Venous thromboembolism: risks and prevention

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Venous thromboembolism (VTE) is a major cause of morbidity and mortality in both hospital and community settings causing an estimated 60 000 deaths a year in the UK. Within this population up to 25 000 are potentially preventable with implementation of VTE prevention strategies. This was recognized in a Health Select Committee report in 2005, which identified that VTE prophylaxis was not being effectively implemented in the UK.1 This was also more recently supported by data published in an international audit of risk assessment and thromboprophylaxis prevention.2 Two influential reports followed in 2007 addressing this issue, both recommended that on admission to hospital all adults should have a VTE risk assessment that is formally documented and appropriate prophylaxis prescribed and instituted.3–5 The initial document published by the National Institute for Clinical Excellence (NICE) focused on surgical inpatients, but this has been recently superseded and now provides guidance for all acute hospital admissions. It also includes guidance for certain high-risk outpatient populations, including during pregnancy and those with lower limb plaster casts. These reports have formed the basis of the National Venous Thromboembolism Prevention Programme in England which continues to raise awareness among professionals and the public of VTE prevention. This has coincided with other patient group information campaigns which are empowering individuals to question their own management of this potentially life-threatening condition.

What is the relevance to anaesthetists? As part of the clinical team, anaesthetists have a responsibility to check that appropriate thromboprophylaxis has been prescribed for every patient. This was reinforced in recent medical case law when the anaesthetic team was found partially culpable for a venous thromboembolic event in a patient who had not been prescribed adequate thromboprophylaxis.6 Recognition that all members of the clinical and nursing team have a responsibility to provide appropriate prophylaxis should ensure this is considered in all patients.

Prevalence and risk factors

The exact prevalence of venous thrombosis is unknown. Clinical signs and symptoms are non-specific, only occurring in up to 50% of patients while sensitivity and specificity of screening tests to detect disease in asymptomatic patients is low. Population studies have suggested that the overall age- and gender-adjusted annual incidence of deep vein thrombosis (DVT) formation in the general population is 0.5–1 per 1000. However, this figure increases up to an estimated one in four hospitalized patients who possess one or more of the risk factors described below, but which often remain clinically silent. The majority of DVTs are related to specific identifiable trigger factors such as hospitalization, malignancy, major trauma, and prolonged immobility. An underlying predisposition, present as either a genetic or acquired factor in combination with a triggering event, then leads to the development of a DVT. The most serious, potentially life-threatening complication is a pulmonary embolus (PE) and occurs in about a third of those with an identified DVT. A similar number will also suffer from chronic post-thrombotic leg syndrome typified by symptoms with leg pain, swelling, and skin ulceration.

Venous thrombosis occurs when red blood cells, fibrin and, to a lesser extent, platelets, and leucocytes form a mass within an intact vein. Historically, a consensus view proposed a triad of factors that cause thrombosis: alterations in blood flow (stasis and turbulence), vascular endothelial injury, or alterations in the blood coagulability. These components are commonly described as Virchow’s triad named after a German pathologist Rudolf Virchow.
Table 1 provides a summary of recognized risk factors. There is good evidence demonstrating previous VTE, some thrombophilias, malignancy, varicose veins, oestrogen containing oral contraceptive pill, obesity, and increasing age are significant risk factors.

Pathophysiology of deep venous thrombosis

Venous thrombi typically develop at a site of vascular trauma, around intravascular catheters, in areas of sluggish blood flow or in both, such as valve cusps, the venous sinuses of the pelvis and calf, the superior vena cava, upper extremity veins, portal venous system, and right chambers of the heart. Accumulation of fibrin and platelets causes rapid growth in the direction of blood flow, potentially reducing venous return. Endogenous fibrinolysis results in partial or complete resolution of the thrombus; however, any residual thrombus will organize and may result in incomplete recanalization of the vein potentially narrowing the lumen and causing valve incompetence. An extensive collateral network may then develop, giving rise to a more chronic syndrome.

