Prophylaxis of Deep Venous Thrombosis in Trauma Patients: A Review

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Abstract
Trauma patients are at high risk for venous thromboembolism. While a variety of risk factors predispose them to deep venous thrombosis and pulmonary embolism, the goal of aggressive chemical prophylaxis needs to be balanced against the risk of hemorrhage, making this a most challenging population to adequately prophylax. The use of titration of the prophylaxis to ant factor Xa levels is discussed. Special consideration needs to be taken in some particularly challenging trauma subpopulations, including those with renal failure, nonoperatively managed solid organ injury, traumatic brain injury with intracranial hemorrhage, spinal cord injury and the bariatric trauma patient, which are reviewed.

Keywords: Trauma; Deep venous thrombosis; Venous thromboembolism; Prophylaxis

Introduction
Venous thromboembolism (VTE) is a common disease in both medical and surgical patients. VTE is comprised of the entities of deep venous thrombosis (DVT) and pulmonary embolism (PE). It is the most common cause of preventable deaths in patients that are hospitalized [1]. VTE affects an estimated 900,000 patients annually in the United States, and approximately 300,000 mortalities annually [2]. It is known that in patients that develop a DVT, the risk of progression to a fatal PE is 1.68% [3]. In addition, the cost of each VTE event is considerable, ranging from $7594 to $16644 when analyzed [4].

Trauma patients have the risk factors of Virchow's Triad, including stasis, injury and thrombophilia, whether or not they have undergone an operation. The natural history is that up to 58% of high risk trauma patients will develop a DVT with no prophylaxis [5,6]. DVT has been described to occur in 15% of trauma patients, despite chemical prophylaxis with subcutaneous heparin, when it is looked for with screening duplex in one series [7].

In many cases, DVT’s are not recognized clinically, and up to 75% of cases that are suspected clinically do not have a DVT on imaging [8]. The paucity of signs and symptoms, coupled with the unreliability of physical exam underscores the importance of prophylaxis for DVT and PE. Therefore, the rationale for prophylaxis is based on the prevalence, the challenge in diagnosis, the morbidity and mortality of unprevented DVT’s, as well as the cost.

Trauma patients taken in total, represent a higher risk subset of patients in terms of DVT and PE. PE is the third most common cause of death in trauma patients who survive beyond the first 24 hours of admission [9]. In a retrospective analysis by Knudson et al., the following risk factors were identified on multivariate regression analysis: age ≥ 40 years old, lower extremity fracture, head injury, ventilator days >3, venous injury, and major operative procedure [10]. In the guidelines from the Eastern Association for Trauma (EAST), in their meta-analysis, they found that the most significant risk factors were spinal fracture, and spinal cord injury [11]. In trauma patients, it is common for multiple risk factors to be present simultaneously [12]. Finally, central venous lines, in particular in the femoral position, which is common in trauma patients, are associated with DVT [13].

It is known that the critically injured patient, while initially coagulopathic due to traumatic bleeding, then goes into a hypercoagulable state, due to the systemic inflammatory response seen in post trauma patients, and specifically the increase in C reactive proteins in blood in these patients [14-16]. This phenomenon of a progression from coagulopathic to hypercoagulable, coupled with the dangers of ongoing hemorrhage in subgroups such as nonoperative management of solid organ injury, or the traumatically brain injured patient with intracranial hemorrhage, make the prophylaxis for DVT and PE in trauma patients one of the most challenging issues in thromboprophylaxis. Although the risk of DVT increases with age, young trauma patients are still at risk for DVT and PE, and thromboprophylaxis should not be withheld simply for youth [17,18].

Current Recommendations
The most recent guidelines to address prophylaxis of VTE in the trauma patient were published in 2012 from the American College of Chest Physicians. They suggest that for “major trauma patients...the use of LDUH or LMWH, or mechanical prophylaxis, preferably over IPC, over no prophylaxis” [19]. The use of the Caprini risk assessment model is encouraged to stratify the level of risk [20]. The Eastern Association for the Surgery of Trauma (EAST) has practice management guidelines regarding DVT prophylaxis which were published in 2002 [11]. Using the Caprini risk assessment model, developed at the University of Michigan health system, assessing patients for risk of VTE is essential for initiating appropriate prophylaxis [20]. Patients are given a base risk assessment which results in a cumulative risk score, which is then correlated with the incidence of DVT. Based on this stratified risk assessment for each patient, appropriate prophylaxis is recommended, based on the current ACCP Guidelines (9th Edition) [21]. There are several challenging trauma patient subtypes that will be detailed below and their VTE prophylaxis issues.

