Prospective Evaluation of the Safety of Enoxaparin Prophylaxis for Venous Thromboembolism in Patients With Intracranial Hemorrhagic Injuries

Scott H. Norwood, MD; Clyde E. McAuley, MD; John D. Berne, MD; Van L. Vallina, MD; D. Brent Kerns, MD; Thomas W. Grahm, MD; Kevin Short, MD; Jerry W. McLarty, PhD

Background: Patients with traumatic intracranial hemorrhagic injuries (IHIs) are at high risk for venous thromboembolism (VTE). The safety of early anticoagulation for IHI has not been established.

Hypothesis: Enoxaparin can be safely administered to most patients with IHI for VTE prophylaxis.

Setting: Level I trauma center.

Design: Prospective, single-cohort, observational study.

Patients and Methods: One hundred fifty (85%) of 177 patients with blunt IHI received enoxaparin beginning approximately 24 hours after hospital admission until discharge. Brain computed tomographic (CT) scans were performed at admission, 24 hours after admission, and at variable intervals thereafter based on clinical course. Patients were excluded for coagulopathy, heparin allergy, expected brain death or discharge within 48 hours, and age younger than 14 years. Complications of enoxaparin prophylaxis were defined as Marshall CT grade progression of IHI, expansion of an existing IHI, or development of a new hemorrhagic lesion on follow-up CT after beginning enoxaparin use.

Results: Thirty-four patients (23%) had CT progression of IHI. Twenty-eight CT scans (19%) worsened before enoxaparin therapy and 6 (4%) worsened after beginning enoxaparin use. No differences between operative patient (2/24, 8%) and nonoperative patient (4/126, 3%) complications were identified (P = .23). Study group mortality was 7% (10/150). All 6 patients who developed progression of IHI after initiation of enoxaparin therapy survived hospitalization. A deep vein thrombosis was identified in 2 (2%) of 106 patients.

Conclusion: Enoxaparin can be safely used for VTE prophylaxis in trauma patients with IHI when started 24 hours after hospital admission or after craniotomy.

Arch Surg. 2002;137:696-702

BUNTL MULTISYSTEM trauma is a significant risk factor for venous thromboembolism (VTE), and patients with intracranial hemorrhagic injuries (IHIs) are at particularly high risk.1 Venous thromboembolism rates as high as 17%2-6 are reported despite the use of conventional methods of prophylaxis.

Low-molecular-weight heparin is the simplest and most effective VTE prophylaxis for most trauma patients.7 Current contraindications to the early initiation of low-molecular-weight heparin prophylaxis include intracranial bleeding and incomplete spinal cord injuries, conditions that are present in up to 25% of patients admitted to the hospital after major blunt trauma.7 There continues to be a reluctance to use anticoagulants in head-injured patients owing to the perceived risk of exacerbating intracranial hemorrhage. To our knowledge, no studies support this concern for trauma patients with established IHIs that are not actively bleeding. The existing randomized studies5,6 in trauma patients examining the efficacy of the low-molecular-weight heparin enoxaparin sodium for preventing VTE excluded patients with head injuries. However, a recent prospective, single-cohort study8 examining the use of enoxaparin in preventing VTE in high-risk blunt trauma patients included a subgroup of 55 patients with blunt IHIs. This study8 reported no bleeding complications in the subgroup of head-injured patients, suggesting that administration of enoxaparin might be a beneficial method for VTE prophylaxis in patients with IHIs. These findings prompted our group to further consider enoxaparin use in patients with IHIs.

Several studies3,6,8 have proven the effectiveness of enoxaparin therapy for preventing VTE in trauma patients, and one study9 also supported its cost-effectiveness in terms of cost per additional life-
PATIENTS AND METHODS

Potential study candidates included all patients with a blunt mechanism of injury and documented IHI by computed tomographic (CT) scan who were admitted for at least 48 hours to East Texas Medical Center, Tyler, between December 16, 1999, and May 31, 2001. The study design was reviewed and approved by the institutional review board of East Texas Medical Center, Tyler.

