Managing deep vein thrombosis and thrombophlebitis

The first part of this article (published December 2010) reviewed the clinical features and differential diagnosis of superficial thrombophlebitis and deep vein thrombosis. This second part discusses how these conditions are managed.

Dr Nabil Aly Consultant Physician, DME, University Hospital Aintree, Lower Lane, Liverpool L9 7AL
email nmaly@doctors.org.uk

Superficial thrombophlebitis and deep vein thrombosis (DVT) are common peripheral venous conditions. They share some clinical features and risk factors, but it is important to differentiate between the two disorders because they are managed differently. As part one of this article discussed, noninvasive studies, such as D-dimer testing, are the diagnostic tests of choice when evaluating patients with suspected DVT. This second part of the article will review management options for both conditions.

Thrombophlebitis

The treatment of thrombophlebitis is aimed at improving patient comfort and preventing superficial thrombophlebitis from progressing to involve the deep veins; damage to deep vein valves leads to chronic deep venous insufficiency (often referred to as postphlebitic syndrome) as well as to recurrent pulmonary embolism (PE) and an increased risk of death. Non-steroidal anti-inflammatory drugs (NSAIDs), low-molecular weight heparin (LMWH) and antibiotics should be considered in these patients. However as infection is not usually the cause of thrombophlebitis, antibiotic use is unnecessary in most patients; therefore, drug treatment should be limited to anti-inflammatory analgesics.[1]

NSAIDs

Along with LMWH, NSAIDs are the first-line treatment to resolve symptoms and prevent extension of thromboembolism. They have a similar efficacy to LMHW in reducing the risk of extension of superficial thrombophlebitis into the deep venous system and are often more practical and more easily administered than LMHW.[2]

Anticoagulation

Heparin is essential for patients with superficial thrombophlebitis that is progressive and for those patients with particular risk factors for progression or recurrence, particularly in thrombophlebitis involving the greater saphenous vein. Heparin works by activating antithrombin III to slow or prevent the progression of venous thrombosis, but it does not dissolve existing clots. Fractionated LMWH has largely replaced unfractionated heparin as it offers several distinct advantages, and it is associated with a lower risk of bleeding.[2]

Anticoagulation with LMWH is better than unfractionated heparin at reducing local signs and symptoms, along with reducing propagation to a DVT.[2] Additionally, it is useful in preventing the progression of thrombosis and is recommended when there is evidence for DVT.

Antibiotics

Antibiotics are not routinely indicated for the treatment of superficial thrombophlebitis, as the erythema and tenderness represent a local inflammatory reaction; thus, they are neither an infection nor an allergic reaction. However, if suppurative thrombophlebitis might be present, then antibiotics should cover both skin flora and anaerobic organisms, especially if an abscess is present.

Local thrombolytic agents

No adequate studies have been performed on the use of local thrombolytics; therefore, their use is not recommended.

Other therapies

There are several non-pharmacological therapies that can be used for the management of thrombophlebitis:

- Continued ambulation is important to limit venous stasis and reduce the progression of thrombosis. Recognised causes of venous stasis, such as air travel or extended bed rest, are not recommended in patients with thrombophlebitis of any type. Guidelines from the American College of Chest Physicians, the Institute for Clinical Systems Improvement, and the Scottish Intercollegiate Guidelines Network (SIGN) support ambulation for all patients if possible[3–5]
- Warm compresses: these are indicated for symptomatic relief. Care should be taken to avoid hot compresses that can lead to skin burning
- Compression stockings: a gradient compression stocking is an often-overlooked adjunctive therapy that is both benign and effective. Gradient compression hose are highly elastic stockings that provide a gradient of compression that is highest at the toes (at least 30–40 mmHg) and gradually decreases to the level of the thigh. This amount of compression reduces capacitive venous volume by approximately 70% and increases the measured velocity of blood flow in the deep veins by a factor of five or more.[6] Stockings also have been shown to increase local and regional intrinsic fibrinolytic activity.[6]

Surgical treatment

Data suggest that surgery may be beneficial with regard to local recurrence and extension of thrombosis, allowing for superior symptomatic relief from pain. It should be reserved for those who are poor candidates for NSAID and LMWH therapy, or for those who have recurrent thrombophlebitis.[6]

DVT

The goals of pharmacotherapy in venous thrombosis are to reduce morbidity, to prevent PE, and to prevent the postphlebitic syndrome, while causing the minimal amount of adverse effects and cost. Most of the current guidelines recommend short-term anticoagulation with subcutaneous LMWH or unfractionated heparin (intravenously) followed by oral anticoagulation. A vitamin K antagonist such as warfarin should be initiated together with LMWH or unfractionated heparin on the first day of treatment.[3]

