

Early Venous Thromboembolism Prophylaxis With Enoxaparin in Patients With Blunt Traumatic Brain Injury

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Objective: To determine the safety of early enoxaparin for venous thromboembolism (VTE) prophylaxis in patients with blunt traumatic brain injury (TBI).

Methods: Prospective observational study of patients with TBI who received enoxaparin within 48 hours after admission. Brain computed tomography (CT) scans were obtained at the time of admission, at 24 hours, and at variable intervals thereafter based on clinical course. Patients were excluded from the study for intracerebral contusions ≥ 2 cm, multiple contusions within one brain region, subdural or epidural hematomas ≥ 8 mm, increased size or number of lesions on follow-up CT, persistent intracranial pressure > 20 mm Hg, or neurosur-

geon or trauma surgeon reluctance to initiate early pharmacologic VTE prophylaxis. Bleeding complications were defined as CT progression of hemorrhage by Marshall CT Classification or radiologists' report, regardless of any neurologic deterioration. Main outcomes measured were intracranial bleeding complications, discharge Glasgow Outcome Score, and hospital mortality.

Results: Five hundred twenty-five patients were studied. Eighteen patients (3.4%) had progressive hemorrhagic CT changes after receiving enoxaparin, 12 of whom had no change in treatment, neurologic status, or outcome. Six patients (1.1%) had a change in treatment or potential outcome, including three who required subsequent

craniotomy. Twenty-one patients (4.0%) died, and pharmacologic prophylaxis may have contributed to one death (0.2%). Discharge Glasgow Outcome Scores were 445 (84.8%) good recovery, 19 (3.6%) moderate disability, 36 (6.8%) severe disability, 4 (0.8%) persistent vegetative state, and 21 (4.0%) dead.

Conclusion: Enoxaparin should be considered as an option for early VTE prophylaxis in selected patients with blunt TBI. Early enoxaparin should be strongly considered in those patients with TBI with additional high risk traumatic injuries.

Key Words: DVT prophylaxis in traumatic brain injury, Enoxaparin, DVT prophylaxis complications.

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Trauma surgeons have struggled with the appropriate timing for initiating venous thromboembolism (VTE) prophylaxis ever since Geerts et al.¹ quantitated the risks for deep vein thrombosis (DVT) and pulmonary embolism (PE) in high risk trauma patients. Bleeding complications are intuitively considered higher the earlier anticoagulation is started after injury. There is little data to assist surgeons in determining when bleeding risks are adequately diminished to allow for safe VTE prophylaxis. PE may occur early after injury,²⁻⁴ but most surgeons are reluctant to initiate VTE prophylaxis within the first few days after major head or torso trauma.⁵

Patients with blunt traumatic brain injury (TBI) are a particularly difficult group to evaluate risks and benefits of early pharmacologic prophylaxis. Geerts et al.¹ showed that 39% of patients with blunt TBI without prophylaxis devel-

oped DVT. This risk increases with the addition of other organ system injuries.¹ In the absence of scientific data, initiating pharmacologic prophylaxis remains a subjective decision. Such decisions are usually based on individual anecdotal experiences and perceived risks. Two earlier studies suggested that low molecular weight heparin for VTE prophylaxis can be safely administered in selected patients with TBI.^{6,7} The purpose of this study was to determine whether enoxaparin sodium (Sanofi-Aventis Pharmaceuticals, Bridgewater, NJ), a low molecular weight heparin, could be initiated early in patients with blunt TBI.

MATERIALS AND METHODS

The study design was reviewed and approved by the Institutional Review Board of East Texas Medical Center in Tyler, TX. Potential study candidates were enrolled from December 29, 2000 through December 31, 2005 and included all patients with blunt mechanism TBI by computed tomography (CT) scan. Trauma service policy since 1998 is to begin enoxaparin sodium, 30 mg subcutaneously every 12 hours, early after admission in all patients considered at risk for VTE. Surveillance Doppler studies are not routinely performed unless VTE prophylaxis is delayed for 5 or more days. Patients with coagulopathy (international normalized ratio ≥ 1.5 or current use of aspirin or clopidogrel), heparin allergy, expected brain death or discharge within 48 hours of admission, age less than 14 years, and solid organ injuries, or

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spinal canal hematomas that precluded early anticoagulation were ineligible for enrollment.

