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Inflammation and the Host Response to Injury a Large-Scale Collaborative Project: Patient-Oriented Research Core Standard Operating Procedure for Clinical Care X. Guidelines for Venous Thromboembolism Prophylaxis in the Trauma Patient

Joseph Cuschieri, MD

Department of Surgery, University of Toronto, Ontario, Canada.

Brad Freeman, MD

University of Washington, Seattle, Washington; Department of Surgery, University of Toronto, Ontario, Canada.

Grant O'Keefe, MD, MPH

Department of Surgery, University of Toronto, Ontario, Canada.

Brian G. Harbrecht, MD

Washington University, St. Louis, Missouri; Department of Surgery, University of Toronto, Ontario, Canada.

Paul Bankey, MD, PhD

University of Louisville, Louisville, Kentucky; Department of Surgery, University of Toronto, Ontario, Canada.

Jeffrey L. Johnson, MD

University of Rochester Medical Center, Rochester, New York; Department of Surgery, University of Toronto, Ontario, Canada.

Joseph P. Minei, MD

Denver Health Medical Center, University of Colorado at Denver, Denver, Colorado; Department of Surgery, University of Toronto, Ontario, Canada.

Jason Sperry, MD

University of Texas Southwestern, Dallas, Texas; Department of Surgery, University of Toronto, Ontario, Canada.

Michael A. West, MD, PhD

University of Pittsburgh, Pittsburgh, Pennsylvania; Department of Surgery, University of Toronto, Ontario, Canada.

Avery Nathens, MD, PhD, MPH

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Address for reprints: Joseph Cuschieri, MD, Department of Surgery, Harborview Medical Center, 325 9th Avenue, Box 359796, Seattle, WA 98104; jcuschie@u.washington.edu..

*Additional participating investigators in the Large Scale Collaborative Research Agreement entitled, "Inflammation and the Host Response to Injury" are listed in the Acknowledgments.

Northwestern University, Chicago, Illinois; and Department of Surgery, University of Toronto, Ontario, Canada.

Ernest E. Moore, MD

University of Rochester Medical Center, Rochester, New York; Department of Surgery, University of Toronto, Ontario, Canada.

Ronald V. Maier, MD

Department of Surgery, University of Toronto, Ontario, Canada.

the Inflammation and the Host Response to Injury Collaborative Research Program*

OVERVIEW

Venous thromboembolism (VTE) in seriously injured patients is a common problem that can potentially lead to substantial morbidity, mortality, and resource expenditure.¹⁻³ In fact, patients recovering from trauma have the highest rate of VTE among all subgroups of hospitalized patients.⁴ Depending on the patient cohort and diagnostic modality, rates of deep venous thrombosis (DVT) and pulmonary embolism (PE) may be as high as 40% and 20%, respectively.^{5,6} Not only is the development of VTE in the form of a massive PE a cause of late death in the injured patient, VTE development anytime after injury complicates management and can lead to significant long-term sequelae. To reduce the risk of VTE, many practitioners administer mechanical or pharmacologic thromboprophylaxis or both.

Although, numerous interventions have been evaluated for potential efficacy in preventing VTE in selected subpopulations of injured patients, the data on the optimal method of prophylaxis that balances risk of VTE with risk of complications from therapy remains inconclusive.^{7,8} On the basis of the current data, several evidence-based guidelines have been proposed with varying degrees of application and effectiveness, primarily due to concerns of increased bleeding.⁶ However, delay in the initiation of prophylaxis is associated with a 3-fold increase in the incidence of VTE.⁹ This increased incidence in VTE occurring with delayed initiation is most likely secondary to an earlier than expected development of VTE. In fact, VTE has been diagnosed in a significant number of patients within the first 24 hours after injury and approximately one-third of all cases of VTE are diagnosed within 1 week of injury.^{9,10} The lack of consistent data emphasizes the need for adequately designed prospective evaluations to define optimal practice in this area. As part of the Inflammation and the Host Response to Injury Large- Scale Collaborative Research Program, the participating investigators have developed guidelines for VTE prophylaxis based on best available evidence and expert opinion to standardize this aspect of care among participating centers.

PROTOCOL GOALS

The goals of this protocol are to (1) base prophylaxis on an estimate of VTE risk and potential for anticoagulant-associated morbidity; (2) provide a framework for use of low molecular weight heparin (LMWH) as well as nonpharmacologic interventions (sequential compression devices [SCD], venous foot pumps, vena cava filter [VCF]); and (3) guide VTE surveillance in high risk patients with multiple injuries.

