Risk Factors for Venous Thromboembolism in Orthopedic Surgery

Htwe M. Zaw MBBS MRCS, Ian C. Osborne MBBS, Philip N. Pettit MBBS MRCS and Alexander T. Cohen MBBS MSc MD FRACP

Vascular Diseases Research Group, Academic Department of Surgery, Guy's King's & St Thomas' School of Medicine, London, UK.

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Venous thromboembolism is a recognized complication of trauma and elective orthopedic surgery with significant mortality and morbidity [1,2]. The silent nature of the disease and the notorious difficulty in clinical diagnosis, along with the high prevalence among orthopedic patients, justifies the need for thromboprophylaxis. Despite the publication of consensus guidelines advocating routine prophylaxis [1–3] there is still reluctance by some orthopedic surgeons to use it [4]. Furthermore, a significant number of patients still die from fatal pulmonary embolism after elective total hip replacement despite the use of the best available antithrombotic agents – currently between 30 and 40 patients per 10,000 post-total hip replacements [3]. The belief that routine thromboprophylaxis is mainly justified by the reduction in the rate of fatal PE [4] does not address the non-fatal complications of deep vein thrombosis. There is significant risk of long-term morbidity from post-thrombotic venous insufficiency and chronic venous ulcers. The concern over bleeding is often given as the main reason for withholding therapy. There is an increase in bleeding as compared to placebo-control populations, but no increase in associated morbidity or mortality. In particular, wound complications including infection have not been found to be increased in prospective comparative studies. Sequential changes from unfractionated heparin and low molecular weight heparin to more efficacious agents such as pentasaccharides [5,6] have not been associated with an increase in wound complications. The clinical benefit and cost-effectiveness of thromboprophylaxis can be maximized by accurate assessment of patients' risk factors for the development of VTE [7]. This allows selective use of specific agents and regimens to those most at risk. The present article reviews the current understanding of risk factors for venous thromboembolism in orthopedic surgery, which can be broadly divided into the operative setting and patient factors.

Operative setting

Elective and trauma surgery is associated with several prothrombotic processes, which are in essence one or more components of Virchow's triad: venous stasis, endothelial damage, and hypercoagulability. Injury to bone and muscle causes extensive endothelial damage that stimulates the release of tissue factor, initiates local activation of the clotting cascade, and increases the activity of plasminogen activator inhibitor. Table 1 summarizes the thrombogenic factors associated with orthopedic surgery.

Operative procedure

The duration and type of surgery are well-established independent factors that influence thromboembolic risk. Hip arthroplasty carries additional risks with distortion of the femoral veins intraoperatively and localized tissue edema. This local impedance in venous flow, combined with the patient's pre- and postoperative immobility, leads to venous stasis in the lower limbs. Consequently, a higher rate of proximal DVT [3] is seen following hip arthroplasty when compared with other elective lower limb procedures [Table 2]. Demers et al. [8] found that relatively minor procedures such as arthroscopy also carry a significant risk of thrombosis. There is evidence that the use of cement can also be a risk factor for thrombosis. The generation of heat during polymerization of cement may account for the higher rates of DVT after cemented total hip replacement compared with a non-cemented prosthesis [9].

Anesthesia

There is growing recognition that the incidence of VTE is significantly reduced with regional blocks compared to general

Table 1. Thrombogenic factors in orthopedic surgery

Coagulation activation from tissue & bone injury
Vein dilatation or injury with endothelial damage
Vein distortion during surgery
Heat due to cement polymerization in THR
Patient immobility causing venous stasis
Reduced venous emptying peri- or postsurgery

Adapted with permission of A.T. Cohen [7]

Table 2. Prevalence of VTE following elective orthopedic and trauma surgery (%)

	Total VTE (%)	Proximal DVT (%)	Clinical PE (%)	Fatal PE (%)
Total hip replacement	45–57 [3]	23–36 [3]	10 [4]	0.1–0.4 [3]
Total knee replacement	40–84 [3]	9–20 [3]	1.8–7 [3]	0.2–0.7 [3]
Hip fracture surgery	36–60 [3]	17–36 [3]	4.3–24 [3]	3.6–12.9 [3]
Trauma	58 [13]	18 [13]	2–22 [14]	0.4–2.0 [3]
Arthroscopy	18 [8]	5 [8]	–	–

PE = pulmonary embolism
VTE = venous thromboembolism

anesthesia. Eriksson et al. [10] compared low molecular weight heparin with a recombinant hirudin for thromboprophylaxis after total hip replacement and found that regardless of the agent used, patients receiving regional anesthesia had a lower incidence of DVT.

Trauma

Although impressive advances were made in the last two decades in the prevention of venous thromboembolism, the incidence of fatal PE still remains high in trauma patients despite the use of the best available prophylaxis. Perez et al. [11] performed an autopsy study from 1953 to 1992 of 581 patients who died after hip fracture surgery. The rate of PE remained unchanged over the 40 year period and was the fourth most common cause of death, accounting for 14% of all deaths. This reflects the presence of additional risk factors within this subgroup, including an increase in age, co-morbidity, dehydration, and delayed hospital admission. Similar results were reproduced in more recent consensus statements, according to which PE accounted for 15–20% of deaths after hip fracture surgery [6,12]. While VTE is a common complication of major trauma, there are few well-designed studies in the current literature [13,14]. This reflects the inherent difficulty with trauma patients who may have contraindications to the use of anti-coagulants, for example, spinal, abdominal and intracranial injuries. In 1994 Geerts et al. [13] performed a prospective study of 443 major trauma patients who did not receive any thrombo-prophylaxis. The incidence of venographically proven DVT was 58% with proximal DVT, accounting for 18% of cases. The subgroups particularly at risk are patients with acute spinal cord injury, pelvic or lower limb fractures, multi-system trauma and major head injuries.

