Clinical Significance of Quantitative D-Dimer Testing IN Suspected Deep Vein Thrombosis

Thesis

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List of Abbreviations

AAD ..... Acute aortic dissection
AP..... Emergency department.
APAs..... Antiphospholipid antibodies
APC ..... Activated protein C
APTT ..... Activated partial thromboplastin time
ATIII..... Antithrombin III
BMI..... Body mass index
CBC ..... Complete blood count
CCDS..... Colour coded duplex sonography
CT..... Computed tomography
CTPA ..... Computed tomographic pulmonary angiography
CTV ..... Computed tomographic venography
CUS ..... Compression ultra sonography
DIC ..... Dissamenated intravascular coagulation
DVT ..... Deep venous thrombosis
ELISA ..... Enzyme-linked immuno-sorbent assay
FII ..... Prothrombin
FRM..... Fibrin related marker
HIT ..... Heparin-induced thrombocytopenia
K٢-EDTA..... Potassium ethylene diamine tetra-acetic
MRI ..... Magnetic resonance imaging
MTHFR:..... Methtelentetrahydrofolate reductase
NPV ..... Negative predictive value
OCPs..... Oral Contraceptives pills
PC..... Protein C
POC ..... Point of care
PPP..... Platelet Poor Plasma
PPV..... Positive predictive value
PS..... Protein S

LIST OF ABBREVIATIONS (CONT.)

PSGL-١ ..... P-selectin glycoprotein ligand ١
PT ..... Prothrombin time
PTT ..... Partial tromboplastin time
RCL ..... Reactive centre loop
ROC ..... Receiver operating characteristic
S ..... Sensitivity
SD ..... Standard deviation
SLE ..... Systemic lupus erythematosus
SNP ..... Single nucleotide polymorphism
SP ..... Specificity
T ..... Thrombin
TLC ..... Total leucocytic count
TM ..... Thrombomodulin
TM ..... Thrombomodulin
t-PA ..... Tissue plasminogen activator
U-PA ..... Urokinase-type plasminogen activator
US ..... Ultra sonography
V/Q Scan ..... Ventilation–perfusion scintigraphy
Va ..... Activated factor V
VIIIa ..... Activated factor VIII
Vitamin B ..... Pyridoxal phosphate
Vitamin B١٢ ... Cobalamin
VTE ..... Venous thromboembolism
X^2 ..... Chi-square test
A٥٠٦G ..... Prothrombin gene mutation

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✍ *Rasha Mohamed Attia*

INTRODUCTION

Deep venous thrombosis (DVT) is a common condition with significant morbidity and mortality if not diagnosed and treated in a timely manner. The clinical signs and symptoms of DVT are non- specific and objective testing is required for diagnosis ***(Heim et al., ٢٠٠٤).***

Accurate diagnosis of deep-vein thrombosis minimizes the risk of thromboembolic complication and averts the exposure of patients without thrombosis to the risk of anticoagulant therapy ***(Wells et al., ٢٠٠٣).***

Diagnostic imaging with venography was previously the gold standard for DVT evaluation and may still be utilized if other techniques are inconclusive. Although effective, the technique is invasive, expensive, time consuming, requires specialized personnel and may introduce a variety of complications ***(Fox and Bertoglio, ٢٠١١).***

Compression ultra sonography (CUS) is a highly accurate method for the detection of deep vein thrombosis in symptomatic outpatients and has replaced venography and other diagnostic methods in common practice ***(Bernardi et al., ٢٠٠٨).*** However ultrasonography is expensive and time consuming ***(Chen et al., ٢٠٠٨).***

Moreover, a significant proportion of out patients may be lost at follow-up and has poor sensitivity for detection of calf vein

thrombosis**.** In addition, three fourths or more of the patients with suspected DVT have negative ultra sound findings and require repeated imaging to identify the further ٢٪ to ٦٪ in whom occlusive proximal DVT becomes apparent in a week ***(Kelly et al., ٢٠٠٢).***

Therefore, diagnostic strategies have been developed aiming at reduction of the need for imaging techniques and instead including D-dimer testing ***(Jennersjo et al., ٢٠٠٩).*** Plasma D-dimers are generated when the endogenous fibrinolytic system degrades fibrin.as in venous thromboembolism, and they consist of ٢ identical subunits derived from ٢ fibrin molecules. Unlike fibrinogen degradation product, which are derived from fibrinogen and fibrin ***(Kelly et al., ٢٠٠٢).*** It's a degradation product of cross linked fibrin.D-dimer assays are sensitive but non-specific marker for venous thromboembolism ***(Wells, ٢٠٠١).***

D-dimer testing has become rapid simple and inexpensive and it has the potential to detect thrombosis in any part of the venous system. If the sensitivity of the D-dimer test for deep venous thrombosis consistently very high, its negative predective value will also be high and reliably exclude the presence of disease. Therefore D-dimer assays has been suggested as an initial test to rule out DVT to reduce the number of patients requiring diagnostic imaging ***(Heim et al., ٢٠٠٤).***

Normal result from a highly sensitive D-dimer test effectively ruled out deep vein thrombosis among patients with

either low or moderate clinical. This makes ultrasound testing unnecessary ***(Fancher et al., ٢٠٠٤).***

When D-dimer testing is positive, CUS or colour coded duplex sonography (CCDS) should initially be performed to accurately exclude or confirm DVT. In patients with suspected DVT, serial CUS can be avoided if the D-dimer test is negative. Whereas in cases of negative sonographic findings, an additional negative D-dimer test allows exclusion of acute proximal DVT ***(Melly et al., ٢٠٠٦).***

AIM OF THE STUDY

The aim of this study is to assess the role of D-Dimer and its effectiveness in diagnosis and ruling out DVT in clinically suspected patients, as well as the possibility of reducing the need of ultrasoungraphy.

