low or moderate clinical suspicion. After appropriate validation, the assay can be 100% sensitive in ruling out DVT or PE, but will not confirm the presence of VTE as numerous other diseases and procedures can increase levels.

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