PROTOCOL RATIONALE

Risk of VTE in the Injured Patient

The risk of VTE after major trauma is well established. In a prospective observational study of injured patients not receiving VTE prophylaxis, Geerts et al.¹ reported an incidence of lower extremity DVT documented by venography of 58%, with 18% of individuals having proximal thrombus extension. In subsequent studies, several patient and injury-specific risk factors have been identified which place the injured patient at increased risk for VTE. These factors include advanced age (age >50), hypercoagulable state, obesity, malignancy, smoking, and pregnancy.⁸ Injury-specific risk factors include massive blood transfusion, surgery, femur or tibia fracture, pelvic fracture, spinal cord injury, closed head injury, and prolonged immobilization.¹⁻³

Given the high risk of VTE among injured patients, strategies directed toward prevention are essential. As a result, VTE prophylaxis in some form is considered standard of care after trauma.⁷ Protocols guiding VTE prophylaxis should be in place in all hospitals caring for injured patients in conjunction with quality assurance measures to document compliance and effectiveness.¹¹ Unfortunately, prophylactic measures only reduce the incidence but do not eliminate the occurrence of VTE. Even with the use of routine thromboprophylaxis, risk of DVT, and proximal DVT in trauma patients is still estimated to be as high as 31% and 6%, respectively.⁶ Clinicians caring for acutely injured patients should maintain a high index of suspicion for VTE development, despite strict adherence to protocols. In fact, only 1% of patients with VTE manifest any clinical evidence before diagnosis, thus emphasizing the role of screening of patients at increased risk.^{1,11}

Prophylaxis in VTE

To reduce the risk of VTE, both mechanical and pharmacologic methods have been advocated.^{7,8} Mechanical prophylaxis includes intermittent pneumatic compression devices, and VCF. Pharmacologic prophylaxis presently includes unfractionated heparin (UFH) and LMWH, with the potential use of Factor Xa inhibitors in the future.¹²

Mechanical Prophylaxis: Intermittent Pneumatic Compression Devices—

Mechanical methods of VTE prophylaxis include both foot pumps and SCD. The devices are thought to mediate their effect primarily through an increase in venous outflow or reduction in stasis or both.^{7,8} Additionally, some benefit may be obtained through secretion of endothelial-derived anticoagulants resulting in an alteration of the coagulation and fibrinolytic mechanisms.¹³

Despite these theoretical benefits, the literature supporting the use of these devices has methodologic limitations and remains limited in patients suffering from trauma. Nonetheless, some generalizations can be made on the basis of available information. Although intermittent pneumatic compression devices have demonstrated a reduction in the risk of DVT in a number of patient subgroups compared with no prophylaxis, they do not reach the protection offered by pharmacologic prophylaxis.^{14,15} Furthermore, mechanical prophylaxis interventions have not been shown to reduce the risk of PE or death.^{16,17}

Despite this limitation, the combination of both mechanical and pharmacologic prophylaxis may result in increased efficacy over each individually.¹⁶ Overall, the primary advantage of these mechanical devices over pharmacologic prophylaxis is the low risk of bleeding complications. However, these devices have been associated with severe skin changes, wound complications, and relatively poor compliance with utilization even when routinely ordered.¹⁸ As a result, proper application must be insured when applied.

Mechanical Prophylaxis: Vena Cava Filter—Inferior vena caval interruption devices have been used with variable frequency in trauma patients to prevent PE. Although no current prospective data exists, the use of this device may result in a reduction in the PE occurrence in patients unable to be anticoagulated for a number of reasons.¹⁹⁻²¹ This includes patients with lower extremity thrombus and contraindications to anticoagulation, those with recurrent PE while adequately anticoagulated, and those with free-floating iliofemoral thrombus.²²

The placement of this device for prophylaxis in a patient without evidence of VTE, however, remains controversial. Several studies have reported the use of VCFs for prophylaxis in patients at high risk for PE. Most of these studies demonstrated a significant reduction in the incidence of PE in patients treated with prophylactic VCFs compared with historical controls.^{19,20,23} However, unlike the majority of studies, one study by McMurtry et al.²¹ did not demonstrate an overall reduction in PE with the use of a prophylactic VCF.