All patients enrolled in the study were administered enoxaparin sodium (Aventis Pharmaceuticals Inc, Bridgewater, NJ) in 30-mg subcutaneous doses every 12 hours beginning approximately 24 hours after initial evaluation in the emergency department. Brain CT scans were performed at the time of initial patient evaluation, at approximately 24 hours (ie, just before administration of the first dose of enoxaparin), and at variable intervals thereafter based on clinical course. Patients were excluded from the study if any of the following criteria were present: coagulopathy, heparin allergy, expected brain death or hospital discharge within 48 hours, and age younger than 14 years. Enoxaparin prophylaxis was delayed until 72 hours after hospital admission for patients with splenic injuries that were managed nonoperatively. Enoxaparin administration was continued throughout hospitalization unless one of the study exclusion criteria or a bleeding complication developed. Initially, enoxaparin therapy was not withheld for craniotomy or cranioplasty. However, after 2 early perioperative bleeding complications in the first 22 patients enrolled in the study, the protocol was modified to withhold administration of enoxaparin for 24 hours after all initial and subsequent craniotomies or cranioplasties. Pneumatic compression devices were used only before the first dose of enoxaparin was given and perioperatively when enoxaparin therapy was interrupted for a craniotomy or cranioplasty.

Patients were excluded from the study if enoxaparin use was not initiated within 24 hours (other than patients with splenic injuries) or if prophylaxis was interrupted for longer than 12 hours for any reason other than craniotomy or cranioplasty. All study patients, except those who developed a bleeding complication, continued enoxaparin therapy until discharge from the hospital.

All of the study patients were admitted and remained on the trauma service throughout their hospitalization. Every study patient was examined daily by at least 1 attending trauma surgeon (S.H.N., C.E.M., J.D.B., and V.L.V.) and 1 attending neurosurgeon (T.W.G.) to assess neurologic status and to ensure protocol compliance. The radiologist CT reports were reviewed for all study patients, and all brain CT scans were independently graded by a board-certified radiologist (K.S.) using the Marshall Head CT Classification System.10 This system categorizes patients based primarily on abnormalities from IHIs identified on head CT scans. The categories that were used are as follows: diffuse injury I indicates no visible pathologic change seen on CT; diffuse injury II, cisterns present, with shift of 0 to 5 mm, lesion densities present, or both, with no lesion greater than 25 mL (the scan may include bone fragments and foreign bodies); diffuse injury III, cisterns compressed or absent, with shift of 0 to 5 mm and no lesion greater than 25 mL; diffuse injury IV, midline shift greater than 5 mm, with no lesion greater than 25 mL; evacuated mass lesion, any surgically evacuated lesion; and nonevacuated mass lesion, any lesion greater than 25 mL not surgically evacuated. A complication of enoxaparin prophylaxis was defined as (1) CTgrade progression of IHI by the Marshall classification or year saved from fatal pulmonary embolism (PE). The present study was designed to determine the safety of administering enoxaparin to patients with traumatic IHIs for VTE prevention.

RESULTS

A total of 1428 trauma patients were admitted during the 18-month study; 1288 patients (90%) were injured by blunt force mechanisms, and 177 of these (14%) had a documented IHI on initial CT scan. Twenty-seven patients (15%) with IHIs were excluded from the study owing to protocol violations (n=8, 3%), documented coagulopathy (n=7, 4%), age younger than 14 years (n=5, 3%), surgeon reluctance to start anticoagulant therapy (n=4, 2%), and discharge or death within 48 hours of hospital admission (n=3, 2%).

