D-Dimer as a Predictive Marker for Recurrence Following the First Unprovoked Attack of Venous Thromboembolism

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Abstract

Definition of the optimal period for anticoagulation following the first unprovoked attack of venous thromboembolism is quite challenging. This study tried to identify a D-dimer as a possible marker for the prediction of recurrence of venous thromboembolism.

Patients and Methods: The study included 121 patients diagnosed with a first unprovoked episode of deep venous thrombosis of the lower limb and/or pulmonary embolism, and were prospectively investigated after the discontinuation of oral anticoagulant therapy. D-dimer levels in plasma were measured 1 month after stopping of the oral anticoagulant therapy. The study endpoint was the occurrence of recurrent attack of venous thromboembolism.

Results: Twenty six patients (21.7%) had recurrent VTE during an average follow up period of 12 months, 17 patients (14.2%) had elevated D-dimer level, while 9 patients (7.5%), had normal D-dimer level.

Conclusion: D-dimer measurement following the discontinuation of oral anticoagulant therapy following an attack of venous thromboembolism seems to have a good predictive value for the occurrence of recurrence, however multiple risk factors are involved, that have to be considered, and if optimized D-dimer would be a useful predictor marker.

Key Words: DVT – D-dimer – Thromboembolism.

Introduction

IN treatment of venous thromboembolism, perhaps one of the challenging problems is to define the duration of the oral anticoagulant therapy after the first unprovoked attack of deep venous thrombosis (DVT).

Although prevention of further attacks can be achieved by continuous anticoagulation, this can be both costly and inconvenient, on the other hand stopping anticoagulation carries an increased incidence of recurrence, with its clinical consequence, including early (fatal in 5% of patients) or late (post-thrombotic syndrome) complications [1].

Therefore, defining the optimal duration of anticoagulation can be challenging, as there is no conclusive evidence about the length of treatment following the first attack [2]. Both prolongation or discontinuation of the anticoagulant therapy, has risk of the occurrence of serious haemorrhagic problems that can reach 1-3% or the recurrence of DVT with subsequent mortality associated with it [3].

In patients with transient risk factors for DVT following trauma or prolonged immobilization, the recurrence rate is less than in patients with chronic risk factors as protein C and protein S deficiency. On the other hand patients with unprovoked first attack of DVT have a risk of recurrence reaching 5% during the first year, and decreasing on subsequent years [4].

Thus the use of a marker may be valuable in defining the duration required for the anticoagulant therapy required following the first event of unprovoked DVT. Several prognostic factors have been applied to predict the recurrence of DVT, including age, gender, duration of oral anticoagulant therapy (OAT), and APTT level [5,6].

Although D-dimer level have been used as a good diagnostic test for DVT [7], it may also be a valuable prognostic test for the prediction of recurrence of DVT following the discontinuation of OAT, [8].

The aim of the current study was to investigate the prognostic value of D-dimer level in the prediction of recurrence of DVT, by measuring its level 1 month after the discontinuation of oral anti-
coagulant therapy OAT, following the first attack of unprovoked DVT.

**Patients and Methods**

The current study included 121 patients from Kasr Al-Aini Teaching Hospital and Doha Clinic Hospital, Qatar, diagnosed with a first unprovoked episode of deep venous thrombosis (DVT) of the lower limb and/or pulmonary embolism, and were prospectively investigated after the discontinuation of oral anticoagulant therapy (OAT). During the period from December 2007 till October 2010. The mean age of the patients at the time of presentation with the first attack was 51 (27-71), with 78 (64.5%) females and 43 (35.5%) males.

Inclusion criteria in the current study included all patients with a first unprovoked attack of venous thromboembolism, excluding patients with transient risk factors as surgery, or permanent risk factors as patients diagnosed with cancer. Deep venous thrombosis was diagnosed by means of Ultrasonography, or in case of pulmonary embolism by perfusion-ventilation scan, or spiral CT.

In the 121 patients included in the study, deep venous thrombosis in the lower limb was found affecting the proximal deep venous system in 81 (66.9%) patients, DVT with symptomatic PE in 16 (13.2%) patients, isolated distal DVT in 22 (18.2%) and isolated Pulmonary embolism in 2 (1.7%) patients.

All patients were treated with low molecular weight heparin during the acute attack, overlapped with oral anticoagulant in the form of warfarin or marivan, that was continued for 3 months after the first attack of venous thromboembolism, aiming to keep the international normalized ratio between 2.0 to 3.0 (target being 2.5). The duration of the oral anticoagulant therapy following the diagnosis of venous thromboembolism has been subjected to many controversies, however in the current study we followed the guidelines according to the 2008 8th edition of the American College of Chest Physicians (ACCP), that recommended at least 3 months of treatment by OAT for an unprovoked DVT or PE [9].

D-dimer levels in plasma were measured 1 month after stopping of the oral anticoagulant therapy, using quantitative MDA D-dimer assay (Trinity Biotech Ltd. Co., Wicklow, Ireland) and a cutoff value of 500ng ml⁻¹, where levels above that was considered positive.

Patients were followed up for a period of 16 months and were instructed to wear elastic stockings and to report immediately any symptoms suggesting recurrence of another episode of venous thromboembolism.

Recurrence was diagnosed as the occurrence of deep venous thrombosis (DVT) or pulmonary embolism (PE). Recurrent DVT was diagnosed if the patient had thrombosis in another leg or arm affected by the previous attack, affection of another deep vein than the previously affected, or more extension of the thrombosis in the same deep vein beyond the limit that was recorded in the first attack. Pulmonary embolism was confirmed either by perfusion-ventilation scan, or spiral CT.