Criteria for withholding early prophylaxis were mutually determined by the Neurosurgery Section and the Trauma Service: (1) intracerebral contusions or hematomas ≥ 2 cm in diameter, (2) multiple smaller contusions within one region of the brain, (3) subdural or epidural hematomas ≥ 8 mm in thickness, (4) persistent intracranial pressure greater than 20 mm Hg, (5) increased size or number of brain lesions on follow-up CT scan at 24 hours after admission, and (6) surgeon (neurosurgeon or trauma surgeon) reluctance to initiate early pharmacologic VTE prophylaxis. These criteria were followed for the duration of the study. In those patients where prophylaxis was initially withheld, enoxaparin was initiated at variable intervals after 48 hours on mutual agreement by the trauma surgeon and neurosurgeon on call. Patients were not enrolled in the study unless the first dose of enoxaparin was given within 48 hours of admission.

Brain CT scans were performed at the time of admission, at approximately 24 hours and at variable intervals thereafter based on clinical course. Enoxaparin was withheld 12 hours preoperatively and 24 hours postoperatively for all cranial operations and 12 hours before ventriculostomy removal. Emergency craniotomies and ventriculostomies were not delayed regardless of whether enoxaparin was given before the decision to perform a procedure.

Enoxaparin was continued throughout hospitalization unless one of the study exclusion criteria or a bleeding complication developed. All patients were admitted by and remained on the trauma service until discharge. Every patient was examined daily and any new brain CT scans were reviewed by the trauma service and neurosurgery attendees. Final CT reports were reviewed for all study patients, and all brain CT scans were graded using the Marshall Head CT Classification System.⁸ Bleeding complications were defined as (1) any CT grade progression of TBI by the Marshall classification or (2) any enlargement of an existing hemorrhagic lesion by radiologist CT report at any time during a patient's clinical course while receiving enoxaparin or (3) development of a new hemorrhagic lesion at any time while receiving enoxaparin.

Brain CT scan reports, patient demographics, mechanism of injury, derived Injury Severity Scores (ISS), Head Abbreviated Injury Scale (AIS) scores, admission and subsequent Glasgow Coma Scale (GCS) scores, all cranial procedures, ventriculostomies, and all documented episodes of DVT and PE occurring on the trauma service during the study period were recorded. An additional review of all head CT scans by a neuroradiologist was requested in those patients where the attending trauma surgeon or neurosurgeon questioned the initial radiologist's CT findings. The principle outcomes measured were (1) intracranial bleeding complications during VTE prophylaxis, (2) hospital mortality, and (3) discharge Glasgow Outcome Score (GOS). Bleeding complications were considered a negative effect on treatment if craniotomy

was subsequently necessary or if a permanent change in GCS occurred. Bleeding complications were considered to have a negative effect on patient outcome, regardless of the patient's neurologic condition before the onset of the bleeding complication, if the discharge GOS was anything less than "Good Recovery." Categorical data were analyzed using the Fishers exact test. Analysis of variance was used to analyze continuous variables.

RESULTS

A total of 6,668 patients were admitted during the study period, 1,996 (30%) of whom had ISS scores of 16 or higher. A total of 2,398 (36%) patients had AIS head injury scores ≥ 2 with 2,331 (97%) injured by blunt mechanisms. Two thousand twenty-one patients survived for greater than 48 hours, and 525 (26%) patients were enrolled in the study. A total of 1,496 (74%) patients were excluded from the study. Reasons for exclusion were (1) continued coagulopathy (international normalized ratio >1.5) at 48 hours postadmission or aspirin or clopidogrel intake at the time of admission ($n = 52$, 3.5%), (2) age <14 years ($n = 171$, 11.4%), (3) blunt liver or splenic injury ($n = 387$, 25.9%), (4) spinal cord injury or severe spinal fracture ($n = 66$, 4.4%), (5) isolated AIS 2 patients with TBI admitted for ≤ 48 hours, ($n = 166$, 11.1%), (6) surgeon reluctance to initiate early VTE prophylaxis because of bleeding concerns despite meeting all criteria for entry into the study, ($n = 365$, 24.4%), and (7) unknown reason or failure to enroll the patient into the study ($n = 289$, 19.3%).