Despite these limited data, a growing interest in prophylactic VCF use in the setting of trauma has increased as a result of the emergence of retrievable VCFs with an acceptable safety profile.^{23,24} The challenge is defining the patient population at the appropriate increased risk for the development of VTE. At present, this high-risk patient population is thought to consist of severe closed head injury defined as a Glasgow Coma Scale less than 8, spinal injury with paraplegia or tetraplegia, complex pelvic fracture with associated long bone fractures, multiple long bone fractures, and massive transfusion.⁷ There, however, is no data supporting that this approach is effective at preventing PE, either when implemented in all high-risk trauma patients or when coupled with use of noninvasive screening modalities. Additionally, the rate of removal of these retrievable VCFs remains relatively uncommon.²⁵ Thus, the efficacy and safety of prophylactic VCF insertion in the setting of trauma remains debated. Until better data are available on the utilization of prophylactic VCF to reduce the incidence of PE in high-risk injured patients, the one universally accepted indication for VCF insertion will remain those patients that have a documented VTE and contraindications for anticoagulation.

Pharmacological Prophylaxis: Unfractionated Heparin—UFH given in doses of 5,000 units subcutaneously two to three times per day represents the standard pharmacologic treatment for VTE prophylaxis in medical and general surgical patients. Although this prophylactic dose has been used extensively in hospitalized patients, prospective data demonstrating efficacy of UFH in trauma patients remains lacking.

In a prospective nonrandomized study involving 395 trauma patients with an Injury Severity Score (ISS) >9, Dennis et al.²⁶ found that VTE prophylaxis with either UFH or mechanical

prophylaxis resulted in lower rates of DVT than no prophylaxis. In contrast, in a prospective randomized study enrolling 400 patients, Knudson et al.²⁷ reported that the risk of VTE was no different in patients receiving UFH compared with those treated receiving no form of thromboprophylaxis. Similarly, while lacking a no anticoagulation control arm, a prospective controlled trial by Geerts et al.⁶ comparing LMWH and UFH found that the incidence of DVT in patients in the UFH arm did not differ from the incidence predicted by statistical modeling in patients receiving no form of prophylaxis. Additional observational studies suggest lack of benefit of UFH as VTE prophylaxis in the setting of trauma. Although many of the studies in examining the effect of UFH in trauma have methodologic shortcomings, available evidence suggests that UFH is ineffective in preventing VTE in severely injured patients especially at a dose of only 5,000 units administered subcutaneously twice per day.⁷ The potential benefit of dosing three times per day is unclear but has been shown to have increased benefit in some trials.^{8,28}

Pharmacological Prophylaxis: Low Molecular Weight Heparin—The use of LMWH after trauma, in the form Enoxaparin or Daltaparin, for the prevention of VTE has been demonstrated to be superior to UFH. Several studies have evaluated the efficacy of LMWH use in the setting of trauma. In a prospective study, Geerts et al.⁶ randomized 344 patients after major trauma to either LMWH or UFH as VTE prophylaxis. Administration of these agents was initiated within 36 hours of hospitalization. Exclusion criteria included intracranial hemorrhage, ISS <9, or evidence of ongoing bleeding or coagulopathy. In comparison to historical controls, LMWH was associated with a 30% reduction in all DVT (44% with UFH vs. 31% with LMWH, $p = 0.014$) and a 58% reduction in proximal DVT (15% with UFH vs. 6% with LMWH, $p = 0.012$). Major bleeding complications were infrequent (1.7%) and although there was a slight increase risk of bleeding complications in patients receiving LMWH, this did not reach statistical significance (0.8% with UFH vs. 3.9% with LMWH). Formal economic analysis suggests that the use of LMWH in the trauma setting is cost-effective.²⁹

The administration of LMWH is known to be complicated by variations in patient demographics. As a result, several investigators have suggested differences in the dose of LMWH based on these specific characteristics. Included among the patient characteristics are obesity, renal failure, and edema. Although effectiveness of LMWH can be followed using anti-Xa levels, both obesity and edema dosages appear that they can be safely administered with appropriate therapeutic levels based solely on patient weight.^{30,31} Renal failure, on the other hand, should have appropriate reduction of the dose of LMWH if the CrCl <30 mL/min.³² As a result of these modifications, no substantial risk of increased risk for VTE or bleeding has been reported.

Several situations encountered in the practice of trauma are characterized by either an increased risk of bleeding or excessive morbidity should a bleeding event occur, and constitute a relative contraindication to the administration of LMWH. These situations include severe closed head injury with intracranial hemorrhage, ongoing hemorrhage, coagulopathy, intra-abdominal solid organ injury managed non-operatively, and spinal column fracture with epidural hematoma.⁸ In addition, in 1997, the Food and Drug Administration issued a public health advisory reporting that a series of patients developed

perispinal hematoma after receiving LMWH in conjunction with spinal or epidural anesthesia.³³ Although many patients had other factors that may have predisposed them to bleeding complications (i.e., underlying hemostatic abnormalities, coadministration of anticoagulants, anatomic or vascular vertebral column abnormalities, traumatic needle insertion, etc), an appreciable number that suffered a perispinal hematoma after epidural anesthesia while on LMWH experienced neurologic impairment despite surgical decompression.