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Prophylactic Agents

**Mechanical Prophylaxis**

Intermittent pneumatic compression devices (IPC) are used in the prophylaxis of DVT in both medical and surgical patients. They are mainly used in trauma patients when there is a contraindication to chemical prophylaxis, such as active bleeding, or added adjunctively to trauma patients receiving chemical prophylaxis. The devices work as by sequentially inflating and deflating, to provide an intermittent gradient of pressure to propel the flow of blood centrally. The mechanism is to prevent stasis, and activate the fibrinolytic pathway [22].

IPC are effective in reducing the incidence of DVT. If used, they should be on the patient, except during ambulation, to derive the full benefit. When compared in a large, prospective, randomized trial with IPC against LMWH in trauma patients by Ginzburg et al., the IPC was found to be equivalent to the LMWH in terms of DVT prophylaxis [23]. However, noncompliance with these devices can be as high as 26% when studied, and educational initiatives had no impact on the low compliance [24]. In addition, it is common for trauma patients to have anatomic contraindications to bilateral lower extremity IPC placement. These contraindications include recent lower extremity surgery, soft tissue trauma to the lower extremity, and lower extremity fractures. As an alternate, many clinicians place the IPC on a solitary lower extremity, or on an upper extremity, but there is little evidence for this practice. In select cases where the lower leg contraindicates an IPC, and the foot is intact, a foot compression device should be considered, although there is limited data specific to the trauma population [25,26].

**Chemical prophylaxis**

Low dose unfractionated heparin (UFH) has been evaluated across numerous studies [27]. UFH (Heparin 5000 units subcutaneously every 8 to 12 hours, with the high risk patients it is recommended to use the every 8 hours dosing) is usually started 2 hours preoperatively, and continued for 7 days postoperatively, or until patients are ambulatory. Overall incidence of DVT in postoperative patients with UFH has been shown to decrease three fold, from 25% to 8% [28]. The overall risk reduction of fatal PE using heparin prophylaxis is 89% [29]. However, this data on UFH is on surgery patients, and not the even higher risk trauma patients.

Low dose unfractionated heparin (LDUH) is not effective in trauma patients, and has been shown to be equivalent to no prophylaxis in high risk trauma patients [30]. Therefore, LDUH should not be used to prophylax in trauma patients, unless a low molecular weight heparin (LMWH) is contraindicated. LMWH in major trauma patients, in the enoxaparin 30 mg subcutaneously every 12 hours dose, without intracranial hemorrhage, is superior to LDUH in preventing proximal DVT in trauma patients with a risk reduction of 58% [31]. LMWH should be initiated when primary hemostasis has occurred, and is the method of choice to provide DVT prophylaxis in the high risk trauma patient.

At most institutions, including the authors, the LMWH prescribed is enoxaparin. Other LMWHs include dalteparin, and tinzaparin, which are less commonly prescribed at most centers. Enoxaparin has the advantage of being dosed in milligrams, or milligrams per kilogram, while other LMWH agents get dosed in IU (international units), or IU per kilogram. For a LMWH, the IU designates the anti-Xa activity, which then determines the dose of the agent. The relationship exists that 1 mg of enoxaparin inhibits 100 anti-Xa units, while the other LMWHs do not have this simple mathematical relationship that simplifies dosing. As most other drugs are dosed in milligrams, and clinicians are most familiar with dosing medications based on weight, rather than IU, this explains why most hospitals use enoxaparin as their formulary choice for a LMWH [32]. As such, throughout this review, when referring to dosages for LMWH, they will be provided for enoxaparin in milligrams.

Fondaparinux is a antifactor Xa inhibitor with indications for DVT prophylaxis postoperatively after hip replacement, knee replacement and hip fracture as well abdominal surgery in patients at risk for VTE, acute DVT treatment and acute PE treatment. It is administered 2.5 mg daily via the subcutaneous route for DVT prophylaxis. It has been less studied in the trauma population, and does not have the indication currently. In one series of trauma patients, fondaparinux was found to be an effective prophylactic agent for VTE [33].

