Venous Thromboembolism Prophylaxis

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An understanding of the pathogenesis and prevention of venous thromboembolism (VTE) is of importance to the surgeon caring for patients in the developing world. A large proportion of patients encountered in the mass casualty setting, the emergency department, or the surgical clinic will present with either acute or subacute orthopedic trauma placing them a high risk for developing VTE. In the hospital, both medical and surgical patients are at significant risk for VTE. Estimates for rates of VTE in surgery patients without prophylaxis range from 10 to 40 % in general surgery to as high as 40–60 % after major orthopedic surgery [1].

There exists virtually no evidence originating from the developing world to guide the use of prophylactic anticoagulation. Therefore, it falls to the healthcare provider to interpret the appropriateness of evidence-based practices developed in the non-resource-limited setting within the local environment. This often requires the combined use of locally available pharmaceutical agents with either standard or improvised mechanical prophylaxis.

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This chapter will summarize the *Antithrombotic Therapy and Prevention of Thrombosis, 9th Edition: American Association of Chest Physicians Evidence-Based Clinical Practice Guidelines* [2–4] and will be interspersed with interpretations of these guidelines for the practitioner confronted with resource limitations. The recommendations provided within this chapter are not intended to be prescriptive, but rather to serve as a guide to be tailored as appropriate to each individual setting.

20.1 Epidemiology

Venous thromboembolism is a common complication in the trauma patient. In the acute setting, VTE carries the potential for central propagation leading to extremity congestion, edema, and pain. The most feared complication is pulmonary embolism leading to cardiopulmonary compromise and possibly death. Long-term sequelae of lower extremity deep venous thrombosis include chronic venous insufficiency, extremity edema, and if left unchecked, chronic debilitating soft tissue ulceration. The inability to effectively manage these complications in the resource-limited setting highlights the importance of implementing prophylactic therapy whenever possible.

A prospective study of the incidence of VTE after major trauma in the United States revealed

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the near ubiquity of this problem [5]. With the caveat that this study used non-targeted imaging in asymptomatic patients, the results were quite impressive. Of the 716 patients admitted to a single trauma center, 201 (58 %) developed peripheral venous thrombosis and 63 (18 %) developed proximal venous thrombosis when no prophylactic anticoagulation was used. The incidence of thrombosis was dependent on location and type of injury with thrombosis identified in 65/129 (50 %) of those with chest or abdominal trauma, 49/91 (54 %) of those with major head trauma, 41/66 (62 %) of those with spinal trauma, and 126/182 (69 %) of those with lower-extremity orthopedic trauma. In a subsequent study of 312 patients with either pelvic, acetabular, femoral, or tibial fractures receiving either mechanical or chemical prophylaxis, 36 (12 %) developed deep venous thrombosis [6].

When limited to symptomatic VTE, the incidence is significantly lower, but still quite common in the major trauma population [3]. Across available studies of poly-trauma patients, the risk of symptomatic VTE ranges between 1 and 10 % with higher rates in those with spinal fractures (2 %), traumatic brain injury (5 %), and spinal cord injury (6 %) despite timely initiation of pharmacologic prophylaxis.

The epidemiology of VTE is less well defined in the developing world since these studies require access to significant numbers of subjects' medical records living in the same geographic areas. Two studies, one in California, USA, and the other in Waitemata, New Zealand, have looked at race and ethnicity in VTE prevalence [7, 8]. These studies demonstrate that African Americans have the highest risk of VTE, followed by Caucasians, Hispanics, and lastly Asians. Both of these studies included medical and surgical cases.

With respect to the trauma population, however, the dramatically increased risk of VTE exists regardless of race or ethnicity. In a post-mortem study of 989 patients in Nigeria, 29 cases of confirmed VTE were identified of which 24 % were associated with "neuromuscular paralysis"; 17 % associated with "multiple trauma of the pelvis, abdomen, and head"; and 14 % associated with "major surgery" [9].

20.2 Pathogenesis

The triad of venous stasis, endothelial injury, and hypercoagulable state, known eponymously as Virchow's triad, was first described in 1856 and continues to define the constellation of events that lead to VTE. In the absence of the muscular contractions that occur during normal movement in the non-debilitated individual, venous stasis allows for the aggregation of activated platelets and coagulation factors in the surgical patient.