The bleeding concerns associated with the use of LMWH in trauma patients with multiple injuries have lead to disagreement with respect to the timing of administration. Despite these concerns, recent reports have suggested that LMWH has an acceptable safety profile when administered to patients with closed head injury or solid organ trauma or both.³⁴⁻³⁶ Nonetheless, in the absence of more complete information regarding the safety of LMWH in these and comparable situations, the decision as to whether and when LMWH can be safely prescribed after major trauma is left to clinician discretion. However, this discretion does lead to marked variations in practice patterns that may actually significantly delay appropriate prophylaxis increasing the risk for VTE. The risk of delayed initiation of prophylaxis appears to increase significantly by 4 days after injury, with a 3-fold increase risk of VTE.⁹ As a result, a number of investigators have suggested earlier initiation of prophylaxis with safety demonstrated within 24 hours for solid organ injury and 72 hours for head injury.^{35,36} This recommendation is based on current data, but as further prospective studies are performed evaluating the safety of LMWH earlier initiation of prophylaxis may be recommended.

Although bleeding remains the most common complication of both UFH and LMWH administration, patients should be carefully followed for the development of heparin-induced thrombocytopenia (HIT). This prothrombotic syndrome is a result of patient antibodies against platelet factor 4-heparin complexes.³⁷ Binding of the platelet factor 4-heparin-antibody complex to the platelet surface FcγIIa receptor causes platelet activation and the paradoxical thrombocytopenia and thromboembolic complications.³⁸ The larger more sulfated heparins, such as UFH, are more commonly associated with HIT than the LMWH.³⁹ Although thought to occur only in approximately 1% of patients receiving heparin, injured patients and those with previous exposure are at increased risk.⁴⁰ As a result, therapy for patients suspected of having HIT should begin with immediate discontinuation of heparin in any form followed by pharmacologic inhibition of thrombin (e.g., recombinant hirudin (lepirudin), argatroban, danaparoid sodium).⁴¹

Screening of VTE—Venous doppler ultrasonography is currently the most widely used method for the diagnosis of lower extremity DVT because of its accuracy, wide availability, and noninvasive nature.⁷ However, there are limitations to the application of doppler ultrasonography as a screening modality in the setting of trauma. Specifically, the presence of splints and dressings limit adequate visualization of extremity veins. Deep pelvic veins, which are often the source of emboli after pelvic fracture, are rarely visualized. The ability of this technique to reliably detect venous thrombosis compared with venography has not been thoroughly studied after major injury. In addition, while duplex ultrasonography has

been used to screen for asymptomatic VTE in the injured patient, its utility in reducing VTE-associated morbidity and mortality is not established.⁴²

Other less frequently used screening tools consist of imaging with magnetic resonance venography and laboratory evidence of clot formation with D-dimer. Although infrequently used, magnetic resonance venography has been prospectively evaluated in patients with pelvic fractures undergoing operative fixation allowing the identification of asymptomatic deep pelvic vein thrombosis in 18% of injured patients.⁴³ Identification of these deep pelvic vein thromboses is not possible with routine venous doppler ultrasonography. However, the majority of these patients had other sites of DVT that could be picked up by venous doppler ultrasonography. D-dimer, on the other hand, is a simple and an inexpensive laboratory study that has been used by some investigators to rule out VTE. Although D-dimer has been associated with a negative predictive value for VTE as high as 100% in some studies, other studies have demonstrated no predictive value to the use of D-dimer due to injury induced elevations which can remain elevated for prolonged periods in the most seriously injured.⁴⁴⁻⁴⁷ Thus, until further large prospective studies are performed the routine use of D-dimer as a screening tool cannot be fully advocated.

As discussed, there are significant limitations in the available evidence on the optimal method of VTE prophylaxis in severely injured patients. Nevertheless, the Program's investigators were charged with attempting to standardize care among the participating centers for patients entered into the Program's study. The protocol below attempts to reflect the best available evidence and, when evidence is inadequate or not available, the consensus of the program's investigators was used instead. The investigators acknowledge that emerging data may modify these recommendations, as additional high quality studies on VTE are performed.

