4.6 Thromboembolic prophylaxis

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1 Vein thrombosis in orthopedic trauma surgery

1.1 Introduction

Factors that predispose to venous thrombosis were originally described by Virchow in 1856 and include:
- stasis;
- vascular injury;
- hypercoagulability.

Accordingly, patients undergoing orthopedic trauma surgery represent one of the groups with highest risk of venous thromboembolism (VTE) [1].

- The risk of venous thromboembolism depends on multiple factors, including age, medical condition, type of surgery, duration of immobilization, and underlying thrombophilia.

Venous thrombosis most often occurs in the veins of the lower limbs, although it can occur in any vein of the body. It includes both deep vein thrombosis (DVT), and pulmonary embolism (PE).

1.2 History

Before the use of thromboembolic prophylaxis became widespread the risk of venous thromboembolism following major orthopedic surgery was substantial [2]. Improvements in surgical and anesthetic techniques, along with the use of thromboembolic prophylaxis and early postoperative mobilization, have decreased this risk significantly. Despite the routine use of antithrombotic agents in patients undergoing orthopedic trauma surgery, a significant number of patients still experience thrombotic events that can result in acute and long-term morbidity and death.

2 Clinically important outcomes

2.1 Deep vein thrombosis (DVT)

Thrombosis causes significant morbidity and mortality and may lead to serious complications that include:
- deep vein thrombosis;
- recurrent venous thromboembolism;
- long-term postthrombotic syndrome;
- pulmonary embolism (PE).

- Thrombosis involving the deep veins of the leg may be confined to the calf, but 15–25% of calf venous thromboembolism propagate and may extend into the popliteal or proximal veins [3].

Inadequately treated DVT involving proximal veins is associated with a high risk of clinical recurrence and PE.

2.2 Pulmonary embolism (PE)

- PE is the most serious complication of venous thrombosis; it can be life-threatening and occurs in about 10% of patients with acute proximal DVT.

The mortality rate among patients who undergo total hip or total knee replacement and develop a PE has been estimated at 18%, but the risk of a PE being fatal is even higher among patients undergoing hip and pelvic fracture surgery [4].
2.3 Postthrombotic syndrome and recurrent deep vein thrombosis

Postthrombotic syndrome of the lower leg is the most common complication of DVT. Signs and symptoms include:
- pain;
- edema;
- skin hyperpigmentation;
- skin ulceration.

Postthrombotic syndrome may be caused by persistent venous obstruction or valve damage resulting in venous hypertension.

- Postthrombotic syndrome is a chronic condition that develops in 20–50% of patients with symptomatic DVT, with most cases occurring within two years [5].

Recurrent DVT is common within the first year after the incident, although the risk persists for several years [3]. Underlying risk factors, such as a history of venous thromboembolism, malignancy, thrombophilia, chronic cardiovascular or respiratory disease, and genetic factors increase the likelihood of a recurrence [6].

3 Diagnosis

3.1 Deep vein thrombosis (DVT)

Symptomatic patient
Virtually, all patients develop some degree of lower extremity swelling after orthopedic trauma. The clinical features of localized swelling, redness, tenderness, and edema are not specific to DVT and laboratory tests are needed to confirm the diagnosis. Careful review of patient risk factors is necessary in order to determine the probability of DVT.

D-dimer forms when cross-linked fibrin is cleaved, and is often increased in patients with VTE. D-dimer blood testing is a sensitive, but not specific, assay for DVT and cannot be used alone to diagnose DVT [1]. Normal laboratory values can, however, be used to exclude DVT. A noninvasive test most often used to diagnose DVT is venous ultrasonography.

- Venous duplex ultrasonography is highly accurate for the detection of proximal DVT in symptomatic patients, though it is less precise for symptomatic calf vein thrombosis.

Ultrasoundography has supplanted venography, which is now rarely used due to its invasiveness and its exposure of the patient to an x-ray contrast media. Patients in whom DVT is strongly suspected but ultrasound results are unclear may be forwarded to magnetic resonance imaging (MRI).

