The Practice of Venous Thromboembolism Prophylaxis in the Major Trauma Patient

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**Background:** The incidence of venous thromboembolism (VTE) without prophylaxis is as high as 80% after major trauma. Initiation of prophylaxis is often delayed because of concerns of injury-associated bleeding. As the effect of delays in the initiation of prophylaxis on VTE rates is unknown, we set out to evaluate the relationship between late initiation of prophylaxis and VTE.

**Methods:** Data were derived from a multicenter prospective cohort study evaluating clinical outcomes in adults with hemorrhagic shock after injury. Analyses were limited to patients with an Intensive Care Unit length of stay \( \geq 7 \) days. The rate of VTE was estimated as a function of the time to initiation of pharmacologic prophylaxis. A multivariate stepwise logistic regression model was used to evaluate factors associated with late initiation.

**Results:** There were 315 subjects who met inclusion criteria; 34 patients (11%) experienced a VTE within the first 28 days. Prophylaxis was initiated within 48 hours of injury in 25% of patients, and another one-quarter had no prophylaxis for at least 7 days after injury. Early prophylaxis was associated with a 5% risk of VTE, whereas delay beyond 4 days was associated with three times that risk (risk ratio, 3.0, 95% CI [1.4–6.5]). Factors associated with late (>4 days) initiation of prophylaxis included severe head injury, absence of comorbidities, and massive transfusion, whereas the presence of a severe lower extremity fracture was associated with early prophylaxis.

**Conclusions:** Clinicians are reticent to begin timely VTE prophylaxis in critically injured patients. Patients are without VTE prophylaxis for half of all days within the first week of admission and this delay in the initiation of prophylaxis is associated with a threefold greater risk of VTE. The relative risks and benefits of early VTE prophylaxis need to be defined to better direct practice in this high-risk population.

**Key Words:** Venous thromboembolism, Prophylaxis, Deep venous thrombosis, Pulmonary embolism, Knowledge translation

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Venous thromboembolism (VTE) in high-risk trauma patients is a frequent event. Depending on the cohort and the diagnostic modality, rates of deep venous thrombosis and pulmonary embolism might be as high as 40% and 20%, respectively.\(^1,2\) Proximal lower extremity venous thrombosis has been documented in as many as 10% of patients, whereas over 1% of patients experience a symptomatic pulmonary embolism.\(^1,3\) Not only is the development of VTE in the form of a massive pulmonary embolism a frequent contributor to late death in the injured patient, its development complicates management and leads to late sequelae. To reduce the risk of VTE, many practitioners administer pharmacologic thromboprophylaxis, an approach supported by several randomized controlled trials and evidence-based guidelines.\(^4,5\)

Pharmacologic thromboprophylaxis is associated with a low but clearly quantifiable bleeding risk in the range of 1% to 3%, depending on the agent used.\(^1\) This risk, however low, requires the treating physician to balance the risk of bleeding with the risk of VTE and the perceived benefit of thromboprophylaxis. The ability of the physician to assess the risks and benefits might be limited, particularly when caring for patients at high risk for both bleeding and VTE. We postulated that because of the inability to define the risks and benefits of prophylaxis, many physicians would simply delay the initiation of pharmacologic VTE prophylaxis until the bleeding risk had sufficiently abated. To ascertain practice patterns in relation to this clinical dilemma, we sought to...
evaluate (1) the timing of pharmacologic prophylaxis; and (2) the effects of delayed prophylaxis in a severely injured cohort of patients admitted to the intensive care unit.

METHODS

Study Design

This is a secondary analysis of data collected in the context of an ongoing large multicenter prospective cohort study whose primary objective is to evaluate the relationship between the inflammatory response to injury and posttraumatic multiple organ failure. In this analysis, the exposure represented the time to pharmacologic VTE prophylaxis and the primary outcome was the development of VTE within 28 days of injury.