A total of 150 patients (85%) admitted to the hospital with IHIs were enrolled in the study. The mean±SD time from hospital admission until initiation of the first dose of enoxaparin was 26.5±11.5 hours (median, 24 hours; range, 4-74 hours). There were 4 patients (3%) with nonoperative splenic injuries, 4 (3%) with nonoperative liver injuries, and 3 (2%) with large retroperitoneal hematomas. The clinical characteristics of the study patients are given in Table 1. The predominant types of IHI are listed in Table 2. Forty-seven patients (31%) had 2 or more lesions documented on initial CT scan. Head AIS scores were as follows: AIS 2 in 4 patients (3%), AIS 3 in 83 (55%), AIS 4 in 46 (31%), and AIS 5 in 17 (11%). A total of 24 patients (16%) required craniotomy, and 25 nonoperative patients (17%) required ventriculostomy. Fifty-eight patients (39%) had isolated head injuries, whereas 92 (61%) had 1 or more additional body region injuries. Seventeen patients (11%) had 1 or more spinal fractures, and 5 (3%) had complete spinal cord injuries. Seven patients (5%) had femoral vein catheters inserted.

Venous color flow duplex ultrasound scans were obtained within 24 hours of hospital discharge on 106 patients. There were 2 patients (2%) with DVTs (1 proximal and 1 distal) and no documented PEs in the study group. Most patients were not evaluated with either CT pulmonary angiography or conventional pulmonary angiography to identify occult or asymptomatic PEs. Also, a determination cannot be made concerning the possibility of asymptomatic DVTs in the 44 patients who were not screened for DVT before hospital discharge. Only 1 patient in the study group required placement of a vena caval filter after developing a bleeding complication after systemic heparinization for a proximal (popliteal) DVT. Both patients who developed DVTs survived hospitalization.

Continued on next page
Drug was therefore discontinued. There was no increase after beginning enoxaparin therapy, and use of the identified by CT scan.

Further changes in the size or the number of lesions identified by CT scan were obtained in all 28 patients, and there were no changes in the CT findings, prophylaxis was initiated at approximately 24 hours in all 28 patients after discussion with the attending neurosurgeons. Follow-up CT scans were obtained in all 28 patients, and there were no further changes in the size or the number of lesions identified by CT scan.

Based on the low incidence of deep vein thrombosis (DVT) in our first study, we no longer routinely evaluate asymptomatic patients for DVT during hospitalization or before hospital discharge if enoxaparin is used for DVT prophylaxis. High-risk patients who cannot receive enoxaparin are screened with Doppler examination before hospital discharge. Despite this, most patients in the present study were examined for DVT by Doppler duplex color flow ultrasound examination of the lower extremities before discharge. The Doppler study included examination of the deep and superficial femoral, popliteal, calf, and saphenous veins. Proximal vein thrombosis was defined as a thrombosis of the popliteal vein or any more proximal vein. Distal vein thrombosis was defined as a thrombosis of 1 or more calf veins. Lower-extremity Doppler ultrasound studies were also performed at any time during hospitalization if DVT was clinically suspected. All venous duplex studies were performed by experienced vascular technicians, and results were confirmed by a board-certified vascular surgeon (D.B.K.). All studies were performed using an ultrasound machine (ALT 3000; Advanced Technology Laboratories, Bothell, Wash) equipped with gray scale and Doppler color flow capabilities using a 4- to 7-MHz linear array transducer.

Because there were no available published studies of anticoagulant VTE prophylaxis in patients with IHIs, a literature review of heparin prophylaxis in patients undergoing elective neurosurgery was initiated. Three randomized studies were identified. A pooled average of the bleeding complication rates in these 3 studies was 2.7%.

We postulated that the bleeding complication rate in trauma patients with IHIs who received enoxaparin would be similar to the published rate observed in elective neurosurgical patients who received heparin prophylaxis. Therefore, a population of at least 139 patients with IHIs who received enoxaparin prophylaxis would provide sufficient statistical power to our study if we observed no difference in the rate of bleeding complications in patients with IHIs compared with those undergoing elective neurosurgery. The principal outcome measured was progression of an IHI or development of a new IHI after initiating administration of enoxaparin for VTE prophylaxis.