Risk assessment and prevention

Identification of at risk patients before or on admission to hospital, or in the outpatient setting, is key to initiating appropriate preventative treatment (Tables 2 and 3). A robust risk assessment process should be adopted for all elective and emergency patient admissions. This is likely to involve a multidisciplinary approach from the preoperative assessment clinic to ward assessment and involve nursing staff and clinicians depending on particular patient pathways. Appropriate thromboprophylaxis would then be initiated by following one of a number of evidenced-based, nationally recognized guidelines, including guidance from NICE. As part of the NICE guidance, a simplified risk assessment document and care pathway have been included. This is designed to replace other more complicated risk assessments and scoring systems that are available. Risk assessment of a hospitalized patient is based on patient-related factors and reason for admission (procedural risk). The decision to use thromboprophylaxis will then depend on the absolute thrombosis risk and subsequent choice of method will be determined by the thrombosis and bleeding risks, targeting the at risk groups. There is disagreement about optimum pharmacological prevention, because of potential bleeding and infection risks. This article, therefore, aims to present the current range of potential interventions that can be used to minimize VTE risk in individual patients.

Mechanical methods

Anti-embolism stockings

Anti-embolism stockings (AES) exert graded circumferential pressure from distal to proximal regions of the leg conforming to a Sigel pressure profile. These increase blood velocity, promote venous return, and have been shown to be effective. AES should not be used if the patient has peripheral vascular disease, arteriosclerosis, severe peripheral neuropathy, massive leg oedema or pulmonary oedema, oedema secondary to congestive cardiac failure or local skin/soft tissue diseases, and in patients with acute stroke. Thigh length stockings may be considered preferable as more effective but current evidence is poor; however, if these are not suitable because of compliance or fit, knee length versions should be used.

Intermittent pneumatic compression

Intermittent pneumatic compression periodically compresses the calf and or thigh muscles with inflation pressures of 35–40 mm Hg at a rate of about 10 beats min⁻¹. They mimic the muscle pump effect of walking, promote fibrinolysis, and have been shown to reduce VTE risk.

Foot impulse devices

Foot impulse devices (or foot pumps) increase venous outflow and reduce stasis in immobilized patients. They are designed to mimic normal walking by compressing the plantar venous plexus producing a pulsatile flow in the veins. These have been shown to be...
effective after orthopaedic surgery in reducing asymptomatic DVT. There is no evidence that they reduce risk of symptomatic DVT.

Pharmacological methods

Pharmacological prevention involves perioperative administration of anticoagulant drugs. The agents relevant to UK practice currently are unfractionated heparin, low-molecular-weight heparins (LMWHs), oral Direct Factor Xa inhibitors, warfarin, aspirin, danaparoid, fondaparinux, lepirudin, and dextran.

Unfractionated heparin

Heparin is a naturally occurring anticoagulant derived mainly from porcine intestine or bovine lung. It is a large polysaccharide varying in size from 5 to 40 kDa. It binds to endogenous antithrombin, producing a complex that inhibits activated coagulation factors, including factors Xa and IIa (thrombin). Unfractionated heparin is effective in VTE prevention; however, subcutaneous administration is less predictable than LMWH. It does have an easily measurable mode of action, is reversible, and may be preferred in patients with renal failure (estimated glomerular filtration rate <30 ml min$^{-1}$ 1.73 m$^{-2}$). For most patients, it is inconvenient to deliver, may induce greater bleeding risks when compared with LMWH, and may cause the rare complication of heparin-induced thrombocytopenia (HIT). Unfractionated heparin is delivered as a twice or three times per day subcutaneous injection. The anticoagulant effect of heparin is measured using the activated partial thromboplastin time (aPPT). This not required for prophylactic heparin use; however, because of the risks of HIT, platelets should be monitored intermittently up to Day 14 of administration.