Patients

The Inflammation and the Host Response to Injury is a collaborative program supported by the National Institute of General Medical Sciences (NIGMS) to better define the proteomic and genomic response in injured patients at high risk for posttraumatic multiple organ failure. This report focuses on patients admitted to any one of seven participating institutions during the interval April 2004 through February 2006. Criteria for enrollment were age $\geq 16$ years, blunt trauma, arrival to hospital within 6 hours of injury, either hypotension ($<90$) or an elevated base deficit ($\geq 6$), blood transfusion within 12 hours of injury, any body region exclusive of the brain with an Abbreviated Injury Scale score ($\geq 2$), and an intact cervical spinal cord to exclude those with isolated severe head injuries or spinal cord injuries, respectively. As the primary objective of this analysis was to evaluate the practice of pharmacologic VTE prophylaxis in the Intensive Care Unit (ICU) and subsequent VTE, we further limited inclusion to subjects surviving at least 48 hours and who were in the ICU for at least 7 days. Standard operating procedures (SOP) for clinical care were developed to minimize variation across centers. During the time interval of this analysis, the SOP for VTE prophylaxis had not yet been finalized. The institutional review board of each participating center approved the cohort study.

Data Collection

Clinical data were obtained by trained nurse abstractors and entered into TrialDb, a Web-based data collection platform. Injuries were coded by body region using the AIS with AIS $\geq 3$ considered a severe injury. The Injury Severity Score (ISS) was used as a global measure of injury severity. Data integrity was evaluated centrally through an assessment of missing values, range checks, evaluation for implausible values and internal consistency. Additionally, data were validated through an external review of a random sample of charts by a physician and independent chart abstractor.

Timing of VTE Prophylaxis

We evaluated the timing of initiation of pharmacologic VTE prophylaxis during the first 7 days of ICU admission. Agents were considered prophylactic if administered as one of the following regimens: heparin 5000 IU bid or tid; enoxaparin 30 mg bid; or dalteparin 5000 IU, each administered by subcutaneous injection. Additionally, when applicable, the date of insertion of an inferior vena caval filter was recorded.

VTE

VTEs were diagnosed by pulmonary angiogram, computed tomographic pulmonary angiography, or duplex ultrasonography (in the case of deep venous thrombosis). All subjects were followed for at least 28 days or until hospital discharge, whichever occurred first.

Statistical Analyses

The relative risk of VTE as a function of the timing of initiation of pharmacologic prophylaxis was evaluated using a Poisson model. The results obtained identified an inflection point allowing the classification of timing of initiation into early or late, where the latter was associated with an increased risk of VTE. We then determined the relationship between late initiation of VTE prophylaxis and several patient and/or injury characteristics using the $\chi^2$ test for categorical variables and the $t$ test for continuous variables. All variables with $\alpha < 0.1$ on univariate analyses were entered into a forward stepwise regression model to identify risk factors for late initiation of prophylaxis. Model parameters for entry and exit into the model were $\alpha = 0.1$ and $\alpha = 0.05$, respectively. All analyses were performed using Stata Version 8 (College Station, Tex).

RESULTS

There were 731 patients enrolled during the interval of study. Of this cohort, only 315 spent the first 7 days of their admission in the ICU. Of these 315 patients, 34 (11%) had a diagnosis of VTE: 16 DVT, 14 PE, and 4 with both. One-third of events occurred in the first week after injury (Fig. 1).
Four patients had evidence of DVT within the first 48 hours after admission and were excluded from further analysis given the lack of available opportunity for prophylaxis, leaving a final cohort of 311 patients.

Pharmacologic prophylaxis was initiated within 48 hours of injury in one-quarter of all patients, and another one-quarter went without prophylaxis for at least 7 days after injury (Fig. 2). The delay in prophylaxis was not because of mitigation of the risk of pulmonary embolism with the placement of IVC filters, as only 37 (12%) patients had filters inserted during the course of their admission. Three-quarters (29) of filters were placed before VTE prophylaxis was initiated.

The proportion of patients developing VTEs increased significantly with delays in initiation of pharmacologic prophylaxis (Fig. 3). Early prophylaxis was associated with a 5% risk of VTE, whereas a delay beyond 4 days was associated with three times that risk (risk ratio: 3.0, 95% confidence interval [1.4–6.5]). There was no further increase in risk with delays beyond this time. Specifically, beginning prophylaxis on day 7 was no worse than on day 5. All the increased risk was assumed through delays in excess of 4 days.