Endothelial injury, a phenomenon present in all surgical patients, exposes procoagulant molecules such as tissue factor, von Willebrand factor, and collagen to circulating platelets and can serve as a nidus for thrombosis formation. Interestingly, postsurgical patients are at risk for developing thrombosis in veins distant from the surgical site. Microvascular injury does occur at these distant sites – the mechanism of which is not completely understood.

Hypercoagulable state often refers to genetic predispositions to thrombosis (e.g., Factor V Leiden, prothrombin gene mutation, and mutations to protein C, S, and antithrombin III, etc.). It is now appreciated, however, that even in the absence of such mutations the surgery patient is in a state of hypercoagulability from the endogenous release of tissue factor and from alterations in the normal coagulation and fibrinolysis pathways.

20.3 Review of the Evidence

When considering prophylactic anticoagulation in the patient with orthopedic trauma, the *American Association of Chest Physicians Evidence-Based Clinical Practice Guidelines* makes a clear distinction between the patient with multiple traumatic injuries and the patient with isolated lower extremity orthopedic trauma. In both cases, however, the existing evidence comes from non-resource-limited settings and in

general is of relatively low quality with few adequately generalizable trials. Therefore, these guidelines must be interpreted with respect to each individual patient and the locally available resources.

When determining whether to initiate prophylactic anticoagulation in the poly-trauma patient, the surgeon must balance the estimated risk of VTE with the estimated risk of hemorrhagic complication. From the available evidence, as eluded to above, the estimated risk of symptomatic VTE is approximately 5 %, with rate of up to 10 % in those with spinal cord injuries. The risk of hemorrhage is directly related to the type and location of concomitant injury with higher bleeding risk associated with major head trauma, laceration of the liver or spleen, or the presence of an epidural hematoma. In the absence of pharmacologic prophylaxis, the estimated risk of hemorrhagic complication is approximately 1 %. This increases to approximately 3–4 % when chemical prophylaxis is initiated. The studies from which these data are derived typically define hemorrhagic complications as hemorrhagic changes identified by computed tomography scan of the head or as clinical bleeding requiring transfusion of more than 4 units of packed red blood cells.

It is estimated that the initiation of either pharmacologic or mechanical prophylaxis in major trauma patients with average-to-high risk of VTE and average bleeding risk will prevent between four and ten times the number of nonfatal thromboembolic events as the number of iatrogenic bleeding complications incurred. In the group at high risk of VTE, there is some evidence to suggest that the use of pharmacologic prophylaxis in combination with mechanical prophylaxis will provide added benefit [2–4]. For patients with major trauma at high risk of bleeding (i.e., those with major head injury or solid viscera injury), there is little relative benefit to pharmacologic prophylaxis. Mechanical prophylaxis in this group likely averts many thromboembolic events without significantly increasing risk of bleeding complications.

The *American Association of Chest Physicians Evidence-Based Clinical Practice Guidelines* include the following recommendations for patients with traumatic injuries (exclusive of those with isolated lower extremity injuries, see below):

- For major trauma patients, the use of low-dose unfractionated heparin (LDUH), low molecular weight heparin (LMWH), or mechanical prophylaxis with intermittent pneumatic compression (IPC) is recommended over no prophylaxis.
- For major trauma patients at high risk for venous thromboembolism (including those with acute spinal cord injury, traumatic brain injury, and spinal surgery for trauma), the addition of mechanical prophylaxis to pharmacologic prophylaxis is recommended when not contraindicated by extremity injury.

For major trauma patients in whom LDUH and LMWH are contraindicated, the use of mechanical prophylaxis with IPC is recommended over no prophylaxis. The addition of pharmacologic prophylaxis is recommended when the risk of bleeding diminishes. It should be noted that these recommendations are all classified as *Grade 2C*, which implies a basis on low- or very-low-quality evidence and existing uncertainty in the estimates of benefits and risks. When interpreting these recommendations with respect to the resource-limited setting, the major salient point is that mechanical prophylaxis is likely to be of benefit, with virtually no additional risk, in most situations when not contraindicated by extremity injury.