One hundred forty-six (28%) of the study patients had isolated brain injuries, and 379 (72%) patients had multiple body region injuries. Time from admission until the first dose of enoxaparin was 36.2 ± 12.7 hours (mean \pm SD) with a median time of 25.5 hours. The study population was comprised primarily of men ($n = 387$, 74%). Other clinical characteristics are provided in Table 1. Twenty-one patients (21 of 525, 4%) died as a result of their injuries. The number of patients within each head AIS category and associated mortality rates within each group are provided in Table 2. Lower extremity venous Doppler ultrasound studies were performed in 151 patients, and six patients (1.14%) were diagnosed with DVT. There were no documented episodes of PE within the study group. A total of 1,330 patients with TBI hospitalized ≥ 48 hours were not entered into the study for reasons listed above. Review of trauma registry data identified 11 cases of VTE in this group (2 PE, 9 DVT, 0.83%). This was not significantly different from the VTE rate in the study group of patients with TBI ($p = 0.59$, Fisher's exact).

Table 1 Clinical Characteristics of 525 Study Patients

Variable	Mean \pm SD	Median (Range)
Age	39.6 \pm 19.7	37 (14–96)
ISS	22.8 \pm 10.9	21 (9–66)
Admission RTS	10.1 \pm 2.8	12 (2–12)
Admission GCS	10.4 \pm 4.8	13 (3–15)

Table 2 Mortality Rates by Head Abbreviated Injury Scale (AIS) Score

AIS	No. Deaths, n (%)	Total Patients, n (%)
2	0 (0)	16 (3)
3	2 (1)	273 (52)
4	5 (3)	164 (31)
5	14 (19)	72 (14)
Total	21 (4)	525 (100)

A total of 10 cases of PE and 26 cases of DVT were diagnosed for the entire trauma patient population (n = 6,668, 0.54%) during the study period with 20 patients receiving inferior vena cava (IVC) filters. Only one study patient received an IVC filter for a nonneurologic complication of full heparin anticoagulation following a documented proximal DVT. This patient bled from a nonoperatively treated liver injury on day 8 of hospitalization. No operation was required, and full dose heparin was discontinued. There were no identified noncranial bleeding complications in the study group from enoxaparin VTE prophylaxis.

Sixty-five patients (12.4%) required craniotomies or cranioplasties, and 71 (13.5%) patients received ventriculostomies. Sixty-two patients (12%) had CT progression of their

TBI by Marshall CT classification or radiologists' CT report. Progressive hemorrhagic injury was documented in 44 (8.3%) patients within 24 hours of admission and before beginning enoxaparin. This resulted in delayed initiation of enoxaparin prophylaxis until 48 hours. Progressive hemorrhagic injury was documented by CT scan in 18 (3.4%) patients after starting enoxaparin and pharmacologic prophylaxis was temporarily discontinued. Detailed information on the 18 patients with brain CT scan progression after starting enoxaparin is provided in Tables 3 and 4. There were no differences in age, ISS, admission RTS, admission GCS score, hours until first enoxaparin dose (following admission), or mortality rate when those patients who progressed on head CT scan following enoxaparin (n = 18) were compared with those patients who did not progress following enoxaparin (n = 507). Twelve of the 18 patients developed minimal changes on CT that were considered clinically insignificant (Table 3). There were no changes on neurologic examination, and the CT changes were not considered significant enough by the neurosurgeons or trauma surgeons to alter their treatment (other than temporary discontinuation of enoxaparin). Patient mortality and GOS were not affected.

Table 3 Twelve Patients With CT Progression of Blunt Traumatic Brain Injury and No Change in Treatment or Outcome

Patient #	Time to 1st Dose Enoxaparin (h)*	Head AIS	Outcome	Glasgow Outcome Score	Cranial Surgery	Disposition	Head CT Change
1†	17.5	3	Lived	Good Recovery	No	Rehab	New contusion, small hygroma
2†	12	5	Lived	Good Recovery	No	ECF	Increase in size of contusions
3	24	4	Lived	Good Recovery	No	Home	Development of small SDH
4	24	4	Lived	Good Recovery	No	Rehab	Increase in ventricular blood
5	44	2	Lived	Good Recovery	No	Rehab	New small contusion developed
6	46	3	Lived	Good Recovery	No	ECF	Increase in size of contusions
7†	43	5	Lived	Good Recovery	No	Home	Bled with ventric removal
8	24	3	Lived	Good Recovery	No	Home	New small contusion developed
9	27.5	5	Died	Died	No	Died	New small contusion developed
10†	24	5	Lived	Good Recovery	Yes	Rehab	Recurrent SDH (chronic)
11†	24	4	Lived	Good Recovery	Yes	Home	Size of SDH increased
12	24	3	Lived	Good Recovery	Yes	Home	New small contusion, thin SDH

* Hours from admission until first dose of enoxaparin.