PROTOCOL DETAILS

- A.** Patients expected to be hospitalized for at least 48 hours and who have sustained major trauma (pelvic or long bone fracture, spinal cord injury, complex lower extremity venous injury, Glasgow Coma Scale <9, ISS >15, massive transfusion), are anticipated to be immobilized for at least 48 hours, or who have preinjury conditions associated with increased risk of VTE (history of hypercoagulable state, obesity, pregnancy, age >50) are identified and considered high risk (Fig. 1). Patients not considered high risk can be treated with mechanical prophylaxis with or without either UFH or LMWH.
- B.** Patients are screened for conditions representing potential contraindications to LMWH use (severe closed head injury, intracranial hemorrhage, craniotomy, epidural catheter use or epidural hematoma, ongoing hemorrhage, coagulopathy, significant intra-abdominal solid organ injury managed nonoperatively, spinal column fracture).
- C.** In the absence of potential contraindications, LMWH (e.g., enoxaparin sodium 30 mg subcutaneously every 12 hours) is prescribed in conjunction with mechanical prophylaxis (SCD or venous foot pumps). SCD should be used if feasible. Relative

contraindications to the use of SCD include the presence of large extremity wounds, nonfixated fractures, the presence of external fixators, the presence of extremity casts, or recent vascular reconstruction. SCD may be used on fractured extremities after open reduction and internal fixation. Venous foot pumps should be used when contraindications to SCD are present. For patients with renal insufficiency ($\text{CrCl} < 30 \text{ mL/min}$), dose adjustment of LMWH is recommended (e.g. enoxaparin sodium 30 mg subcutaneously every 24 hours). For obese patients (body mass index > 30), dose adjustment of LMWH should be considered (e.g., enoxaparin 40 mg subcutaneously every 12 hours).

- D.** VTE prophylaxis should continue until the patient is ambulatory. For Patients discharged before achieving ambulatory status, VTE prophylaxis should continue postdischarge until a suitable level of mobility is achieved.
- E.** In the presence of contraindications to LMWH, patients are evaluated for the potential placement of a prophylactic VCF (spinal cord injury with tetraplegia or paraplegia, complex pelvic fractures in association with long bone fractures, multiple long bone fractures, contraindications to LMWH expected to persist beyond 72 hours). The decision as to whether a VCF should be placed, as well as whether the device placed is permanent or retrievable is left to physician discretion. For solid organ injury, unless other contraindications exist, LMWH can frequently be started in stable injuries within 36 hours to 48 hours of injury. Although prophylaxis with LMWH for closed head injury can frequently be started within 72 hours in patients with stable injuries unless other contraindications exist.
- F.** In the absence of indications for VCF placement, VTE prophylaxis is provided initially by mechanical prophylaxis. Patients are continuously reassessed for resolution of contraindications to LMWH use. Once LMWH contraindications resolve, LMWH should be initiated in addition to maintenance of mechanical prophylaxis. If contraindications to LMWH persist for a prolonged period of time, patients should undergo surveillance for lower extremity thrombus using noninvasive methods. Because the optimal frequency of duplex surveillance has not been established, surveillance studies should be considered early within 48 hours to 72 hours of hospitalization. Consideration should be given for repeating duplex surveillance studies every 5 days to 7 days for as long as contraindications to pharmacologic prophylaxis persist. Detection of proximal lower extremity thrombus requires therapeutic anticoagulation or VCF placement or both.
- G.** Suspicion of PE should be rapidly evaluated with chest computed tomography angiography. In the presence of an intravenous contrast-dye allergy or renal insufficiency, evaluation can be performed with ventilation perfusion scanning. Suspicion of lower extremity thrombus should be evaluated by Doppler ultrasound. In the presence of either a PE or proximal lower extremity thrombus, the patient requires therapeutic anticoagulation or VCF placement or both depending on their risk assessment for morbidity therapy versus repeated or recurrent VTE.

SUMMARY

Standardization of VTE prophylaxis may offer significant benefit in the care of the critically ill trauma patient. Current randomized, prospective controlled trials on the effectiveness of various VTE prophylaxis remain lacking. The potential problems with currently available trials, associated with the potential ramification of bleeding and HIT in subsets of trauma patients, require caution in adopting an extremely aggressive approach to VTE prevention. However, improved understanding and administration of VTE prophylaxis appears to be a promising and prudent approach to decreasing morbidity and mortality in injured patients. The goal of this standard operating procedure (SOP) was to standardize the management of injured patients enrolled in the Inflammation and Host Response to Injury Large-Scale Collaborative Program across multiple clinical sites. It is based on the available medical evidence and expert opinion when evidence is not available. The steps in this SOP represent one method of attempting to reach the goal of VTE prevention. Additional prospective randomized controlled trials will likely provide additional information that may stimulate further revisions of this SOP as the VTE prevention in critically ill trauma patients is better defined.

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Fig. 1.

Protocol for venous thromboembolism prophylaxis following injury.