Asymptomatic patient
DVT is often clinically inapparent, while the importance of clinically undetected venous thromboembolism is not fully understood. Screening with conventional ultrasound to detect asymptomatic DVT has been suggested as a strategy to improve management of high-risk orthopedic patients, but it is insufficiently sensitive.

3.2 Pulmonary embolism (PE)

The diagnosis of PE is challenging because it is associated with a wide spectrum of symptoms. Typically, patients with PE present with acute dyspnea and chest pain, or tachycardia [3]. As with DVT, a clinical assessment of the probability of PE is
4.6 Thromboembolic prophylaxis

Thromboembolic prophylaxis is recommended to help choose further diagnostic tests. Clinical prediction rules, such as those set forth by Wells and the prospective investigative study of acute pulmonary embolism diagnosis (PISA-PED) group, have been shown to be simple and accurate [7].

Diagnostic testing for PE is difficult as there is no noninvasive test that is both sensitive and specific. Currently, helical computed tomography angiography (CTA) with intravenous contrast is one of the most specific tests available for PE. MRI has not been as carefully evaluated for the detection of PE, but appears to have similar accuracy to CTA [8]. As with DVT, D-dimer testing is often used in ruling out PE in combination with clinical assessment. Even with the combination of clinical prediction rules, results of noninvasive testing are nondiagnostic in 30–60% of patients with suspected PE, and PE is prevalent in 20% of these patients [8]. Pulmonary angiography can be performed in patients with nondiagnostic test results, but pulmonary angiography is difficult to perform, costly, and is associated with serious side effects.

4 Risk factors

The appropriate use of thromboembolic prophylaxis depends on knowing the specific risks of thromboembolism in different patient groups or in individual patients [9]. Trauma patients will have more than one risk factor for VTE, and these factors are generally additive [10].

4.1 Patient risk factors

The following factors have proven to influence the manifestation of venous thromboembolism. They have been derived from several studies that consistently report significantly higher relative risk estimates in multivariate analysis [11]:

- age;
- immobility;
- previous history of VTE;
- pregnancy/antepartum;
- oral contraception;
- hormone replacement therapy;
- malignancy;
- family history of VTE;
- inherited or acquired thrombophilia.

Age

Age is an important risk factor for VTE, with the absolute risk in hospitalized patients increasing by nearly 2-fold for every decade of life [12]. The incidence in childhood is negligible.

Immobility

Immobility is known to be a strong, independent factor influencing the risk of VTE. Patients hospitalized for nonsurgical reasons have an increased risk of VTE of 6–11 times that of nonhospitalized patients, largely due to immobility [10]. The influence of immobility as a risk factor is particularly striking in studies of patients with hemiplegia, where the paralyzed limb of stroke patients has a 9-fold increase in DVT compared with the nonparalyzed limb. Fracture management, however aggressive, contains an element of immobilization, and in the affected limb this may be prolonged.

Previous thromboembolism

A history of VTE predisposes to subsequent VTE events, with the relative risk ranging from 1.7–4.7%. Recurrent thrombosis may be partially related to genetic and hematological risk factors. It is important to enquire for a history of thromboembolism in the trauma patient [11].
Pregnancy, oral contraception, and hormone replacement therapy (HRT)

VTE complicates between one in 500 and one in 2,000 pregnancies, and pulmonary embolism is a leading cause of maternal death [13]. VTE is more common postpartum than antepartum, and risk of DVT is twice as high after cesarean delivery than after vaginal birth [14]. Modern “low-dose” oral contraceptives (OC) are associated with a 3-fold to 6-fold increased relative risk of VTE [13]. The risk of thrombosis increases within 4 months of the initiation of therapy, but is unaffected by duration of use. A 2-fold to 4-fold increased risk of VTE is associated with the use of hormone replacement therapy (HRT) [11]. Other factors such as obesity, factor V mutation, history of VTE, and thrombophilia can interact with pregnancy, OC and HRT use, further increasing the risk of VTE [13].