Low-molecular-weight heparins

LMWHs are made from short-chain polysaccharides with a molecular weight <8 kDa. They have a similar mode of action to unfractionated heparin, but a more predictable dose–response with primarily anti-factor-Xa activity and only limited anti-IIa activity. A range of products are obtained by various methods of fractionation or depolymerization of heparin which include enoxaparin, daltaparin, and tinzaparin, which give varying chemical, physical, and biological properties. LMWHs are more effective at reducing the risk of both DVT and PE with a lower risk of bleeding, HIT, and osteoporosis than unfractionated heparin. LMWHs are cleared by the kidneys and should be used with caution in severe renal failure. Doses of LMWHs depend on the formulation but all are delivered as a once daily subcutaneous injection. LMWHs require no laboratory monitoring although an anti-Xa assay can be used if drug accumulation is suspected in cases of severe renal failure. Platelets should be monitored because of the risks of HIT as with unfractionated heparin.

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**Table 2 Comparison of pharmacological thromboprophylaxis**

<table>
<thead>
<tr>
<th>Pharmacological</th>
<th>Effector site</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>Inhibits factor Xa and thrombin</td>
<td>Reversible, measurable effect</td>
<td>Bleeding, HIT, osteoporosis</td>
</tr>
<tr>
<td>LMWH</td>
<td>Predominantly inhibits factor Xa (some effect on thrombin)</td>
<td>Predictable, lower risk of major bleeding</td>
<td>Bleeding, low incidence of HIT</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Inhibits vitamin K dependent factors (II, VII, IX and X)</td>
<td>Oral, single daily dose</td>
<td>Bleeding, unpredictable effect, multiple INR checks, slower to reach therapeutic range</td>
</tr>
<tr>
<td>Direct factor Xa inhibitors</td>
<td>Inhibits factor Xa</td>
<td>Oral, single daily dose</td>
<td>Limited licensed use, bleeding concerns</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Inhibits COX-1 → TXA2 production</td>
<td>No association with HIT</td>
<td>Efficacy for VTE prophylaxis</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>Inhibits factor Xa</td>
<td>Very low incidence of HIT</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Inhibits factor Xa</td>
<td>Prophylaxis for suspected or confirmed HIT</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>Direct thrombin inhibitor</td>
<td>Lower bleeding risk</td>
<td>Delivered as an infusion, bleeding</td>
</tr>
<tr>
<td>Dextran</td>
<td>Reduces adhesiveness of RBC and platelets</td>
<td>Enhances antithrombin</td>
<td>Fluid overload, interferes with blood cross matching, hypersensitivity reactions</td>
</tr>
</tbody>
</table>

**Table 3 Comparison of pharmacological dosing and monitoring requirements**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose frequency</th>
<th>Route</th>
<th>Laboratory monitoring</th>
<th>Therapeutic range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>BD/TDS</td>
<td>SC</td>
<td>aPPT and platelets</td>
<td>N/A</td>
<td>Anticoagulant monitoring not routine</td>
</tr>
<tr>
<td>LMWH</td>
<td>OD</td>
<td>SC</td>
<td>Anti-Xa assay and platelets</td>
<td>N/A</td>
<td>Anticoagulant monitoring not routine</td>
</tr>
<tr>
<td>Warfarin</td>
<td>OD</td>
<td>PO</td>
<td>International Normalised Ratio</td>
<td>1.3–1.5</td>
<td>Every 3 days until stable then weekly</td>
</tr>
<tr>
<td>Direct factor Xa inhibitors</td>
<td>OD</td>
<td>PO</td>
<td>Prothrombin Time</td>
<td>N/A</td>
<td>Anticoagulant monitoring not routine</td>
</tr>
<tr>
<td>Aspirin</td>
<td>OD</td>
<td>PO</td>
<td>N/A</td>
<td>N/A</td>
<td>Not recommended for VTE prophylaxis</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>BD</td>
<td>SC</td>
<td>Anti-Xa assay and platelets</td>
<td>N/A</td>
<td>Anticoagulant monitoring not routine</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>OD</td>
<td>SC</td>
<td>Anti-Xa assay</td>
<td>N/A</td>
<td>Anticoagulant monitoring not routine</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>Infusion</td>
<td>IV</td>
<td>aPPT</td>
<td>2.0–3.0</td>
<td>Use if HIT suspected or confirmed</td>
</tr>
<tr>
<td>Dextran</td>
<td>Infusion intraoperatively</td>
<td>IV</td>
<td>N/A</td>
<td>N/A</td>
<td>Not recommended for VTE prophylaxis</td>
</tr>
</tbody>
</table>
**Warfarin**
Warfarin inhibits the production of the vitamin K-dependent coagulation factors II, VII, IX, and X in the liver. Warfarin should be administered at a dose that minimizes the hazards of bleeding and its effects should be monitored using the INR. Evidence is variable when comparing its VTE and PE prevention effects with LMWH, although major differences in bleeding risks have not been determined. Warfarin is delivered as a single oral daily dose, which is its main advantage, aiming for an INR of 1.3–1.5. Disadvantages with its use include an unpredictable effect on coagulation, delay in reaching therapeutic effect and potential drug interactions. Monitoring is therefore required every 3 days until stable and then weekly.