Patients whose CT scans progressed before receiving enoxaparin, by either CT report or by the Marshall CT classification, were compared with the remainder of the study group to determine whether enoxaparin use increased the risk of progression of IHI. This comparison was performed using the McNemar χ² test.

A comparison of complication rates was performed using the Fisher exact test between patients who required craniotomy and those who were treated nonoperatively. This test was also used to compare the rate of bleeding complications in the present study to the pooled average of bleeding complications in previously published elective neurosurgery patients.

* Data are given as number (percentage) of patients. CT indicates computed tomographic; NEML, nonevacuated mass lesion.

### Table 1. Clinical Characteristics of 150 Study Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>39.5 ± 21.2</td>
<td>36 (14-96)</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>21.0 ± 10.0</td>
<td>19 (9-54)</td>
</tr>
<tr>
<td>Revised Glasgow Coma Score</td>
<td>10.0 ± 3.0</td>
<td>12 (2-12)</td>
</tr>
<tr>
<td>Admission Glasgow Coma Scale</td>
<td>10.0 ± 5.0</td>
<td>12 (3-15)</td>
</tr>
<tr>
<td>Hospital day ambulatory</td>
<td>6.2 ± 7.6</td>
<td>3 (1-43)</td>
</tr>
<tr>
<td>Intensive care unit length of stay, d</td>
<td>8.8 ± 11.3</td>
<td>4 (1-74)</td>
</tr>
<tr>
<td>Hospital length of stay, d</td>
<td>12.8 ± 13.2</td>
<td>8 (2-78)</td>
</tr>
</tbody>
</table>

A total of 468 brain CT scans were performed in the study group. Thirty-four patients (23%) had CT progression of IHI by Marshall classification, radiologist CT report, or both. The IHI became worse in 28 patients (19%) before beginning enoxaparin therapy. Despite these changes in the CT findings, prophylaxis was initiated at approximately 24 hours in all 28 patients after discussions with the attending neurosurgeons. Follow-up CT scans were obtained in all 28 patients, and there were no further changes in the size or the number of lesions identified by CT scan.

The CT scans of 6 patients (4%) showed progression after beginning enoxaparin therapy, and use of the drug was therefore discontinued. There was no increase in the rate of progression of IHI when patients whose scans worsened before receiving enoxaparin (n = 28) were compared with the remainder of the study group (n = 122). A statistically significant decrease in the rate of progression of IHI was observed after 24 hours and after initiation of enoxaparin therapy (P = .002) (see the Discussion at the end of this article). Two (8%) of 24 patients who underwent craniotomies developed postoperative bleeding and required another operation. Both of these complications occurred early in the study, before the pro-
protocol was modified to withhold heparin for 24 hours after craniotomy.

Four bleeding complications occurred in 126 nonoperatively treated patients (3%). One of these patients had progression of a large epidural hematoma that was initially treated nonoperatively. This patient required craniotomy and had no further bleeding complications. The other 3 patients did not require surgical intervention. Two patients who developed bleeding complications were study protocol violations: 1 received the first dose of enoxaparin 12 hours before the scheduled time for initiation of prophylaxis and the other received a double dose within the first 30 hours of initiating the prophylaxis protocol. These 2 patients were not excluded from the study because both demonstrated IHI progression on CT scan. There were no bleeding complications among the other 8 patients who were excluded from the study for protocol violations.

All 6 patients whose CT scan findings worsened after initiating enoxaparin therapy survived hospitalization. The Glasgow Outcome Scale scores for the study group are provided in Table 3. Overall mortality in the study group was 7% (10/150). There were no deaths attributable to bleeding complications from enoxaparin prophylaxis.