Malignancy

The frequency of DVT and PE increases 2-fold to 6-fold in patients with confirmed malignancy [12].

Genetic predisposition

Some families carry a genetic predisposition to thrombosis. Among patients hospitalized for DVT, those with a positive family history have a greater than 3-fold increase in risk. Patients with a family history of VTE presenting with idiopathic thrombotic events suggest a thrombophilia condition.

- The prevalence of antithrombin, protein C, or protein S deficiency is low in the general population (< 1%), but relatively high (5–10%) among patients with VTE [11].

Factor V Leiden mutation is the most prevalent hereditary thrombophilia among the Caucasian population. The prevalence of this mutation is 4–6% in the general population who are heterozygous for this autosomal dominant trait. The risk of VTE is increased by nearly 3 times in the presence of the prothrombin 20210 A allele [15]. Increased levels of coagulation factors VIII, IX, and XI have been associated with twice the thrombotic risk compared with physiological levels [11]. The molecular basis for enhanced levels of these factors is unknown, although a genetic component is suspected.

4.2 Surgery risk factors

- The absolute risk of DVT is high in patients who sustain a fracture of the hip, spine, pelvis, or lower extremity (Tab 4.6-1).

<table>
<thead>
<tr>
<th>Condition</th>
<th>DVT %</th>
<th>PE %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Proximal</td>
</tr>
<tr>
<td>Polytrauma [16]</td>
<td>29–63</td>
<td>8–32</td>
</tr>
<tr>
<td>Spinal cord injury [31]</td>
<td>47–90</td>
<td>17–35</td>
</tr>
<tr>
<td>Pelvic or acetabular fractures [17, 18]</td>
<td>10–61</td>
<td>10–29</td>
</tr>
<tr>
<td>Isolated lower extremity fracture [20]</td>
<td>17–45</td>
<td>1–8</td>
</tr>
</tbody>
</table>

Tab 4.6-1 Risks of VTE in orthopedic trauma and fracture surgery.
Polytrauma
VTE is a common complication of polytrauma and can be life-threatening. Without prophylaxis the risk of DVT exceeds 50%, and fatal PE is a leading cause of death in those who survive the first day [16]. Among trauma patients, those with spinal fracture and spinal cord injury have the highest rates of DVT, ranging from 47–90%. Patients with pelvic or acetabular fractures experience DVT at a rate of between 10% and 61% [17] and PE at a rate of between 2% and 8%. Additional factors associated with an increased risk in trauma patients include a concomitant lower extremity fracture [16], advanced age [18], obesity [19], and immobility for longer than 3 days [19].

Hip fracture
In hip fracture patients who do not receive prophylaxis, the incidence of DVT can be as high as 60% and that of PE up to 11% [16]. The rate of fatal PE is reported to range from 1–7.5% [16], accounting for 14% of all deaths in this population. Factors that increase the risk of VTE in addition to hip fracture surgery include advanced age and delayed surgery [11, 16].

Isolated lower extremity fracture
Lower extremity fractures, common in persons of all ages, have been poorly studied with respect to VTE epidemiology and prevention.

DVT rates of 17–45% have been reported, with PE rates of 1–5% [20].

- The risk of DVT appears to increase with the proximity of the fracture to the knee; tibial plateau fractures have the highest risk (43%), followed by fractures of the tibial shaft (22%), and then the distal tibial and pilon fractures (13%).

Advanced age and obesity [20, 21] are further risk factors for developing a VTE following an isolated lower extremity injury.

5 Basics of thromboembolism prophylaxis

5.1 Methods

5.1.1 Mechanical

Compression stockings
Graduated compression stockings have not been formally tested in trauma patients. Nevertheless, many surgeons recommend combining graduated compression stockings with pharmacological methods for VTE prophylaxis in trauma patients.