If pharmacologic prophylaxis is available, it should be initiated when no major risk of bleeding is present. However, one needs to consider the possibility of unidentified head or visceral injuries in settings where advanced diagnostic imaging is unavailable. A further consideration is the availability of blood products or intravenous fluids. If such resources are limited or unavailable, the ability to recognize and rescue a hemorrhagic complication is hindered and one may choose to err on the side of caution with respect to chemical prophylaxis.

The *American Association of Chest Physicians Evidence-Based Clinical Practice Guidelines*

includes the following recommendations for patients with isolated lower extremity trauma:

- No prophylaxis rather than pharmacologic prophylaxis in patients with isolated lower-leg injuries requiring leg immobilization is recommended.

As with the guidelines for the major trauma population, this recommendation is classified as *Grade 2C* and should be interpreted with caution. It is known that the risk of VTE increases with the proximity of the injury and the degree of patient immobilization. With regard to the resource-limited setting, this patient group is at a much-decreased risk of VTE relative to the major trauma population, and pharmacologic agents should be reserved for those in higher-risk categories. The goals of care in this population should include early ambulation and return to daily activities as soon as possible.

Aspirin can also be considered as a prophylactic agent for VTE in this patient population. There has been a successful trial in orthopedic patients that demonstrated benefit of perioperative aspirin in VTE risk reduction. The Pulmonary Embolism Prevention (PEP) trial demonstrated efficacy of perioperative aspirin in preventing VTE after hip fracture surgery [10]. Treatment dose consisted of 160 mg aspirin daily for 5 weeks, starting with a presurgical dose. In the hip fracture population, there was a 36 % reduction in symptomatic DVT or pulmonary embolism (absolute risk reduction, 0.9 %; $P = .0003$) [10]. The cumulative data on aspirin resulted in the following Grade 1B recommendation in the *American Association of Chest Physicians Evidence-Based Clinical Practice Guidelines* for patients with hip fractures:

- In patients undergoing hip fracture surgery (HFS), the use of one of the following rather than no antithrombotic prophylaxis for a minimum of 10–14 days, LMWH, fondaparinux, LDUH, adjusted-dose VKA, *aspirin* (all Grade 1B), or an IPCD (Grade 1C), is recommended [3].

20.4 Authors' Experience

The patient with multiple traumatic injuries presents a challenging scenario in the developing world for prevention of VTE since resource availability varies contextually. Most anticoagulation guidelines are developed assuming unlimited access to common heparin-based anticoagulants, mechanical compression devices, and intravenous fluid or blood products if needed to rescue the patient from bleeding complications. The reality in the developing world is that in many situations, *none* of these resources are available. Factors such as lack of a constant source of power for pneumatic compression devices or sufficient supply chains and proper drug storage greatly influence available resources. In some settings, none of these things may be available leaving early mobilization, when possible, the only means by which VTE prophylaxis may be addressed.

A consideration for pharmacologic prophylaxis in the absence of heparin derivatives is standard aspirin. Antiplatelet agents are used as second-line prophylactic anticoagulants in elective orthopedic surgery when patients are unable or refuse to take injectable agents and when the newer oral anticoagulants are unavailable. While there is limited evidence for antiplatelet use as primary prophylaxis in the trauma patient, it likely provides some marginal benefit.

If the setting has no intermittent pneumatic compression devices or any chemoprophylaxis agents, elastic compression stockings can be used if available. Care must be exercised in the use of these stockings because there have been reports of skin breakdown or necrosis from the stockings.

In a large trial using thigh length gradual compression stockings for DVT prevention in stroke patients, there was a 5.1 % incidence of skin breaks, blisters, ulcers, or necrosis [11]. Stockings should be applied with care to avoid folds in the fabric, and skin should be examined at least daily to make sure there are no developing skin issues. If none of the above are available, mobilization by staff or family members should be encouraged. If the patient can ambulate, that is

best, but if they are unable to do to fractures or spinal injuries, then active and passive range of motion exercises should be done on the extremities.

Prophylactic anticoagulation, like most aspects of surgical care in the developing world, provides the opportunity for the surgeon to make use of his or her creativity and ingenuity after assessing available resources. Attention to VTE prophylaxis is a critical consideration, regardless of setting, for anyone taking care of surgical and trauma patients and can help avert potential morbidity and mortality in these patients.

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