**Results**

The study included 121 patients, one was excluded from the study being diagnosed of having cancer, all other patients underwent treatment for VTE attack including low molecular weight heparin, followed by oral anticoagulant therapy, and attended for the D-dimer level one month following the stopping of the OAT. During the follow-up period, 4 patients left the study because they required long term anti-thrombotic therapy for other reasons than venous thromboembolism, 1 patient left the study because of cancer, 4 because of pregnancy, and 7 were lost to follow-up. 2 patients died of recurrent thromboembolism, due to pulmonary embolism. All patients were followed until they left the study, and were included in the study with the exception of the patient who was diagnosed as having cancer.

From the 120 patients with idiopathic VTE included in the current study, 26 patients (21.7%) had recurrent VTE during an average follow up period of 12 months in the period from March 2008 to November 2010.

This included the occurrence of DVT in 21 patients, 9 in the ipsilateral and 12 in the contralateral lower limb, and accompanied by pulmonary embolism in 6 patients. 5 patients had isolated Pulmonary embolism with no diagnosis of the presence of associated acute DVT.

In the 26 patients who had recurrent attack of VTE, 17 patients (14.2%) had elevated D-dimer level, while 9 patients (7.5%), had normal D-dimer level.

**Discussion**

The current study showed higher incidence of recurrence in patients with first unprovoked attack of VTE, occurring in patients with elevated D-dimer values when tested 1 month after stopping.
oral anticoagulation. These results suggested that the level of D-dimer may be used as a valuable marker to predict patients who are at higher risk of developing recurrent VTE, and help in the decision of the period of subsequent anticoagulation following the first attack.

The level of D-dimer is currently considered to be the most reliable laboratory marker for the in vivo clotting activation, that is mainly due to its role in excluding VTE in symptomatic patients [10].

In addition a previous randomized controlled trial that patients with elevated D-dimer values, that continued with OAT, had a significantly lower incidence of recurrence than patients with normal D-dimer values who had discontinued OAT, indicating that treatment decision based on the D-dimer level values may help to reduce the incidence of VTE recurrence [11].

The current study focused on D-dimer level as a predictor for recurrence of VTE in patients with previous unprovoked attack of VTE. It was found that there was a higher incidence of recurrence reaching (14.2%) in patients with elevated D-dimer level, as compared to (7.5%) in patients with normal D-dimer level, when tested 1 month after the discontinuation of the OAT.

These results were more or less similar to the results in previous studies, as in the study by Tait, et al. [12], that showed recurrence rate reaching 25.4% in patients with elevated D-dimer level, compared to 6.8% in patients with D-dimer level, and another study showing significant higher incidence of recurrence of VTE (16.6% Vs. 9.6% at 5 years) after discontinuation of OAT. It has been demonstrated by several other studies that discrimination of patients following the first attack of VTE into high and low risk of recurrence is possible by measuring the D-dimer concentrations [13,14].

The duration of anticoagulation following the first attack, doesn’t seem to affect the risk of recurrence, in fact prolongation of the anti-coagulation seems only to postpone the recurrence, until the treatment is stopped [15].

Also the time of testing the level of D-dimer level after stopping the OAT, seems to be variant across different studies. However a previous systematic review, demonstrated, that as long as the D-dimer level is measured between 3 weeks and 2 months after the discontinuation of OAT, it can be used to predict the risk of recurrence of VTE [16].

Thus the elevated levels of D-dimer is associated with an increased risk of recurrence of VTE and that may justify the resumption or even indefinite continuation of OAT [17]. Nevertheless, the decision of how long to continue on the OAT, requires balancing between the risk of recurrence of case fatality reaching about 5% [18], and the risk of bleeding with an annual risk of fatal bleeding reaching 0.2% [19]. This may require special tailoring for every patient according to his own risk factors.

As demonstrated in previous work, there are other factors that may be involved in the recurrence of VTE, as thrombophilia, shorter duration of anticoagulation following the attack [20].

As a predictive value for choosing the duration of OAT after a first necessary 3-month period, physicians should take into account the estimated individual risk for recurrent VTE. The incidence of recurrence can be evaluated through a two-step decision algorithm taking into account: (1) The baseline characteristics of the index event; and (2) The intrinsic patient’s risk at the time of OAT withdrawal [21].

At last it should be mentioned that the American College of Physicians and the American Academy of Family Physicians [22] have published a very interesting clinical practice guidelines at the end of 2010 that summarizes current approaches for treating VTE:

- LMWH should be used over UFH if possible for the initial inpatient treatment of DVT; either UFH or LMWH is acceptable for PE.
- Outpatient treatment of DVT with LMWH is safe and cost effective for carefully selected patients.
- Compression stocking should be used to prevent the PTS, beginning within 1 month of diagnosis of a proximal DVT and continued for at least 1 year after diagnosis.
- Anticoagulation should be given for 3 to 6 months for DVT or PE secondary to transient risk factors and for more than 12 months for recurrent VTE. Extended-duration therapy is advisable in patients with an idiopathic VTE.
- LMWH is safe and efficacious for the long-term treatment of VTE in select individuals and may be preferable for cancer patients.

In conclusion, measuring the D-dimer level one month after the discontinuation of anticoagulation, in patients with first unprovoked attack of VTE, seems to have a good predictive value for the occurrence of recurrence, however multiple risk
factors are involved, that have to be considered, and if optimized D-dimer would be a useful predictor marker.

References