† Protocol violation patients.

SDH, subdural hematoma; ECF, extended care nursing facility; Rehab, rehabilitation hospital; ventric, ventriculostomy.

Table 4 Six Patients With CT Progression of Blunt Traumatic Brain Injury With Changes in Treatment or Outcome

Patient #	Time to 1st Dose Enoxaparin (h)*	Head AIS	Outcome	Glasgow Outcome Score	Cranial Surgery	Disposition	Type of Complication
1†	36	5	Lived	Severe Disability	No	ECF	2.1 cm contusion enlarged to 2.4 cm
2	22.5	3	Lived	Severe Disability	No	Rehab	1.0 cm contusion enlarged to 1.3 cm
3†	24	4	Lived	Moderate Disability	Yes	Rehab	1.0 cm SDH postcraniotomy
4†	36	5	Lived	Severe Disability	Yes	ECF	1.2 cm SDH postventric removal
5†	19	3	Lived	Good Recovery	Yes	Home	2.3 cm contusion enlarged to 2.5 cm
6†	36	4	Died	Died	Yes	Died	2.1 cm contusion enlarged to 5.3 cm

* Hours from admission until first dose of enoxaparin.

† Protocol violation patients.

SDH, subdural hematoma; ECF, extended care nursing facility; Rehab, rehabilitation hospital; ventric, ventriculostomy.

Six patients (1.1%) developed clinically significant changes on CT resulting in a therapeutic change and possibly a change in outcome. These patients are listed in Table 4. Four patients (#1, 2, 5, 6) had enlarging intracerebral contusions. Three (#1, 5, 6) received enoxaparin inappropriately and were protocol violations. One patient (#6), a 76-year-old woman, died following progression of her TBI, and early DVT prophylaxis may have contributed to her enlarging intracerebral contusion. Patient #4 developed a 1.2 cm subdural hematoma following removal of a 14-day-old ventriculostomy catheter. Enoxaparin was not withheld before removal (protocol violation). His baseline GCS dropped from 6 to 4, and emergency craniotomy was performed. The patient's GCS returned to baseline postoperatively. Patient #3 developed a recurrent 1.0 cm subdural hematoma following emergency evacuation of a large subdural hematoma at the time of admission. Enoxaparin was given 10 hours after the first operation (protocol violation). Neurologic examination did not change, and the subdural hematoma resolved without further surgery.

Protocol violations occurred in 10 of 18 patients who had CT progression following enoxaparin prophylaxis. These are identified in Tables 3 and 4 (†). Eighty-two (15.6%) protocol violations occurred in the entire study group. Seventy-five (14%) study patients received their first enoxaparin dose less than 20 hours after admission. These patients were not excluded from the study to provide a complete representation of our clinical experience and to ensure that all potential bleeding complications related to enoxaparin were reported. Had we excluded all protocol violations, the overall CT progression rate following enoxaparin would be 1.8% (8/443). Discharge GOS scores were 445 (84.8%) good recovery, 19 (3.6%) moderate disability, 36 (6.8%) severe disability, 4 (0.8%) persistent vegetative state, and 21 (4.0%) dead.

DISCUSSION

Surgeons are often reluctant to initiate VTE prophylaxis early after injury or following surgical procedures because of perceived bleeding risks. Over 50% of the patients who were eligible for the current study were likewise excluded. These results were somewhat surprising because we thought that all of our neurosurgical colleagues and trauma surgeons were in agreement with the protocol. We are confident, however, that the majority of these patients were eventually started on enoxaparin later in their hospital course (sometime after 72 hours) because prophylaxis for DVT is monitored daily. The current study group by any measure would be considered very high risk for developing proximal DVT in the absence of VTE prophylaxis.¹ The recurring debate and the issue that rightly concerns neurosurgeons,⁹ is whether the risk of VTE, particularly PE, is higher than the risk of extending a hemorrhagic brain lesion from pharmacologic prophylaxis that may subsequently result in a poor neurologic outcome.