THROMBOPHILIA

Hypercoagulable states can be defined as a group of inherited or acquired conditions associated with a predisposition to venous thrombosis, arterial thrombosis or both. Although most inherited conditions appear to increase only the risk of venous thromboembolic events (VTEs), some of the acquired conditions have been associated with both VTEs and arterial thrombosis. These include cancer, myeloproliferative syndromes, antiphospholipid antibodies (APAs), hyperhomocysteinemia, and heparin-induced thrombocytopenia ***(Deitcher, ٢٠١٠).***

Thrombosis becomes more common as age increases and its occurrence is frequently associated with risk factors such as trauma (accidental or surgical), pregnancy, malignant disease, immonobilisation or oral contraceptives. Thrombosis, however, may develop at a younger age and sometimes in the absence of an easily identifiable risk factor. Recently it has become increasingly recognised that patients who have defects or abnormalities which alter the physiological haemostatic balance in favour of fibrin formation or persistence are at increased risk of clinical thrombosis. These patients may be considered to have thrombophilia. It must, however, be realised that many patients with laboratory evidence of a thrombophilic abnormality remain clinically asymptomatic ***(Dahlbäck, ٢٠٠٨)***.

History of thrombophilia:

Egeberg in ١٩٦٥ was the first to describe a thrombophilia caused by a hereditary deficiency of antithrombin. Members of the family described in the report suffered from recurrent venous thrombosis, and the disorder was inherited in an autosomal dominant pattern. The deficiency of this naturally occurring anticoagulant protein remained the only identified cause of inherited thrombophilia for many years ***(Greer, ٢٠٠٣).***

Since the early ١٩٨٠s there has been an explosion of new knowledge, with the identification of protein C (PC) deficiency, and three years later, protein S (PS) deficiency was described as additional causes of inherited thrombophilia. However, altogether these three defects only account for less than ١٥٪ of selected cases of juvenile and/or recurrent venous thrombosis and for less than ١٠٪ of unselected cases, and this was disappointing at that time.

This situation changed dramatically in ١٩٩٣ when Dahlback and coworkers reported that venous thrombosis often is associated with hereditary resistance to activated protein C (APC) the protease generated by the thrombomodulin-PC anticoagulant pathway to inactivate activated factor V and VIII (Va and VIIIa).

APC resistance is associated with factor V Leiden which is the most frequent cause of inherited thrombophilia, accounting for ٢٠٪ to ٥٠٪ of cases ***(Greer, ٢٠٠٣).***

Mild hyperhomocysteinemia was found in ١٩٪ of patients with juvenile venous thrombosis and family studies showed that in most cases the abnormality was inherited ***(Oger et al., ٢٠٠٧).*** While the genetic lesions for deficiencies of Antithrombin III deficiency, Protein C deficiency, Protein S deficiency, and activated protein C resistance can be found in single genes encoding the defective proteins, inherited hyperhomocysteinemia may be caused by defects in several genes encoding different enzymes involved in the metabolism of the amino acid ***(Oger et al., ٢٠٠٧)***.

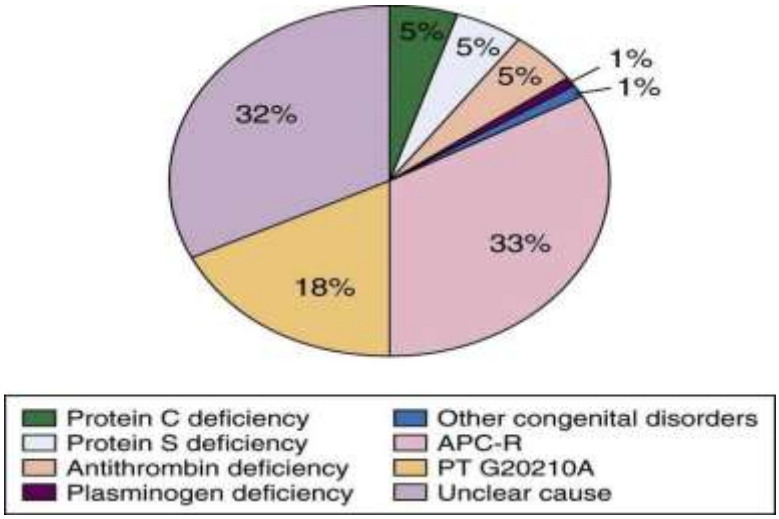

Figure (١): Results of testing for congenital hypercoagulable states. APC-R, activated protein C resistance; PT G٢٠٢١٠A, prothrombin G٢٠٢١٠A mutation ***(Deitcher et al., ٢٠٠٠).***