Initial treatment with LMWH or unfractionated heparin should continue for at least five days and until the international normalised ratio (INR) is >2 for 24 hours.[7] Administration of unfractionated/fractionated heparin followed by oral administration of warfarin remains the mainstay of treatment for DVT. SIGN stated that following initial heparinisation in patients with DVT or PE, maintenance of anticoagulation with oral anticoagulants is recommended in non-pregnant patients.[4]

The intensity and duration of warfarin therapy depends on the individual patient, but treatment of at least three months is usually required and some patients with thrombophilias, such as antiphospholipid syndrome, require lifetime anticoagulation.[7]

Despite the lower (but not zero) risk of PE and mortality associated with calf vein DVT, most guidelines (such as those from the American College of Chest Physicians) recommend short-term anticoagulation for three months in symptomatic patients.[3] Asymptomatic patients with isolated calf vein DVT may not require anticoagulation, and surveillance ultrasound studies over 10–14 days to detect proximal extension is recommended instead.[3] Patients with cancer have a particularly higher rate of DVT recurrence than non-cancer patients and long-term therapy for DVT is strongly recommended by various clinical guidelines, including the one produced by the National Comprehensive Cancer Network (NCCN).[8]

Recent studies have shown that LMWH therapy in patients with DVT is associated with a lower rate of venous thromboembolism (VTE) without an increased risk of bleeding compared with oral anti-coagulation.[9] Reports

also describe that the LMWH compounds may decrease the all-cause mortality rate. Therefore, it is recommended that LMWH therapy is used alone without crossover to warfarin, if it is feasible. For example, in patients at high risk of falling who require short-term anticoagulation following an acute episode of DVT.[9]

Anticoagulation

Anticoagulation remains the mainstay of the initial treatment for DVT. Regular unfractionated heparin was the standard of care until the introduction of LMWH products.

Heparin prevents extension of the thrombus and has been shown to significantly reduce (but not eliminate) the incidence of fatal and non-fatal PE as well as recurrent thrombosis. The primary reason for the persistent, albeit reduced, risk of PE is primarily due to the fact that heparin has no effect on pre-existing non-adherent thrombus, does not affect the size of existing thrombus and has no intrinsic thrombolytic activity.[3]

Heparin therapy is associated with complete lysis in fewer than 10% of patients studied with venography after treatment.[3] It has little effect on the risk of developing postphlebitic syndrome. The original thrombus causes venous valvular incompetence and altered venous return, leading to a high incidence of chronic venous insufficiency and postphlebitic syndrome.

The anticoagulant effect of heparin is directly related to its activation of antithrombin III. Antithrombin III, the body's primary anticoagulant, inactivates thrombin and inhibits the activity of activated factor X in the coagulation process. Unfractionated heparin is given as 80 U/kg IV bolus, followed by 18 U/kg/h maintenance infusion.

LMWH is prepared by selectively treating unfractionated heparin to isolate the low-molecular-weight (<9,000 Da) fragments. Its activity is measured in units of factor X inactivation, and monitoring of the activated partial thromboplastin (aPTT) is not required. The dose is weight adjusted and, like unfractionated heparin, LMW heparin is given in combination with warfarin for four to five days.[7] Compared with unfractionated heparin, it offers distinct advantages: it has a longer biologic half-life, it can be administered subcutaneously once or twice daily, dosing is fixed, and laboratory monitoring is not required. In addition, some adverse effects of unfractionated heparin, such as thrombocytopenia, appear to be less likely.[7] The efficacy and safety of LMWH for the initial treatment of DVT have been well established in several trials. In a systematic meta-analysis, Mismetti and colleagues[10] found that enoxaparin 1 mg/kg twice daily was non-inferior to unfractionated heparin in the treatment of DVT with or without a coexisting PE. Although not statistically significant, a trend favouring enoxaparin over unfractionated heparin was also observed in the incidence of major bleeding and all-cause mortality at three months.

Wells et al compared tinzaparin (the only LMWH to have demonstrated statistical superiority to unfractionated heparin in the prevention of DVT recurrence[11]) with dalteparin. The combined event rates were 4·8% and 5·4% for dalteparin and tinzaparin, respectively, and tinzaparin was not found to be superior to dalteparin. Both therapies provided safe and efficacious outpatient treatment of acute DVT and PE.[11]

Warfarin therapy is overlapped with heparin for four to five days until the INR is therapeutically elevated to 2–3.[7] Heparin must be overlapped with oral warfarin because of the initial transient hypercoagulable state induced by warfarin, which is related to the differential half-lives of protein C, protein S, and the vitamin K–dependent clotting factors II, VII, IX, and X. Long-term anticoagulation is definitely indicated for patients with recurrent venous thrombosis and/or persistent or irreversible risk factors.