Inflammation/infection

In the resting state, endothelial cells have a non-thrombogenic surface. Receptors on the surface of these cells can be activated by acute infection or sepsis, leading to initiation and propagation of coagulation, complement and kinin cascades, eventually resulting in a hypercoagulable state. Chronic inflammatory conditions such as rheumatic and inflammatory bowel disease are also emerging as intrinsic risk factors for VTE, although a consensus has not been reached as to their clinical significance.

Patient factors

These include age, malignancy, immobility, obesity, co-morbid history of previous VTE, venous insufficiency and cardiac disease, racial variation, and the influence of molecular risk factors such as inherited thrombophilias.

Age

Most studies have shown that beyond the age of 40 years, and especially above 60 years, the relative risk of VTE increases exponentially in both men and women [15]. However, it can be argued that the relationship between age and VTE is not an independent one, but is due to an increase in co-morbid states which are themselves risk factors for VTE.

Malignancy

The contribution of individual patient factors to the overall thromboembolic risk is not always clear, having either an independent effect or interacting with other risk factors. The exception to this rule is cancer. Neoplastic cells produce procoagulants, such as tissue factor, which activate the extrinsic pathway through activation of factors VII and X. Cancer can also activate the clotting system indirectly by stimulation of mono-nuclear cells to express similar procoagulants. Direct vascular invasion by cancer cells causes injury to the endothelium, exposing thrombogenic subendothelial components to circulating clotting factors.

The secretion of vascular permeability factors from cancer cells may also account for the accumulation of fibrinogen in the extravascular space around a growing tumor. The use of chemother-apeutic agents adds further thrombotic risk by damage to the vascular endothelium and depletion of natural plasma anti-coagulants.

The relative immobility of the debilitated cancer patient along with extrinsic venous compression from a bulky tumor may lead to venous stasis. Primary prophylaxis for VTE in cancer patients is currently adopted for those with additional risk factors such as surgical intervention, during chemotherapy, and when using long-term indwelling catheters.

Obesity

There is much evidence that obesity is an independent risk factor in the development of venous thromboembolism [16]. Obesity has also been shown to be an independent predictor for recurrence of venous thromboembolism, along with increasing age, malignancy, and limb paresis.

Previous VTE, venous insufficiency and cardiac disease

After active malignancy, a previous history of VTE is the most important intrinsic factor to elicit from the patient's history when assessing his or her risk of developing further DVT or PE. The risk is even greater if the patient has developed chronic venous insufficiency, which is a separate risk factor in itself [16]. Heit et al. [17], in their population cohort study, found that PE (DVT) was an independent predictor of reduced survival for up to 3 months after the initial event.

Racial variation

Epidemiologic studies of both native and immigrant populations have shown that the incidence of idiopathic and recurrent VTE is significantly lower in non-Caucasians [18,19]. Differences in the prevalence of inherited defects (e.g., factor V Leiden mutation) is significantly greater among Caucasians than in Asian, African and Hispanic populations [19], providing a genetic basis for racial variation in VTE risk. Dietary differences have also been postulated to influence the incidence of VTE. Despite the relative reduction in the incidence of VTE in the non-Caucasian subgroups, in real terms the risk of VTE in such patients undergoing orthopedic surgery is still significant and the use of routine prophylaxis should not be withheld.

Hereditary thrombophilias

Inherited thrombophilias – such as antithrombin III, protein C and S deficiencies, antiphospholipid antibody syndrome and hyperhomocysteinemia – are all known prothrombotic states with relatively low prevalence in the general population. However, two common prothrombotic mutations in the Caucasian population have recently been discovered. Heterozygous mutations of factor V Leiden and prothrombin G20210A were found in 12–20% and 6% respectively among Caucasians presenting with the first episode of idiopathic DVT [20]. This is in contrast to prevalence rates of 6% and 2% respectively in asymptomatic Caucasian control populations.

Conclusion

Knowledge of risk factors for venous thromboembolic disease is vital in the preoperative preparation and postoperative prevention of VTE in the high risk arena of orthopedic surgery. Both intrinsic factors and external triggers assert varying degrees of thrombotic risk to the patient, each one ultimately dependent on their role within Virchow's triad. It is also very likely that the ageing orthopedic patient will present for surgery with multiple risk factors. Studies of the cumulative effect of multiple risk factors have consistently shown that the incidence of VTE increases in proportion to the number of risk factors present [15,16].

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Correspondence: Dr. A. Cohen, Vascular Diseases Research Group, Academic Department of Surgery, Guy's King's & St Thomas' School of Medicine, Bessemer Rd, London SE5 9PJ, UK.
Phone: (44-207) 346-3015
Fax: (44-207) 346-3927
email: alexander.cohen@kcl.ac.uk

Capsule

Controlling neuron myelination

Myelination during development of the peripheral nervous system depends on signaling through neurotrophins and their receptors. Cosgaya et al., in analyzing the effects of particular signaling pathways, found that some neurotrophins keep myelination at bay, while others encourage myelination. The shift from glial cell development to axonal myelination is effected by a shift from signaling by neurotrophin-3 and its tyrosine kinase receptor TrkC to signaling by brain-derived neurotrophic factor and the receptor p75NTR. Insight into how myelination is controlled during normal development may lead to an enhanced capability to manage myelination in the context of neuronal injury.

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