Mechanical pumps
Various compression devices exist to replace or enhance the natural muscle pump function. These include the venous foot pumps developed to mimic the effect of weight bearing and sequential pneumatic compression devices that transport venous blood proximally. Generally, mechanical pumps appear to be beneficial in reducing VTE in hip fracture patients. However, their use in trauma patients has not been shown to be beneficial in DVT prevention compared with no prophylaxis [22]. Their use is recommended in patients where anticoagulation is contraindicated.

Vena cava filters
Filter placement is a strategy for the prevention of PE in the face of known or likely thrombosis. Its role in trauma surgery and the risks and benefits of placing the filter prophylactically are not yet fully clear.

- Filters are recommended in very high-risk trauma patients who cannot receive anticoagulation because of increased bleeding risk [18].
There are retrievable ones and nonretrievable ones. A serious long-term complication of inferior vena cava filtration is thrombotic occlusion of the inferior vena cava (IVC) (in 6% to 30% of cases). Retrievable filters can be considered in younger trauma patients in whom contraindications to anticoagulation are expected to be temporary [23].

5.1.2 Chemical
Chemical agents have been the mainstay of thromboembolic prophylaxis in most branches of surgery since the 1970s because of their efficiency. They have, however, not been popular with some surgeons for reasons outlined in chapter 4.6:5.2.

Warfarin
Warfarin is a highly effective anticoagulant taken orally, but is bound by plasma proteins so that other agents (alcohol, antibiotics) have a major effect on its potency. There is a delay in the onset of anticoagulation, which means that other measures must be used first. In fracture surgery, warfarin is most commonly used for the treatment of an established DVT. Its use must be monitored by regular blood tests (international normalized ratio (INR), or prothrombin time ratio). In prophylaxis and treatment, an INR target value of 2.5 (INR range 2.0–3.0) is recommended [16]. Recession of excessive INR values can be achieved with vitamin K, but high doses of this vitamin make the patient Warfarin-resistant for days. Warfarin can be an effective prophylactic method in hip fracture surgery.

Heparins
Heparins are naturally occurring anticoagulants. Activity of unfractionated heparin is monitored employing the APTT (activated partial thromboplastin time) ratio. Administered in full dose, this is the conventional drug to initiate anticoagulation. Full anticoagulation in the postoperative period has a high incidence of bleeding complications. Fractioned heparins contain more low-molecular weight elements (hence, low-molecular weight heparin, LMWH). Their action is best monitored using an assay of anti-factor Xa action. Unfractionated heparin in low doses (LDUH) was widely used for prophylaxis in trauma and orthopedic practice after its successful use in abdominal and elective orthopedic surgery. Heparin prophylaxis (either LMWH or LDUH) appears effective in hip fracture surgery. However, some data suggest that LMWH may be more effective than LDUH in trauma patients [22].

Aspirin
Aspirin is the oldest and least expensive chemical thromboembolic drug available. It works as an antiplatelet agent, and the metaanalysis conducted by the Antiplatelet Trialists’ Collaboration has reestablished its use [24]. Among orthopedic trauma patients in that trial, DVT was reduced from 42% to 36% and the PE rate even halved from 6.9% to 2.8%. It has also been shown to be effective in reducing DVT in hip fracture patients. LMWH appears to prevent more thromboses than aspirin.

5.2 Why is prophylaxis not used more often?
Geerts lays out four widespread opinions about thromboembolic prophylaxis that should be reconsidered. He describes why thromboembolic prophylaxis should be used across disciplines.

- **Opinion 1**: The overall prevalence of VTE among trauma patients in the 21st century is too low to consider prophylaxis.

  **Reply**: This is related to the surgeon’s perception of the magnitude of the problem in his or her individual practice. It remains a significant problem, particularly among the elderly, a population group that is increasing in many countries. Furthermore, prophylaxis success is difficult to appreciate, whereas its failures in terms of VTE despite
Thromboembolic prophylaxis and bleeding complications are highly apparent.

- **Opinion 2:** There are bleeding complications with the use of anticoagulants.