The optimal duration of anticoagulation for a first episode of unprovoked VTE or lower extremity DVT is uncertain. At least six months of anticoagulation has been recommended because of presumed higher rates of recurrence with shorter durations of treatment.[12] However, recent randomised trials indicate that the duration of anticoagulation seems to have little effect on the rate of disease recurrence in patients with unprovoked VTE.[12]

Methods for predicting risk for recurrence, such as D-dimer assay around the time of stopping anticoagulation, may identify low-risk patients who are less likely to benefit from

prolonged anticoagulation.[12] Pooled data from seven studies showed that patients with a high concentration or positive D-dimer assay three weeks to two months after stopping their anticoagulation were twice as likely to have another thromboembolic event than those with a low concentration or a negative result (incidence rate ratio 2·2, 95% CI 1·65 to 2·94).[12]

There is uncertainty regarding thrombolytic therapy in DVT. Thrombolytic therapy is more effective than heparin in achieving vein patency and offers significant advantages over conventional anticoagulant therapy, including: the prompt resolution of symptoms; prevention of PE; restoration of normal venous circulation; preservation of venous valvular function; and the prevention of postphlebitic syndrome.[13] However, it does not prevent clot propagation, re-thrombosis, or subsequent embolisation, and haemorrhagic complications are significant. In addition, thrombolytic therapy is not effective once the thrombus is adherent and begins to organise and anticoagulant therapy must always follow a course of thrombolysis. Catheter-directed intra-thrombus thrombolysis (CDT) is an image-guided therapy where a thrombolytic agent is administered directly into the thrombus and enhances thrombus removal. It could be considered as a therapeutic option in carefully selected patients with acute iliofemoral deep vein thrombosis.[13]

Inferior vena cava filters

The concept of inferior vena cava filters arose from the recognition of the late complications of surgical ligation of the inferior vena cava. The use of an inferior vena cava filter occasionally was indicated when PE recurred despite anticoagulation or there were contraindications to such treatment. These "permanent" filters were inserted transvenously under simple local anaesthesia. Evidence from a single clinical trial showed added benefit from the use of a filter in patients who were receiving anticoagulation.[7] An ideal filter should maintain caval patency, trap emboli, preserve prograde caval blood flow, avoid stasis, and enhance thrombolysis of trapped emboli. It should also achieve a long-term patency rate with very low incidence of recurrent PE.[14]

The Decousus study randomised 400 patients with proximal DVT to filter or no filter groups and both were anticoagulated with unfractionated heparin.[12] It showed a statistically significant reduction of PE in the filter group after 12 days (1·1% versus 4·8%, P=0·03), but this disappeared at two years (3·4% versus 6·3%. P=0·16). The incidence of later DVT was significantly higher in the filter group (21% versus 12%, P=0·02).[15]

These results triggered the development and introduction of "temporary" (optionally retrievable) filters that provide temporary prophylaxis for PE yet avoid the longer-term risk of later DVT.[16] General indications for filter placement may include severe haemorrhagic complications on anticoagulant therapy or other absolute contraindications to anticoagulation; and failure of anticoagulant therapy, such as new or recurrent venous thrombosis or PE, despite adequate anticoagulation.

Compression stockings

The postphlebitic syndrome affects approximately 50% of patients with DVT after two years, particularly among older patients and patients with recurrent ipsilateral DVT.[17] A randomised controlled study to evaluate the efficacy of graduated below-the-knee elastic compression stockings in the prevention of the postphlebitic syndrome strongly recommended the early use and widespread implementation of these stockings with adequate anticoagulant therapy for symptomatic proximal DVT.[17]

Exercise and ambulation

The controversy regarding the role of ambulation in the therapy of DVT still exists. The unsubstantiated fear of dislodging clots by ambulation led clinicians to recommend bed rest and leg elevation to their patients.[18] However, bed rest promotes venous stasis, which is a major risk factor for DVT and, therefore, may actually enhance thrombus propagation and the risk of subsequent PE.[15] A systematic review found that in patients treated for acute DVT, early walking exercise is safe and may help to reduce acute symptoms and that in patients with previous DVT, exercise training does not increase leg symptoms acutely and may help to prevent or improve the postphlebitic syndrome.[18,19]

Prevention

Most hospital inpatients are at risk of DVT and the associated complications of fatal or non-fatal PE and postphlebitic syndrome. Recognised risk factors for DVT are generally related to one or more elements of Virchow's triad (stasis, vessel injury, and hypercoagulability), and include surgery, trauma, immobilisation, malignancy, use of oestrogens, heart or respiratory failure, and smoking.[20]

Surveillance studies have found that the absolute risk of DVT is 10%–20% among general medical patients, 15–40% among general surgical patients, and up to 40%–80% in patients having hip surgery, knee surgery, or major trauma.[20] The postoperative risk of PE can be as high as 5% in the highest risk groups. However, many patients are probably not currently receiving adequate prophylactic measures.[21] Appropriate use of prophylaxis against DVT in hospital inpatients is important for reducing the risk of fatal and non-fatal PE and postphlebitic complications.