Death from PE may be sudden and unanticipated, often occurring early in the patient's hospitalization.²⁻⁴ The current study suggests that early VTE prophylaxis with enoxaparin

can be given to selected patients with TBI with a lower risk of clinically significant bleeding complications (1.1%) than the known risk of proximal DVT (18%) and PE (4.8%) in patients without prophylaxis.¹ The risk of proximal DVT in patients with TBI without prophylaxis is even higher (19.8%) when screened by contrast venography.¹ This risk increases with the addition of other injuries and the need for mechanical ventilation.^{1,10} In the current study, 72% of patients had multiple injuries. The majority required prolonged mechanical ventilation. We think that our protocol, as part of an overall strategy to minimize VTE, is safe and more cost effective than routine venous Doppler screening of the lower extremities.^{11,12} Additionally, our approach has minimized the need for IVC filters.

Questions of safety and efficacy can only be definitively answered with a well-designed prospective randomized study. However, given the known high prevalence of proximal DVT in these patients¹ and the early, small but real risk of PE,^{2,4} designing such a study would be very difficult and may have ethical implications.⁷

Cothren et al.⁷ correctly emphasize that bleeding complications are difficult to define in trauma patients with or without pharmacologic prophylaxis because of the heterogeneity of the population and the risk for bleeding from multiple sites. It is not as difficult with TBI because CT scan is very sensitive for documenting intracranial blood. The more difficult issue with TBI is determining whether hemorrhagic changes on CT scan are a natural progression of the TBI, a result of other comorbid or complicating factors (hypertension, unknown use of aspirin, or other medications) or a real consequence of pharmacologic prophylaxis. Patel et al.¹³ identified progression of head injury on subsequent CT scan in 12% of patients. Smith et al.¹⁴ performed a retrospective review of 116 patients to determine the role of early follow-up CT scan in patients with blunt TBI. These investigators identified progression of blunt head injury in 42% of patients.¹⁴ As shown in the current study, the majority of patients who had progression of blunt TBI required no intervention, and only those patients with neurologic changes on examination required surgical intervention.¹⁴ It is unclear from Smith's study whether any of their patients were administered pharmacologic DVT prophylaxis.

The current risk of death from PE in trauma patients, including patients with TBI, is not really known because very few trauma centers are able to perform autopsies on all patients who die after injury. Owings et al.² determined that 25% of pulmonary emboli occurred during the first 4 days after injury and suggested that delaying prophylaxis may be detrimental. Quantifying the long-term neurologic effects of a hemorrhagic progression on brain CT scan, with or without an acute neurologic change, is also difficult. We have reported all hemorrhagic changes identified by CT, regardless of the effects on therapy or outcome. We also chose to keep all protocol violation patients in the study to provide a complete review of our clinical experience. The reader can determine whether the hemorrhagic changes that were identified

on CT are clinically relevant enough to justify withholding pharmacologic prophylaxis from 97% of similar patients who had no bleeding complications. Had we eliminated all patients with protocol violations, our reported bleeding complication rate would have been considerably lower (1.8% vs. 3.4%), with no deaths potentially attributable to enoxaparin prophylaxis. Other investigators have used once daily dosing of dalteparin to minimize protocol violations.⁷ Strict adherence to established protocols and further evaluation of various pharmacologic agents are needed.

A number of studies have emphasized the importance of early prophylaxis to prevent VTE.²⁻⁴ Nathans et al.⁵ showed that 50% of patients with severe injuries who were considered high risk for VTE complications received no pharmacologic prophylaxis within the first 4 days after injury. Twenty-five percent received no pharmacologic prophylaxis within the first 7 days. The delay beyond 4 days resulted in a threefold increase in VTE. Severe head injury was one of several injury-specific factors related to delayed pharmacologic prophylaxis.