**LMWH and Renal Failure**

Because LMWH is cleared by the kidneys, patients with impaired renal function have prolonged elimination, and can have accumulation. Thus, patients with severe renal insufficiency may be at increased risk for bleeding with standard doses of LMWH, particularly after multiple doses. In addition, LMWHs are not fully reversible compared to UFH. Therefore, to avoid excessive bleeding in the renally impaired population, the dose of LMWH for VTE prophylaxis should be adjusted as shown below [34].

\[
\text{CrCl} \geq 30 \text{ ml/min- Enoxaparin 30 mg subcutaneously every 12 hours or Enoxaparin 40 mg subcutaneously daily}
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\[
\text{CrCl} < 30 \text{ ml/min- Enoxaparin 30 mg subcutaneously once daily}
\]

Current contraindications to early initiation of LMWH include the following:

- Active intracranial hemorrhage
- Incomplete spinal cord injury with associated paraspinal hematoma
- Ongoing/uncontrolled hemorrhage
- Uncorrected coagulopathy

The presence of head injury, without frank hemorrhage, complete spinal cord injuries, lacerations or contusions of internal organs such as the lungs, liver, spleen or kidneys, or the presence of a retroperitoneal hematoma associated with a pelvic fracture, do not by themselves contraindicate the use of LMWH prophylaxis as long as the patient has no evidence of active bleeding.

Intermittent pneumatic compression devices (IPC) cannot be recommended as sole routine prophylaxis in trauma. IPC may be beneficial as the initial prophylaxis in patients with the intracranial hemorrhage, or other injury that are at high risk for bleeding, and can be utilized until LMWH may be safely initiated. In addition, the IPC may be used adjunctively with the LMWH for the high risk trauma patient. Graded compression elastic stockings cannot be recommended as DVT prophylaxis in trauma patients.

The use of an inferior vena cava (IVC) filter device (aka: Greenfield filter), should not be used as the primary modality for the prevention of DVT in trauma patients, or other populations. IVC filter insertion is appropriate for treatment of patients with proximal DVT, who have contraindications to anticoagulation, or may require major surgery in the near future. It is preferential that retrievable IVC filters be utilized on a temporary basis for the trauma population, particularly in younger
patients. However, it has been demonstrated that 70% of retrievable filters in one series were left permanently due to patient preference, and lack of follow up [35].

Routine surveillance monitoring with ultrasound for the presence of DVT is not indicated, and should not be performed routinely [36].

Non-operative Management of Solid Organ Injury

The trend over recent decades has been towards nonoperative management of solid organ injury (NOM) in critically injured patients that have sustained blunt solid organ trauma [37]. This has resulted in higher rates of organ preservation. There is limited evidence for the safety of chemical prophylaxis in this group, but it appears to be safe. In two studies that used enoxaparin early (less than 3 days into admission) in patients undergoing NOM, it did not appear to increase the failure rates [38,39]. In situations where ongoing bleeding is of great concern, the patient can be initially prophylaxed with heparin subcutaneously, and later switched to LMWH as the concern abates. It should also be realized that bleeding in the NOM patient later than 72 hours post injury is a rare event. In addition, these patients can also receive mechanical thromboprophylaxis with IPC devices, although definitive evidence is lacking.

Antifactor Xa Monitoring in High Risk Trauma Patients

Recently, research has suggested that standard dosing of LMWH at the highest routinely prescribed trauma doses (namely, enoxaparin 30 mg subcutaneously every 12 hours, may be inadequate prophylaxis in the high risk trauma patient, and can lead to increased rates of DVT [40,41]. In these patients, the dose of LMWH should be monitored, and adjusted to the antifactor Xa level. The normal value of the antifactor Xa is < 0.1, and the level should be sent as a trough before the 4th dose of the LMWH. If the value of the antifactor Xa is normal (< 0.1), then the enoxaparin should be increased to 40 mg subcutaneously every 12 hours. For reference, an antifactor Xa > 0.5 is considered therapeutically anticoagulated, and therefore, for prophylaxis, the target antifactor Xa level is 0.2 to 0.5. If the patient has not bumped their antifactor Xa level to the target, then the dose is increased to enoxaparin 40 mg subcutaneously every 12 hours. If the dose is increased to 40 mg subcutaneously every 12 hours, the antifactor Xa level should be resent before the 4th dose, and if still subtherapeutic (Xa < 0.1) then increased again to 50 mg subcutaneously every 12 hours. A small minority of patients may require enoxaparin doses at 50 mg subcutaneously every 12 hours, or even 60 mg subcutaneously every 12 hours to achieve a bump in the antifactor Xa level into the therapeutic range [42]. With this approach, the majority of patients require the enoxaparin in the 40 mg subcutaneously every 12 hours dose [43].