### COMMENT

Although it is generally accepted that patients with multisystem blunt trauma are at high risk for VTE,1,7 the specific subpopulation of patients with closed head injuries has not been extensively studied to determine a safe and effective method for anticoagulant VTE prophylaxis. Patients who require elective neurosurgery also have a higher risk for VTE,12-14 and heparin prophylaxis in this population reduces the incidence.12-14 The average bleeding complication rate in the previous randomized studies comparing low-dose heparin,12 nadroparin calcium,13 and enoxaparin14 with placebo was 3% (12/444). No difference in the bleeding complication rate was identified in the present study of trauma patients (6/150, 4%; P = .23). Agnelli et al14 compared enoxaparin therapy and compression stocking use with compression stocking use alone in more than 300 patients randomly assigned to receive either enoxaparin or placebo in a masked fashion. There was no difference in the postoperative incidence of intracranial hemorrhage between the groups (3 patients in the enoxaparin group vs 4 in the placebo group), and no deaths occurred due to postoperative intracranial bleeding. Nuromohamed et al,15 in a randomized, double-blind trial, compared nadroparin calcium (Fraxiparine; Sanofi, Paris, France) and placebo in 485 patients. No difference in the incidence of postoperative intracranial hemorrhage was identified (6 patients in the nadroparin group vs 2 in the placebo group; P = .09), and no deaths were attributed to bleeding complications. Cerrato et al12 randomized 100 patients to receive either low-dose unfractionated heparin or placebo. No difference in the rate of postoperative intracranial bleeding was identified (2 patients in the low-dose unfractionated heparin group vs 1 in the placebo group), and no deaths were attributed to these postoperative complications. Details of the magnitude of the postoperative bleeding, or whether a second surgical procedure was required, were not given in these 3 studies.

It has been widely assumed that patients with IHI cannot be safely administered heparin for prophylaxis, although there are no studies to support this perception, to our knowledge. Thus, previous researchers5-6 examining the efficacy of enoxaparin use in preventing VTE in trauma patients have excluded patients with IHI from the enoxaparin treatment arms of their studies. Our previous experience8 in patients with multiple injuries, including 55 patients with IHI, suggested that enoxaparin may be safely administered to reduce the high incidence of VTE in blunt trauma patients with IHI.

Dickinson et al15 evaluated pneumatic compression devices, enoxaparin therapy, and a combination of both forms of prophylaxis in patients who had elective neurosurgery. Although there were no statistically significant differences among the groups, the randomized study was aborted after 5 of 46 patients who received preoperative enoxaparin developed postoperative intracranial hemorrhagic complications. The authors concluded that enoxaparin therapy initiated at the time of anesthesia increased the incidence of postoperative intracranial hemorrhage in patients undergoing elective neurosurgery.

We observed 2 adverse perioperative events early in the present study. One patient developed a recurrent subdural hematoma on follow-up postoperative CT scan. Although he had no clinical deterioration, this patient underwent a second craniotomy to evacuate the hematoma. The second patient, who initially required a decompressive craniectomy and partial frontal lobectomy for a massive intracerebral hematoma, developed an epidural hematoma after a subsequent cranioplasty. He also had no clinical deterioration, and the hematoma was surgically evacuated. Both of these patients survived their injuries. These 2 patients were the 16th and 22nd patients enrolled in the study and the first 2 who required intracranial surgery. As a result of these adverse events, the prophylaxis protocol was modified to delay administering enoxaparin for 24 hours after all initial and subsequent craniotomies or cranioplasties. There were no bleeding complications in the subsequent 22 patients entered into the study who required craniotomies to manage their IHI. Although it was our intent to begin enoxaparin therapy 24 hours after admission to the emergency department, the mean time until initiating prophylaxis was slightly longer. There were also 4 patients who received the first dose of enoxaparin earlier, at 4.0 to 17.5 hours