Our study illustrates the difficulties encountered with protocol compliance. Fourteen percent of study patients were administered enoxaparin less than 20 hours after admission. Review of these cases determined that the majority of the patients received their second CT scan early the next morning following admission rather than waiting for 24 hours. No significant CT changes were identified, and the first dose of enoxaparin was given earlier than 24 hours. Ten of the 18 patients with progressive hemorrhagic changes on CT scan were protocol violations, and it is impossible to determine whether these violations contributed to the changes that developed on follow-up CT scan. Cothren et al.⁷ chose to use a once daily dose of dalteparin as their DVT prophylaxis regimen because of low compliance rates with twice daily dosing regimens at their institution. Recently published data by Slavik et al.¹⁵ raised questions about potentially different clinical effects of dalteparin versus enoxaparin at doses given for prophylaxis. Further studies are needed to determine whether once daily dosing of dalteparin is clinically equivalent to twice daily dosing of enoxaparin for preventing DVT and PE in high risk trauma patients. Once daily dosing with 40 mg of enoxaparin is another potential option that warrants further study.

We think enoxaparin should be strongly considered for VTE prophylaxis in trauma patients, including selected patients with TBI. Mechanical compression devices do not provide the same protection¹⁶⁻¹⁸ and IVC filters for DVT prophylaxis are controversial and need further study.¹⁹⁻²⁴

Although this is the largest study to date examining the safety of pharmacologic VTE prophylaxis in patients with TBI, our analysis has several potential limitations. First, the current study is from a single trauma center and suffers from all of the limitations that are inherent to an observational study. The question of safety and efficacy of early VTE prophylaxis in patients with TBI can only be definitively answered in a prospective randomized multi-institutional trial. Second, our study focused completely on the safety of

early VTE prophylaxis in patients with TBI who were enrolled in the study. No comparisons were made between the study group and the 2,021 patients who were excluded from the study. Such a comparison would have provided valuable information on the natural progression of TBI and the risk of VTE with delayed pharmacologic prophylaxis.

A large number of patients were excluded from the study either because of surgeon reluctance (24.4%) or a combination of unknown reasons or simple failure to enroll patients in the study (19.3%). This could certainly create a bias in patient selection for the study. We agree with Nathans et al.⁵ that determining the precise reasons among surgeons for not initiating early VTE prophylaxis would be helpful in educational planning to translate evidence into practice.

Our definitions for identifying potentially detrimental changes in treatment or outcome also create a bias against early pharmacologic prophylaxis because there is no control group to identify the rate of natural progression of intracranial hemorrhagic injury. Identifying CT progression of TBI regardless of clinical impact is the most objective way to determine potential bleeding complications, but this inflates the number of complications that are clinically relevant. Including protocol violations may also falsely inflate the true number of bleeding complications.

We think that many patients with TBI, particularly those patients with other associated high risk injuries, can be safely administered enoxaparin to reduce DVT and PE with an acceptable low risk of clinically significant intracranial bleeding complications. The current protocol, when carefully followed, provides safe, effective, and early prophylaxis in patients with TBI.

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- thromboembolism is now closely linked to the quality of care a hospital and its physicians provide their patients.
- Routine prophylaxis for venous thromboembolism is a standard of care. However, there is nothing that is standard about this issue. Despite a litany of publications on the subject, there still remains glaring gaps in our knowledge base about this disease, ranging from pathogenesis of thromboembolic disease to the most adequate method of prophylaxis.
- In this paper, the authors try to tackle the issue of timing of initiation of DVT prophylaxis in the blunt trauma patients with concurrent traumatic brain injuries. The benefits of initiating early prophylaxis to help decreased venous thromboembolism have to be balanced with the risk of increasing intracranial hemorrhage, which can have devastating consequences.
- The issue of timing has been previously evaluated in Dr. Norwood's group. In 2002, they published on 150 patients with blunt traumatic injury. In that prospective study, the bleeding complication rate of enoxaparin was 4 percent, with no deaths being attributed to enoxaparin prophylaxis. In the current study, the authors prospectively examine 525 patients with blunt traumatic brain injury admitted over a five-year period.
- Patients were excluded from the study if coagulopathy, documented use of aspirin or anti-platelet medications, heparin allergy, expected brain death, or discharge within forty-eight hours of admission, age less than fourteen or if solid organ injuries or spinal canal hematomas were present.
- After a repeat head CT at twenty-four hours, thirty milligrams of Lovenox was administered every twelve hours. Progression of hemorrhage on CT following enoxaparin was noted in 3.4 percent of the patients, with only 1.1 percent being clinically significant to warrant change in therapy. There was only one patient in whom early pharmacologic prophylaxis may have contributed to mortality.
- The authors have thus concluded that many patients with TBI can be safely administered enoxaparin to reduce DVT and PE risk with acceptably low clinical risk of worsening intracranial bleeding. The questions I have for the authors are as follows.
- Question one, in this study you chose to delay the initiation of enoxaparin prophylaxis in patients with cerebral contusions or hematomas greater than two-centimeters in diameter, multiple smaller contusions within one region of the brain, subdural or epidural hematomas greater than eight millimeters in thickness, and persistent intracranial pressure greater than twenty millimeters.
- With this approach, the average time for initiation of enoxaparin was forty-two hours after admission, with a 3.4 percent bleeding complication rate. Though this may make clinical sense, what was the scientific basis for delaying these categories of patients, especially given data from your own institution showing a comparable 4 percent bleeding rate with enoxaparin given at twenty-six hours after admission without these specific limitations?