Traumatic Brain Injury with Intracranial Hemorrhage

It is known that traumatic brain injury (TBI) patients are at increased risk of DVT [44]. This is due to the hypercoagulability that is induced in the TBI patient from a variety of mechanisms including the release of tissue factor [45]. Pharmacological DVT prophylaxis after TBI has been significantly debated in the literature [46]. The concern for chemical prophylaxis is that it may contribute to the progression of intracranial hemorrhage (ICH), and there is evidence that if started too soon, at less than 24 hours, this may occur [47]. All TBI patients should receive IPC upon admission to the hospital. In addition, in the presence of TBI with intracranial hemorrhage, before chemical thromboprophylaxis is initiated, a repeat Head CT should be obtained, to assess for the lack of progression of further bleeding. The CT scans can be performed serially at 24 hour intervals (or more frequently as clinically indicated) until any bleeding has stabilized by a demonstrated lack of progression. The chemical thromboprophylaxis should then be started in a 24 to 48 hour window after there is no further progression of ICH. The safety of this approach has been documented across studies [48-50].

Spinal Cord Injury

The National Spinal Cord Injury Statistical Center reports the incidence of spinal cord injury (SCI) at 40 cases per million, and approximately 12,000 new cases per each year [51]. DVT and PE are the major complications in SCI associated with motor paralysis. In SCI, the incidence of DVT and PE is three times higher than the general population [52] with an incidence that ranges from 49% to 72% [53]. The other interesting finding is that DVT and PE persist and recur despite adequate anticoagulation in this population.

Numerous studies failed to identify a hypercoagulable imbalance in blood coagulation factors or a decrease in anticoagulant activity. On the other hand fibrinolysis, a process unrelated to hypercoagulability, but closely related to endothelial cell integrity, is predictably altered and contributes to the persistence of venous occlusion by thrombosis. In SCI, interruption of the neurologic impulses and the ensuing paralysis cause profound metabolic changes in blood vessels which promotes venous thrombosis. There is also altered venous competence, manifested by a decrease in venous distensibility, decreased capacitance and an increase in venous flow resistance. Vascular adaptation to inactivity and muscle atrophy, rather than a dysfunctional calf muscle pump and sympathetic denervation, cause thrombosis. Therefore, it follows that venous thrombosis cannot be reversed by anticoagulation alone. Measures to increase venous distensibility and decrease flow resistance are also required, which can be provided by intermittent pneumatic compression.

Given the high risk for VTE in SCI patients, the ACCP recommendations are to provide a combined approach of mechanical and chemical DVT prophylaxis [1]. The chemical prophylaxis in this population should be LMWH, and a recent review suggested that it be started within 72 hours, and for surgical intervention it can be held, and then restarted within 24 hours of the procedure [54].

The routine insertion of a prophylactic IVC filter is controversial in the SCI patient, with nonuniformity of practice patterns of IVC filter insertion [55]. While not specific to the SCI population, or even the trauma population, when studied, IVC filters have did not significantly change the long term mortality in patients, while increasing the risk of recurrent DVT over time [56,57]. Finally, when SCI patients were studied in a rehabilitation facility, the IVC filter quadrupled the incidence of a DVT occurring during the rehab stay compared to those without the filter, and the only PE observed was in a patient with a filter in place [58].

Bariatric Trauma Patients

Obesity is an important independent risk factor for thrombosis, and VTE is common in obese patients. Obesity is regarded as a prothrombotic state, with derangements in normal hemostasis, and a pro-inflammatory state [59,60]. LMWH has theoretic advantages in obese patients as a result of superior subcutaneous bioavailability compared to UFH. However, even LMWH at standard fixed doses may not be sufficient to prevent VTE in morbidly obese patients [61]. Specific data on DVT prophylaxis in obese patients after trauma is very limited, and extrapolated from recommendations on surgery in this population.
Prophylaxis for bariatric patients: [62].
BMI ≤ 50 kg/m² – enoxaparin 40 mg SC every 12 hours
BMI > 50 kg/m² – enoxaparin 60 mg SC every 12 hours

As an alternate regimen, the standard dose of enoxaparin can be increased by 25% in bariatric patients.

Conclusion

Trauma patients are at high risk for VTE. LMWH is the most efficacious method of DVT prophylaxis, and should be used in all appropriate patients. IPC's are used most commonly as an adjunct to the chemical prophylaxis, or as a sole agent when concern for ongoing appropriate patients. IPC's are used most commonly as an adjunct to efficacious method of DVT prophylaxis, and should be used in all patients. It is important to consider the use of electrical or mechanical prophylaxis especially in the setting of NOM of solid organ injury, and stable intracranial hemorrhage, potential bleeding issues in the trauma population, even in the setting of NOM of solid organ injury, and stable intracranial hemorrhage, prophylaxis may be safely accomplished.

References

15. Why is the low molecular weight heparin, enoxaparin (Lovenox) dosed in mg while the other LMWH's (dalteparin (Fragmin) and tinzaparin (Innohep) are dosed in IU/kg and is this difference clinically relevant? Pharmacology Weekly 2012.