To better understand the reasons for delays in the initiation of pharmacologic prophylaxis, we evaluated patient and injury characteristics among patients receiving early (≤4 days) prophylaxis compared with the patients receiving late prophylaxis (>4 days). Almost half of all patients (n = 137, 44%) fell into the latter category. Although there were no differences in age, gender, race, or mechanism of injury across the two groups, patients without significant comorbidity (exclusive of liver disease) appeared to be overrepresented in the late prophylaxis group (Table 1).

There were several injury-specific factors that were related to the timing of prophylaxis (Table 2). Although severe lower extremity injuries were significantly associated with early prophylaxis, severe head injuries and massive early transfusion (>6 units/12 hours) were associated with delays in prophylaxis. Coagulopathy as evidenced by either an elevated INR or the need for fresh frozen plasma was also more frequent in the late prophylaxis group, although this did not reach statistical significance.

To evaluate the independent factors associated with the timing of prophylaxis, we performed a forward stepwise logistic regression model assessing the contributions of co-

![Fig. 2. The day of initiation of pharmacologic thromboprophylaxis (black) and the day of initiation of prophylaxis operating room placement of an inferior vena caval filter (gray). The latter is demonstrated to show that in this particular cohort, the delays in initiation of prophylaxis are not because of a significant use of vena caval filters.]

![Fig. 3. The proportion of patients with VTE in relation to the day of initiation of pharmacologic prophylaxis. Gray shading represents the 95% confidence intervals.]

<table>
<thead>
<tr>
<th>Table 1 Baseline Patient Characteristics Associated With Late Pharmacologic Thromboprophylaxis</th>
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<tbody>
<tr>
<td>Early N = 174</td>
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<tr>
<td>Mean age (SD)</td>
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<tr>
<td>Male gender (%)</td>
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<tr>
<td>Race</td>
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<tr>
<td>White</td>
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<tr>
<td>Black</td>
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<tr>
<td>Asian</td>
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<tr>
<td>Other/unknown</td>
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<tr>
<td>Hispanic</td>
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<tr>
<td>Comorbid disease*</td>
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<tr>
<td>None</td>
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<tr>
<td>Cardiac</td>
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<tr>
<td>Peripheral vascular</td>
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<tr>
<td>Cerebrovascular</td>
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<tr>
<td>COPD</td>
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<tr>
<td>Liver</td>
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<td>Chronic renal failure</td>
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<tr>
<td>Malignancy</td>
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<tr>
<td>Coumadin</td>
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<tr>
<td>Prior history or VTE</td>
</tr>
<tr>
<td>Mechanism of injury</td>
</tr>
<tr>
<td>Motor vehicle crash</td>
</tr>
<tr>
<td>Pedestrian-MVC</td>
</tr>
<tr>
<td>Fall</td>
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<td>Other blunt</td>
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COPD, Chronic obstructive pulmonary disease.
Initiation of Pharmacologic VTE Prophylaxis

Pharmacologic thromboprophylaxis is performed with the intent of abating the risk of venous thromboembolism in patients with high risk of venous thromboembolism (VTE). However, clinical protocols may influence the timing of prophylaxis and suggest that the concern over bleeding may be overrated.2,3,10 Importantly, the practice of pharmacologic prophylaxis and how this practice might be associated with a higher risk of VTE; it cannot infer causality.

The risk of VTE and their clinical significance in the severely injured patient is well established. Our ability as clinicians to balance this risk with the potential for hemorrhagic complications is limited. In this report, we demonstrated that less than half of all patients admitted to the intensive care unit receive pharmacologic thromboprophylaxis within 4 days of injury and another 25% receive no prophylaxis during the first 7 days. It is evident that this delay is associated with a higher likelihood of VTE. Patients in whom prophylactic therapy is initiated beyond day 4 have a threefold greater risk of VTE. It is important to note that these data do not address whether earlier thromboprophylaxis might have reduced this risk, as prophylaxis is typically delayed in higher risk patients. These data simply demonstrate the practice of pharmacologic prophylaxis and how this practice might be associated with a higher risk of VTE; it cannot infer causality.

