The Role of Anticoagulant and Thrombolysis in The Management of Deep Vein Thrombosis

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Deep vein thrombosis (DVT) is a clinical challenge encountered by clinicians of all specialties. The major complication to date is thrombus embolization into the lung which can be fatal.[1] The mainstay of DVT therapy is an anticoagulant to prevent the thrombus development and recurrence. However, anticoagulant has no direct thrombolysis effect and recanalization of DVT largely depends on the effectiveness of the endogenous fibrinolytic system.[2] Many agents are developed to improve the outcome and prevent a post thrombotic syndrome (PTS). The aim of this review is to give explanation on the use of anticoagulant, especially vitamin K antagonist, warfarin and thrombolytic therapy in DVT.

The Management of DVT

The therapy of choice in DVT consist of anticoagulant, vena cava filter, thrombolytic agents and surgical thrombectomy.

Anticoagulant

Anticoagulant therapy in DVT consist of the use of heparin and oral anticoagulant. Due to an unacceptable rate of recurrent venous thromboembolic complication with the use of sole oral anticoagulation, heparin are used for 5-10 days in concomitant with oral anticoagulants.[3] Warfarin, an oral anticoagulant, needs unfractionated heparin or low-molecular-weight heparin during the first few days of warfarin therapy as a "bridge", as warfarin therapy may take up to 5 days to achieve its antithrombotic effect. This is due to the long half-life of circulating prothrombin which is 60 days.[4]

Warfarin is still an important drug with many clinical indication. In the most clinical cases, the rate of thromboembolism is reduced by the use of this vitamin K antagonist. Unfortunately, warfarin interacts with some food and many medicines. The interaction can affects an INR level, an indicator of blood anticoagulation state. Foods that contain high level of vitamin K may affect warfarin activity. Some medicines that can increase or decrease INR level are listed in table 1.

DRUG AND INTERACTION	MECHANISM OF INTERACTION
Can increase the INR	
Acetaminophen[35–37]	Unknown*
Amiodarone[38,39]	2C9 inhibition†
Cimetidine[40,41]	Enzyme inhibition
Ciprofloxacin[42]	Enzyme inhibition
Clarithromycin[43,44]	Enzyme inhibition
Clofibrate[45,46]	Enzyme inhibition
Erythromycin[47,48]	Enzyme inhibition
Fluconazole[49,50]	2C9 inhibition†
Fluvastatin[51,52]	2C9 inhibition
Fluvoxamine[53]	Enzyme inhibition
Gemfibrozil[54]	Enzyme inhibition
Isoniazid[55]	Enzyme inhibition
Itraconazole[56]	Enzyme inhibition
Ketoconazole[57]	Enzyme inhibition
Lovastatin[58]	Enzyme inhibition
Metronidazole[59]	2C9 inhibition†
NSAIDs[76,77]	Platelet inhibition‡
Propafenone[60]	Enzyme inhibition
Simvastatin[61]	Enzyme inhibition
Tamoxifen[62,63]	Enzyme inhibition
Thyroid hormones[75]	Increased vitamin K catabolism
Tramadol[64,65]	Enzyme inhibition
Trimethoprim sulfamethoxazole[66]	2C9 inhibition†
Zafirlukast[67]	2C9 inhibition

Can decrease the INR	
Barbiturates[68,69]	Enzyme induction
Carbamazepine[70]	Enzyme induction
Dicloxacillin[71]	Enzyme induction
Methimazole[75]	Decreased vitamin K catabolism
Propylthiouracil[75]	Decreased vitamin K catabolism
Rifampin[74]	Enzyme induction
Initially increase, then decrease the INR	
Phenytoin[72,73]	Protein displacement/ enzyme induction

*Lesser effect
†Greater effect
‡Only reported with certain NSAIDs and appears to be dose-related