  **Reply:** While it is true that wound hematomas are seen more frequently with these agents, there is sufficient data to demonstrate that the absolute rates of major bleeding with LDUH or LMWH are low [21].

- **Opinion 3:** There will be thrombocytopenia with the use of heparin.

  **Reply:** LMWHs are much less likely to produce heparin-induced thrombocytopenia compared with unfractionated heparin.

- **Opinion 4:** The costs of thromboembolic prophylaxis exceed their benefit.

  **Reply:** Cost-effectiveness studies have concluded that wide use of prophylaxis is cost-effective [6, 16].

5.3 **Rationale for thromboembolic prophylaxis in trauma surgery**

VTE prophylaxis in trauma surgery is based on the following rationale [9]:

- Without prophylaxis, asymptomatic VTE is common and affects at least half of all trauma patients.
- The majority of these thrombi spontaneously resolve.
- For certain patients, the thrombus becomes symptomatic due to either venous occlusion or embolization.
- Symptomatic VTE is a result of the persistence of venous injury, stasis due to prolonged immobility, an impaired natural anticoagulant or fibrinolytic system, or some unidentified factor.
- While high-risk groups for VTE can be identified, it is not possible to predict which specific patients will develop a clinically important thromboembolism.
- Until we are able to identify specific individuals with the highest risks, primary prophylaxis is warranted to all patients undergoing major trauma surgery.

- Prevention of fatal PE is the top priority of prophylaxis programs. However, the prevention of systemic DVT and PE is also important because these are associated with acute morbidity, consumption of resources, and long-term sequelae of clinical and economic significance.

6 **Thromboembolism prophylaxis in specific fracture surgery**

6.1 **Hip fractures**

Complications from thromboembolic events remain an important cause of morbidity and mortality associated with hip fractures. Studies of thromboembolic prophylaxis in this group are generally characterized as small, with the exception of the pulmonary embolism prevention (PEP) trial which compared low-dose aspirin and placebo in over 13,000 patients undergoing surgery for hip fracture. In that study, the incidence of PE and symptomatic DVT among patients allocated to take aspirin was reduced by 43% and 29%, respectively, compared with the placebo group. Aspirin prevented four fatal pulmonary emboli per 1,000 patients compared with the placebo group, and had no apparent effect on mortality from any other vascular or nonvascular cause. There was an excess of six postoperative bleeding episodes resulting in blood transfusion per 1,000 patients assigned to aspirin. Comparing the heparin group to the placebo group, the incidence of DVT was significantly lower, an absolute risk reduction of approximately 16% (or, for every six hip fracture patients treated with heparin prophylaxis, one DVT was prevented). Foot and calf pumping devices appear to prevent DVT in patients with hip fractures (absolute risk reduction of 15.5%), and may protect against PE.
In six hip fracture patients treated with a foot and calf pumping device, one DVT was avoided in comparison with the group that received no mechanical thromboembolic prophylaxis.

Fondaparinux, a new synthetic factor Xa inhibitor, has been found to be better at reducing DVT after hip fracture surgery than enoxaparin, the relative risk reduction being 56% [25]. When the outcome was restricted to proximal DVT, symptomatic DVT or PE, or fatal PE, the relative risk reduction was 73% [26]. Thus, in 29 hip fracture patients treated with fondaparinux instead of enoxaparin, one serious VTE can be prevented. A 4-week fondaparinux regimen has been shown to provide additional benefit over a 1-week prophylaxis, though this resulted in a slight increase in bleeding [25]. Fondaparinux has also been shown to be more cost-effective than enoxaparin in patients with a knee and hip arthroplasty or a hip fracture [6].

■ Surgical delay appears to heighten the risk of VTE in hip fracture patients [27]. If surgery is likely to be delayed, consideration should be given to starting prophylaxis during the preoperative period [16].