**Direct factor Xa inhibitors**
The first oral direct acting factor Xa inhibitors, Rivaroxaban and Dabigatran, have recently been manufactured offering a single daily dosing avoiding the need for the alternative parenteral preparations. They have no effect on prothrombin or platelet function. They are currently licensed in the UK for use in VTE prevention in primary hip and knee arthroplasty. The anticoagulant effects can be measured using the prothrombin time (PT) although routine monitoring is not required. Initial studies have suggested superior thromboprophylaxis to LMWH with similar bleeding risks. Aspirin

**Aspirin**
Aspirin is a salicylate which irreversibly inhibits cycloxygenase 1 (COX-1), thereby preventing thromboxane A2 production, which has an important role in platelet aggregation. Aspirin reduces the risk of DVT and PE compared with no prophylaxis though its effect is significantly less than heparin, with a similar increase in risk of major bleeding. The optimal dose has not been determined and on its own is insufficient for adequate VTE prophylaxis. Aspirin is used as a single daily oral dose of 75–300 mg; however, it is not recommended in any of the recent major international thromboprophylaxis guidelines.

**Danaparoid**
Danaparoid is a heparinoid mixture, which inhibits factor Xa but is chemically distinct from LMWH. It is usually used in patients who have developed HIT. However, there may be some cross-reactivity of the antibody to this molecule. It is as effective as LMWH, but may induce a higher risk of major bleeding. It is administered as a twice daily subcutaneous injection for thromboprophylaxis. Anti-Xa assay levels may be used to monitor the effect; however, this is not required routinely. Platelet monitoring is required for HIT because of potential cross reactivity.

**Fondaparinux**
Fondaparinux is a synthetic pentasaccharide having an almost identical structure to the high-affinity binding site to antithrombin found on heparin. Its effect appears to be via antithrombin as an indirect inhibitor of factor Xa. It has a substantially lower incidence of HIT compared with LMWHs and can be used as a substitute in this situation. Fondaparinux has been demonstrated to be superior to LMWH in prevention of DVT but with some evidence of a higher incidence of major bleeding, although its significance is yet to be established. It is delivered parenterally as a single daily subcutaneous injection. Monitoring can be achieved through an anti-Xa assay; however, this is not required in the uncomplicated treatment situation.

**Lepirudin**
Lepirudin is a recombinant hirudin derived from yeast cells and is a direct thrombin inhibitor. It is used as an anticoagulant in patients who have suspected or confirmed HIT. Despite thrombocytopenia, the risk of thrombosis may be up to 50% unless an alternative coagulant is used. It is delivered as a continuous infusion and its activity is measured using the aPTT. Because of the risks of thrombosis, a ratio of 2.0–3.0 is the target.