DISCUSSION

Dr. Dionne Skeete (Iowa City, Iowa): Prevention of venous thromboembolism remains at the forefront of issues affecting trauma care delivery and prevention of venous

Question two, in this study you were only able to enroll 26 percent of all eligible patients with head injuries. Besides the exclusion criteria, were there any significant differences between the eligible and ineligible patient population that may affect our interpretation of the data?

Question three, for the patients who could not receive enoxaparin at twenty-four hours after admission, was there a standardized approach to each patient that other trauma centers could find applicable to their own patient population? In other words, did you make the decision to administer enoxaparin later based on a stable second follow-up head CT, neurosurgeon judgment, change in clinical status, or a combination of the above?

Question four, what was the incidence of the non-intracranial bleeding events? This would be important to note, as 72 percent of the study patients had other blunt traumatic injuries. Again, I would like to thank EAST for the opportunity to discuss the paper and the authors for attempting to clarify this murky area in the topic of prevention of venous thromboembolic disease.

Dr. Scott Norwood (Tyler, Texas): Thank you for your questions. We decided to postpone DVT prophylaxis in those patients meeting our criteria based partially on our first study, where a 4 percent complication rate involved some of those criteria, and partially in collaboration with our neurosurgeons, some of whom believed that those particular lesions needed more time before initiating enoxaparin.

As far as the 26 percent enrollment of patients, there were some additions to our neurosurgery staff, which partially affected our ability to enroll patients. To some extent, our younger neurosurgeons were not as comfortable with our protocol as the neurosurgeons who had been with us from the beginning, and I think that resulted in fewer study patients.

In terms of follow-up; yes, we started enoxaparin later in patients in which the follow-up scans, say at three to seven days, had stabilized. Finally, I don't have the exact number at this time of non-intracranial bleeding complications. I do know that it was very, very low, if not zero. I should be able to get that information for you.

Dr. Gary A. Lindenbaum (Philadelphia, Pennsylvania): Most of my questions relate to your exclusion criteria. How did you define coagulopathy? What did you mean by surgeon request when you excluded those patients from the study? Finally, I'm curious as to how your heparin allergy patients were managed and the patients that were excluded, how were they managed? Did they receive filters or some other modality?

Dr. Scott Norwood: I think that we have a unique situation in that our neurosurgeon meets with us just about every morning when we round in the ICU and we have discussions with them about every patient. If there was any question at all about the safety of initiating enoxaparin on the part of the neurosurgeon, or the trauma surgeon for that matter, then the drug was withheld and the patient was re-evaluated again for prophylaxis in 24 hours.

There were no study patients with known heparin allergy. Our general approach would be to place an IVC filter in those patients who are very high risk and where enoxaparin cannot be given. However, we only inserted twenty filters in our entire trauma population during the five year study period. We do not use very many filters.

Dr. Bryce Robinson (Cincinnati, Ohio): Dr. Norwood, this is a very interesting study. Could you comment on your experience with full anticoagulation, whether it's with enoxaparin or heparin. We've had difficulties at our own institution with this. What timeframe do you recommend until one can start full anticoagulation with traumatic brain injury?

Dr. Scott Norwood: Full anticoagulation is a big problem, particularly for patients with blunt carotid injuries and a concomitant hemorrhagic brain injury. My partner Dr. John Berne could answer this question better than me, usually our practice is to wait at least seven days before initiating full anticoagulation. We usually use unfractionated heparin initially since it is more easily monitored and reversed if necessary. I would like to thank Dr. Skeete and the other discussants for their interest in our paper and for their thoughtful questions.