Patients with severe head injury, those having received greater than six units of packed red blood cells within 12 hours of injury, and those without significant comorbidity are twice as likely to have pharmacologic prophylaxis delayed beyond day 4. By contrast, the presence of a severe lower extremity fracture was associated with early pharmacologic prophylaxis. Importantly, the presence of lower extremity fractures, a strong risk factor for VTE, did not modify the timing of prophylaxis in patients with severe head injuries, suggesting that the concern over bleeding took precedence. The VTE risk was not obviated by the placement of an IVC filter among patients with this injury combination, as the presence of a lower extremity fracture did not modify the risk of VTE.

**DISCUSSION**

The timing of initiation of VTE prophylaxis after major trauma has been poorly addressed in consensus guidelines and suggested protocols, with most advising the use of mechanical prophylaxis (e.g., intermittent pneumatic compression or venous foot pumps) until the risk of bleeding has abated.4,5,10 However, the assessment of bleeding risk in an individual patient is difficult and in many cases entirely subjective, leaving it up to physician judgment as when it might be safe to initiate pharmacologic thromboprophylaxis. Unfortunately, the evidence supporting the efficacy of me-
Mechanical prophylaxis in this patient population is weak and compliance associated with these devices is relatively low.\textsuperscript{11–13} This challenge is further magnified when one considers that many VTE events might occur within the first few days of injury, suggesting that if there is to be any benefit, prophylaxis should be initiated as early as possible.\textsuperscript{14,15}

We demonstrate that at least a half of severely injured patients receive no pharmacologic thromboprophylaxis within the first 4 days after injury and 25% receive no such prophylaxis within the first week. This later time point is clearly beyond the time at which significant bleeding might occur, even in patients with intracranial bleeding. For example, in trials of pharmacologic thromboprophylaxis in patients undergoing elective neurosurgery, prophylaxis initiated within the first 24 hours after injury is not associated with an increased risk of bleeding.\textsuperscript{16} Although the risk of bleeding might be slightly higher in those with traumatic intracranial hemorrhage, it is very unlikely that this risk remains significantly elevated for as long as 7 days after injury.

A retrospective analysis of patients with splenic injuries treated nonoperatively demonstrated no increased risk of bleeding among those receiving early (<48 hours) versus late pharmacologic prophylaxis with low molecular weight heparin. Although this study design has significant limitations, it does suggest that earlier prophylaxis might be safe even in those with solid organ injuries.\textsuperscript{17}

It is plausible that the failure to initiate early thromboprophylaxis shown in this analysis might reflect an overestimate of the efficacy of mechanical compression devices. Alternatively, it might be failure on the part of clinicians to recognize the risk of VTE. If so, this is not exclusive to trauma. For example, in a multicenter study of critically ill medical patients, 90% met prespecified criteria based on international consensus guidelines for thromboprophylaxis.\textsuperscript{18} However, some form of prophylaxis was administered to only 23% of patients, and in only 16% was this deemed to be appropriate for the level of risk. In contrast to the findings noted in the current report, the presence of risk factors for bleeding did not influence the use or choice of prophylaxis.

Our analysis has several potential limitations. First, chart abstraction did not routinely capture the use of mechanical prophylaxis, thus we cannot estimate the extent to which physicians relied on this modality as the sole means of thromboprophylaxis. This might not have any effect, given the questionable efficacy of sequential compression devices. Second, this analysis focused primarily on the day on which pharmacologic prophylaxis was initiated. Using this approach, we estimate that approximately half of all patient-days within the first week are unprotected. We did not probe further to estimate the frequency at which doses were held after prophylaxis was initiated, suggesting that our data are likely an overestimate of the exposure of patients to thromboprophylaxis. Lastly, it would have been desirable to evaluate the precise rationale and reasons among the physicians electing to withhold prophylaxis, as this would provide information on how to better educate physicians to translate evidence into practice.

Taken together, our data suggest a need to better estimate the risks and benefits of early pharmacologic thromboprophylaxis in major trauma patients. These data can then be incorporated into the development of future consensus guidelines to better direct the physician at the bedside.

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**REFERENCES**


**DISCUSSION**

**Dr. Selwyn O. Rogers** (Boston, Massachusetts): This is a descriptive study reviewing the current practice of venous thromboembolism prophylaxis for critically ill trauma patients. As clearly stated in the conclusions, there is a nested cohort retrospective study with an inflammation and host response to injury study within it.