**Dextrans**
Dextrans are a polysaccharide which, by adhering to red blood cells and platelets, reduces their adhesiveness. Additionally, it enhances the effects of antithrombin. It is available as different molecular weights (e.g. Dextran 10, 40, 60 and 70) which have the additional effect of i.v. volume expanders and which in large volumes provide dilutional anti-thrombotic effects. Dextrans need to be administered intravenously, with volumes in excess of 1500 ml required to achieve an anticoagulant effect. Their use is therefore generally confined to the intraoperative period only. The larger molecules are more resistant to renal excretion and consequently retain their antithrombotic effects for longer. Side-effects include hypersensitivity reactions, fluid overload, and interference with blood group testing because of red cell clumping. Dextran is effective at reducing DVT although this is less effective than other pharmacological treatments. These agents are no longer recommended for thromboprophylaxis.

**Regional anaesthesia**
The use of lower limb neuroaxial block, as either a single injection or a continuous infusion, has demonstrated a significant reduction in VTE formation compared with patients receiving general anaesthesia alone. The effects are an improved blood flow through the legs secondary to sympathectomy-induced vasodilatation. This is at a time when patient immobility and the hypercoagulable state produced by the surgical stress response create a high-risk environment for DVT formation. Consideration must be given to pharmacological dose times and neuroaxial block.

**Patient information**
Although an evidence base for this mode of prevention is lacking, it is still recommended that healthcare professionals offer verbal...
and written information before surgery. This should be as part of obtaining surgical consent, detailing the risks and the effectiveness of prophylaxis. It should extend to information relevant on discharge including signs and symptoms of DVT and PE, the correct use of prophylaxis at home, and potential implications of failure to follow this advice.

Physiotherapy and nursing

Immobility and lack of exercise are widely accepted as risk factors for developing VTE. When normal lower limb venous pump function is lost as a result of bed rest, venous stasis manifests itself in two ways. First, there is a decrease in the linear velocity of blood, affecting venous return from the lower extremities. Secondly, this decrease in the mean flow and pulsation of the venous flow is followed by dilatation of the vein delaying further venous return and leading to venous stasis. Although robust clinical data are lacking, these risks can potentially be mediated by mechanical calf and foot venous compression, bed exercise, active or passive, and early mobilization.

Hydration

Again clinical evidence is lacking; however, avoidance of dehydration in the perioperative period will attenuate the hypercoagulable state produced after surgery and is otherwise good patient management in the majority of clinical situations.

Caval filters

Vena caval filters are placed in the inferior or rarely the superior vena cava by radiologically controlled percutaneous techniques. Their purpose is to prevent embolized thrombus from reaching the pulmonary circulation and can be placed as permanent or temporary/retrievable filters. Evidence for their use in hospitalized patients is limited and therefore they are recommended only for use in patients who have a known large proximal DVT, and who have had an embolism (within 1 month) and in whom anticoagulation is contraindicated. They are associated with a higher incidence of recurrent DVTs.20

Conclusion

The prevalence and prevention of venous thromboembolic disease has historically been poorly recognized and lacked a clinical focus. This is changing with greater public awareness, clinician and nursing education, the high-profile publication of risk assessments, and national guidelines on preventive measures. Evidence is now emerging that VTE risks extend up to 12 weeks post surgery in the presence of certain risk factors.21 This evidence may impact further on recommended duration of prophylaxis for targeted groups, in future VTE guidelines.

Conflict of interest

P.M., as a Lead Investigator, and the Royal Derby Hospital, have received funding for participation and patient recruitment in the venous thromboembolism risk assessment studies, ENDORSE(2006) and ENDORSE UK (2008) by Sanofi-aventis.

References

16. Ginsberg JS, Davidson BL, Comp PC et al. RE-MOBILIZE Writing Committee. Oral thrombin inhibitor dabigatran etexilate vs North


Please see multiple choice questions 16–19.