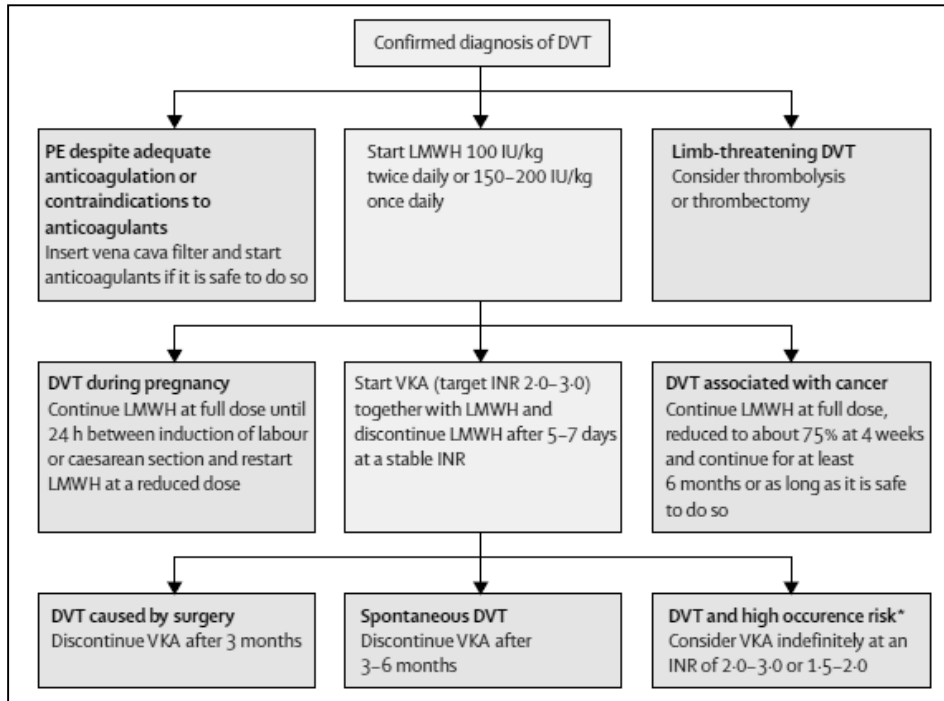Table 1. Medicines that interact with warfarin

Figure 1. Protocol therapy of deep vein thrombosis [9]

Table 2.Monitoring of INR with patients[10]

Frequency of monitoring based on INR	Duration until change of test frequency
Initially, daily for at least five days	Until the INR is in target range for **at least two** consecutive test results
Then, every three to five days	Until the INR is in target range for **at least two** consecutive test results
Then, weekly	Until the INR is in target range for **two to three** consecutive test results
Then, fortnightly	Until the INR is in target range for **two to three** consecutive test results
Thereafter	Test every four to six weeks for most patients. For patients who are very stable, it may be reasonable to extend monitoring frequency to eight weeks.

For the first five to ten days, warfarin initiation consists of the use of unfractionated heparin (UFH), low molecular weight heparin (LMWH) or pentasaccharide (fondaparinux) concurrently with warfarin. Unfractionated heparin could be given with fixed dose 1250 IU/hour or using body weight, 80 IU/kg body weight intravenous bolus and maintain with 18 IU/kg body weight per hour. Alternative use of intravenous UFH is subcutaneous UFH with fixed dose 333 IU/kg body weight dan 250 IU/kg body weight per day. Both modalities, either intravenously or subcutaneously, has already been tested in 972 patients and subcutaneous UFH has comparable efectivity and safety as compare with UFH intravenous.[7]

The American College of Chest Physician (ACCP) recommends warfarin therapy in the first day dan titrated to achieve target INR >2.[8] The length of anticoagulant therapy is based on the clinical disease. Figure 1 shows anticoagulant duration for DVT.

Hemorrhage is still the major concern of oral anticoagulant therapy and warfarin poses this risk.[5] In many clinical studies, treatment with warfarin increases the risk of major bleeding by 0.3-0.5% per year and the risk of intracranial hemorrhage approxiamately 0.2% per year compared to controls. Risk of major bleeding in warfarin use can be lowered with strict monitoring. There is a need to outweigh the risk of bleeding and the benefit of the therapy. Phrotrombin time (PT) or *International Normalized Ratio* (INR) are used to monitor warfarin level. The target of INR in patient using warfarin is 2-3 and this value causes less risk of bleeding as compare to the target of INR > 3.[6] Table 2 show the frequency of monitoring in warfarin initiation.