For patients at low risk of DVT, ambulation is important, and mechanical methods of prophylaxis (such as graduated compression stockings and intermittent pneumatic compression devices) can provide added protection.[22] Graded elastic compression stockings have been associated with a 50% reduction in the incidence of postphlebitic syndrome.[23] Patients at higher risk of DVT should be considered for guideline-based anticoagulation with LMWH, unfractionated heparin, or vitamin K antagonists unless clearly contraindicated.

Limitations associated with warfarin and heparin, such as reduced ability to inactivate thrombin already bound to fibrin and factor Xa within a thrombus, have led to development of new anticoagulants targeting different sites in the coagulation cascade. Several newer anticoagulants are under clinical development. The direct thrombin inhibitors, in contrast to heparin, can inactivate fibrin-bound thrombin.[24] A direct thrombin inhibitor, dabigatran, has been evaluated in clinical studies for prophylaxis in atrial fibrillation. Factor Xa inhibitors, direct (rivaroxaban) as well as indirect inhibitors, are in various stages of development for their antithrombotic effect.

In addition to being administered orally, the newer anticoagulant agents have a more balanced benefit/risk ratio and wider therapeutic window; they have a rapid onset of action; a predictable anticoagulant effect that does not require routine laboratory monitoring; they have minor food and drug interactions, including those with cytochrome P450; and they are highly specific and targeted to a single coagulation factor, and could carry similar or less haemorrhagic risks compared with the older anticoagulant agents. They may also be used in a broader variety of patients, especially the medically ill patients with advanced cancer, and the elderly without any dosage adjustment, regardless of the patient's age, gender, body weight, or in patients with mild renal impairment. Their use in the general world will hopefully confirm the promising results of clinical trials.[25]

The role of aspirin in DVT prophylaxis remains controversial.[4] SIGN advocates aspirin as an effective prophylaxis in surgical patients because of its efficacy in reducing fatal pulmonary embolism.[4] Fondaparinux (a selective factor Xa inhibitor) may provide additional prophylactic options.[4]

The National Institute for Health and Clinical Excellence (NICE) published clinical guidance (CG 92) in March last year,[26] which updates and replaces its previous guidance on the prevention of venous thromboembolism. It now recommends fondaparinux sodium among the agents that can be used for the prevention of this condition.

Complications

For thrombophlebitis, it could be conversion to suppurative thrombophlebitis or extension into deep venous system. Rarely, it could lead to septicaemia and/or septic emboli. Venous ulceration and venous insufficiency of the lower leg, which are long-term complications of DVT affect 0·5% of the entire US population.[5] Extrapolation of this data reveals that as many as five million people have venous stasis and varying degrees of venous insufficiency. The principal long-term morbidity from DVT is the postphlebitic syndrome, which

complicates about a quarter of cases of symptomatic proximal DVT; most cases develop within two years afterward.

Prognosis

The prognosis for superficial thrombophlebitis is generally good. Although not common, superficial thrombophlebitis can progress through perforating veins to involve adjacent deep veins. Therefore, it is not surprising that in people with a diagnosis of superficial thrombophlebitis, the incidence of associated DVT and PE is high.[27]

DVT and its sequel, PE, are among the leading causes of preventable in-hospital mortality. Massive PE resulting from DVT, may cause as many as 300,000 deaths annually in the US.[27] The Longitudinal Investigation of Thromboembolism Etiology (LITE) study determined the incidence of symptomatic DVT and PE in 21,680 participants aged >45 years who were followed for 7·6 years.[28] The age-standardised incidence of first-time VTE is 1·92 per 1000 person-years; the incidence of VTE was higher in men than in women and increased with age in both sexes. Most of the 191 cases of secondary VTE were associated with more than one underlying condition. These included cancer (48%), hospitalisation (52%), surgery (42%), and major trauma (6%). No antecedent trauma, surgery, immobilisation, or diagnosis of cancer was noted in 48% of cases.

In general, mortality from venous thromboembolic disease has decreased significantly in the past 10 to 20 years.[29] In addition, increased survival may be due to better diagnostic strategies, improved recognition of risk factors, and better treatment guidelines.[5]

Conclusion

Administration of unfractionated or fractionated heparin followed by oral administration of warfarin remains the mainstay of treatment for DVT. The optimal duration of oral anticoagulant therapy in patients with DVT of the lower extremities remains uncertain. For superficial thrombophlebitis, the treatment is aimed at patient comfort and preventing superficial phlebitis from progressing to involve the deep veins.

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