The authors found a significant delay in initiation of venous thromboembolism and prophylaxis and correlated this delay with a more than threefold higher venous thromboembolism risk. Interestingly, almost a quarter of the patients did not have prophylaxis for greater than seven days. By definition, this population is a high-risk patient population with immobility, prolonged ICU stay, and abnormal coagulation.

This study clearly describes our current practice variation but does not answer the crucial question of why. I have several questions that the authors may be able to answer, given the data available.

First, were all the CVTs symptomatic? That is, were any of the trauma centers routinely performing surveillance Doppler ultrasounds in this high-risk patient population?

Secondly, data on mechanical prophylaxis were not able to be collected. Do the authors believe that clinicians considered non-pharmacological VTE prophylaxis adequate for this patient population?

Third, given the modern era of retrievable IVC filters, why was this intervention not more widely used for this very high-risk patient population?

Finally, it is difficult to understand why VTE prophylaxis was withheld for such a long period of time in these critically ill patients, because by the time a week has elapsed, you would imagine that the bleeding risk should be minimal. Can you speculate on why VTE prophylaxis was withheld for such a prolonged period of time?

**Dr. Avery B. Nathens** (Toronto, Ontario, Canada): The first question pertained to screening for DVTs, and there is probably some variability across the seven participating institutions as to whether they screen asymptomatic patients. I know that Harborview Medical Center screens selected patients who are considered high risk and can’t be anticoagulated and my sense is that other centers might as well but this is clearly not protocolized.

Your second question is on the use of mechanical prophylaxis. I, personally, don’t think mechanical prophylaxis have a benefit in this high-risk population. The evidence for their efficacy is questionable and we know that when they are ordered, they are used appropriately in only 20% of patients. As a result, we did not evaluate mechanical prophylaxis, because compliance is poor and efficacy is unproven.

Interestingly, retrievable filters should be changing our practice, but unfortunately, there are recent data suggesting that when these filters are placed, the likelihood of removal is not high. Perhaps when be become more aware of who can and cannot benefit from a retrievable filter, our practice might change.

So why was prophylaxis withheld in patients with massive transfusion for as long as four days? That is a very good question. I agree that this practice is probably irrational and I think if we examine our practices closely, we would come to realize that many of us don’t practice as we should. I know most patients are not bleeding on day three or day four. They probably can be started earlier but we tend to find reasons to hold off. For example, we might be holding off because they’re going for an orthopedic procedure, or perhaps there was a drop in the hematocrit.

**Dr. Truswing** (Richmond, Virginia): Two questions. One is, did you look at the role of the need for operative intervention as a cause for delay of initiating therapy, particularly orthopedic procedures, since our orthopedic colleagues sometimes don’t want us to start therapy prior to their intervention?

No. 2 is, we have an algorithm that stratifies patients into moderate, mild, and severe risk for VTE. Do you have that? If you do, do you think we all should have one that would prompt us to start therapy sooner?

**Dr. Avery B. Nathens**: We actually have the data to look at the timing of procedures. This is a worthwhile question to pursue; we just have not addressed it at this point. Our data suggest that about half of patients have prophylaxis started early, day two or day three. My assumption is that they are continued on for the next seven or more days. However, it is likely that the actual exposure to daily prophylaxis is probably much worse than we think it is, because were often holding it because of major orthopedic procedures.
While I don’t think it’s necessary to hold off because of those procedures, the orthopedic surgeons are insistently upon it. This consortium is developing standard operating procedures for DVT prophylaxis in this patient population. There are guidelines available, and I think the guidelines are helpful in directing our practice. But as you know, it is difficult to convert guidelines into clinical practice, and that’s where the obstacle is.

Dr. Charles Yowler (Cleveland, Ohio): That was the basis of my question. Were any of these participating institutions using guidelines during this study? In other words, was this sort of a uniform distribution seen at all centers, or did certain centers have more delay than other centers? Because that could skew, obviously, the data.

Dr. Avery B. Nathens: We did not look at variation across centers. This is a critical question, as the objective within the consortium is to create uniformity in care across centers. Having said that, we haven’t gone to the standard operating procedure for DVT prophylaxis yet, so I imagine there is quite a bit of variability across centers, and that variability might impact the data presented. So, yes, there is variability but, no, we haven’t assessed its impact.