With the use of optimal anticoagulant, repeated venography in six month after DVT therapy in femoral vein and other distal veins shows complete lysis in 38% patients, partial resolution in 54% and propagation in 7%.[11] Moreover, in 1 year after therapy, vein abnormalities using compression ultrasonography were found in 50% patients.[11] Despite anticoagulation, inflammatory reaction may develop within 7-10 days after acute onset of disease. Infiltration of fibroblast and neovascularization will damage the venous valve and cause post thrombotic syndrome (PTS). Post thrombotic syndrome is caused by chronic venous hypertension secondary to venous reflux, venous obstruction and valvular dysfunction. It is estimated that 80% patients with DVT may go on to develop symptoms of PTS while 4-15% progress to leg ulceration.[12] It is believed that rapid recanalization in DVT could prevent the development of PTS.[2] However, studied showed that anticoagulant has no direct thrombolysis effect and recanalization on DVT largely depends on the effectiveness of the endogenous fibrinolytic system.[2] Researchers began to look for agents that could do rapid recanalization in DVT to prevent complication and reccurence.

Thrombolytic Agents

Randomized trials have consistently shown that thrombolytic therapy rapidly resolves thromboembolic obstruction and exerts beneficial effects on haemodynamic parameters. Regimens that are approved are streptokinase, urokinase and rtPA. Approxiamately 94% of patients can be classified based on clinical and echocardiographic improvement within the first 36 hours. The greatest benefit is observed when treatment is initiated within 48 hours of symptom onset, but thrombolysis can still be useful in patients who had symptoms for 6-14 days.[13]

Thrombolytic therapy poses significant risk of bleeding with overall bleeding rate is 13% and 1.8% major bleeding and intracranial hemorrhage.[13] However, even with the increase risk of bleeding, there come the greater benefit of rapid recanalization. The earliest trial in thrombolytic therapy was conducted by Robertson et al. in 1968 that compare streptokinase vs. heparin in 16 DVT subjects. In this trial, there were significant lysis of thrombus in streptokinase group (63%) compared to in heparin group (12%). Risk of bleeding also increased in streptokinase group (25%) compared to in heparin group (12%). In

Cochrane Analysis consisted of 12 studies and 701 subjects overall, relative risks for major bleeding is 1.7 (95% CI, 1.04 to 2.9; 668 subjects in 10 studies) and significant intracranial hemorrhage 1.7 (95% CI, 0.2 to 14; 701 subjects in 5 studies) in thrombolytic group.[10] However, looking at the balance between benefit of rapid recanalization and risk of bleeding, in some patients the benefit of rapid recanalization outweigh the risk of bleeding.

Catheter directed thrombolysis (CDT) is a method to introduce plasminogen activator agents directly into the thrombus. This method is more efficient because it causes local thrombolysis and improves venous patency, and at the same time reduces the risk in systemically used thrombolysis.[12] In the study comparing thrombolytic given systemically and CDT, valvular competence is preserved in 44% of patients using CDT vs. 13% patients using systemic thrombolysis (p=0.049).[14] Most CDT associated complications are local and systemic hemorrhage. CDT related bleeding is 5-11% and higher rates are associated with prolonged infusion time and high doses of thrombolytic agents used.[12]

American College of Physician suggests the use of CDT in selected patients whose life expectancy are > 1 year, good functional status, extensive illiofemoral thrombosis and presenting soon after the onset of symptoms (<14 days) (level 2B evidence). This proposition is based on small RCTs, registry data, institusional series and variety of expert opinions.[15]

Conclusion

Anticoagulant and thrombolytic are two of the modalities use in the management of DVT. Anticoagulant is the mainstay therapy of DVT, but the risk of valve incompetency due to slowly resolving thrombus is high. This could lead to reccurence of DVT and PTS. Thrombolytic is an agent that conveys rapid recanalization to prevent complication of DVT. However the use of thrombolytic agent poses greater risk of bleeding and since the evidence of thrombolysis is based on small RCTs, this therapy is only reserved for selected patients.

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