6.2 Polytrauma

Data are surprisingly sparse to help guide the prophylactic treatment of DVT in polytrauma patients. There is little support to recommend the use of LDUH in this population. In a metaanalysis that included both randomized control trials (RCTs) and cohort studies, there was no difference in the incidence of DVT between patients receiving LDUH and patients receiving no prophylaxis for DVT (odds ratio 0.97) [22]. LMWH was found to reduce DVT more than LDUH in trauma patients. In eight patients treated with LMWH instead of LDUH one DVT in any location was prevented, and in eleven patients one proximal DVT was prevented [28].

Mechanical prophylaxis is often used in trauma patients; however, the evidence to date is conflicting. There are no published RCTs evaluating graduated compression stockings in trauma patients [16]. Pooled results from three RCTs revealed no significant difference in DVT rates between patients who received treatment with sequential compression devices and those who did not [22]. Generally, mechanical prophylaxis is recommended when LMWH is contraindicated [16, 18, 29]. Combining mechanical with pharmacological prophylaxis may have an additive effect, but this has not been tested in trauma patients.

Prophylactic insertion of vena cava filters in this population remains controversial. Most of the studies to this topic compare PE rates using vena cava filters with rates of historical controls. RCTs have yet to be done to determine effectiveness and safety. Current recommendations are against using filters as primary prophylaxis except in very high-risk patients (such as those with severe closed head injury, incomplete spinal cord injury, complex pelvic fractures with associated long-bone fracture, or multiple long-bone fractures), who have contraindication to anticoagulation [16, 18].

6.3 Spinal injuries

The early use of thromboembolic prophylaxis is supported by the high risk of VTE in patients with spinal injury, where PE remains the third leading cause of death [30]. No evidence exists to support the use of mechanical prophylaxis as a single prophylaxis modality, but it is recommended when anticoagulant prophylaxis is contraindicated [16, 18]. The increased risk of VTE in spinal cord patients persist during their rehabilitation phase, and continued thromboembolic prophylaxis should be considered [31].
4.6 Thromboembolic prophylaxis

6.4 Fractures of the pelvis and acetabulum

Proximal vein thrombosis occurs frequently in trauma patients who have sustained pelvic or acetabular fractures, especially in the presence of a concomitant lower extremity fracture. As in other trauma patients, LMWH instead of LDUH is recommended for patients with pelvic or acetabular fractures as a means of thromboembolic prophylaxis after hemostasis has taken place [32]. Mechanical thromboembolic prophylaxis is recommended when LMWH is contrainindicated [16, 18, 29]. Prophylactic vena cava filters are not recommended as primary thromboembolic prophylaxis in this population, except in patients with complex pelvic fractures with associated long-bone fracture who have a contraindication to anticoagulation [16, 18]. As in the polytrauma patient, consider a retrievable filter if patients only require them for temporary indications [23].

6.5 Isolated lower extremity fractures

Four randomized trials addressed the issue of thromboembolic prophylaxis in isolated lower extremity injuries. Two studies, both with marked methodological flaws, demonstrated fewer cases of DVT in outpatients requiring plaster casts who received self-administered LMWH compared with those who received no thromboembolic prophylaxis [21, 11]. Most of the patients in these studies had only soft-tissue damage, only 21–30% sustained fractures. In the other two RCTs, 440 and 300 patients with a lower extremity fracture or ruptured Achilles tendon were randomly selected to receive placebo or LMWH (reviparin or tinzaparin) [20]. Pooled DVT rates from these trials showed an absolute risk reduction of 8.4% with LMWH, suggesting that use of LMWH can prevent one DVT in 12 of these patients [16]. The DVT risk was not significantly reduced by LMWH in patients with fractures. While LMWH is used in some European countries for lower extremity injuries, its use is generally not as common in North America due to the uncertainty of its effectiveness in reducing clinically important VTE [16].

7 Conclusion

The use of prophylaxis against thromboembolism remains controversial. Local, regional, national, and international variations in treatment exist. Large collective RCTs and collaboratives will provide direction for the future in this area.
4 General topics

8 Bibliography


4.6 Thromboembolic prophylaxis


9 Acknowledgment

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