### Table 3. Hospital Discharge Glasgow Outcome Scale Scores for 150 Study Patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good recovery</td>
<td>115 (76)</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Severe disability</td>
<td>14 (9)</td>
</tr>
<tr>
<td>Persistent vegetative state</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Death</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Total</td>
<td>158 (100)</td>
</tr>
</tbody>
</table>
after admission to the emergency department. Early prophylaxis was begun in all 4 patients when the trauma surgeon initially interpreted the CT scan findings as normal. In all 4 cases, the radiologist subsequently interpreted the CTs as showing either a small contusion or subarachnoid blood (these are the 4 patients with head AIS scores of 2). Because the initial CT finding was positive, the patients were entered into the study and enoxaparin therapy was continued. There was no progression of any of these lesions on subsequent CT scans. Enoxaparin therapy was not started until 72 hours and 74 hours in 2 patients with concomitant severe splenic injuries being treated nonoperatively. The VTE protocol that was in force throughout the study required that enoxaparin administration be withheld for 72 hours in patients with nonoperatively treated splenic injuries. This portion of the VTE protocol was initiated based on our limited experience with splenic-injured patients from our first study\(^8\) of enoxaparin for prophylaxis. In this study, we observed a 17% incidence of significant delayed bleeding in nonoperatively treated patients with splenic injuries when enoxaparin was administered within the first 24 hours of hospital admission. We recently relaxed this area of the VTE protocol, and patients with grade I or II, and some grade III, splenic injuries are now administered enoxaparin 24 hours after hospital admission.

The study of VTE prophylaxis in patients with closed head injuries is complicated by the lack of information on the natural progression of IHI. A retrospective review\(^16\) of head-injured patients admitted to one institution between 1985 and 1998 suggested that 12% of patients with blunt, closed head injuries had progression of IHI findings on CT scan. Most of these patients had enlargement of an existing lesion, whereas approximately 10% developed a delayed intracranial hemorrhagic lesion on follow-up scans. The present study identified an even higher incidence of progression of IHI on CT scan (19%) during the first 24 hours after hospital admission. The substantial rate of spontaneous natural progression of IHI must be quantified and considered during any investigations into the safety of any form of VTE prophylaxis in head-injured patients. The present study identified no increase in the rate of progression of IHI in patients who progressed before receiving enoxaparin compared with patients who did not progress on CT before initiation of enoxaparin administration at 24 hours. In fact, the percentage of patients who progressed on CT was significantly lower after starting enoxaparin use. Although this observation does not indicate that enoxaparin therapy reduces the risk of IHI bleeding complications, it emphasizes that progression of IHI within the first 24 hours after brain trauma may be a significant part of the natural progression of the injury, and initiating enoxaparin prophylaxis after 24 hours may provide some protection against clinically adverse bleeding complications.

The present study design can be criticized on several accounts. A prospective randomized study comparing enoxaparin to a control group, either with or without use of low-dose unfractionated heparin or pneumatic compression devices, would provide the definitive proof for accepting the safety of enoxaparin as a prophylactic agent in patients with IHI. However, given the published randomized studies\(^5,6\) comparing enoxaparin with other forms of therapy, and our own prospective observations,\(^8\) we were reluctant to randomize a large number of our high-risk blunt trauma patients to a form of prophylaxis that has been proven to be less effective than enoxaparin therapy. In addition, it has been our experience that prophylactic vena caval filters can be almost totally eliminated in our high-risk patients when enoxaparin prophylaxis is used. Only 1 patient in the present study received a vena caval filter.

Recent studies examining the long-term complications from vena caval filters in trauma patients provide conflicting results. Greenfield et al\(^17\) compared outcomes of trauma patients who had vena caval filters placed for prophylaxis with those who had a filter placed for either a documented DVT or PE. The authors determined that the incidence of developing a new PE (1.5% vs 2.0%) or DVT (11% vs 9%) was no different between the prophylactic and therapeutic groups. A second study\(^18\) in trauma patients identified a 44% incidence of DVT development after prophylactic vena caval filter placement and a 10.4% overall incidence of lower-extremity edema in trauma patients after hospital discharge. It could be argued that the optimal incidence of new PEs and DVTs in any group of patients who receive prophylaxis for what may be considered temporary risk factors (ie, trauma) should approach 0% or at least be significantly lower than that in the therapeutic group if a better form of temporary prophylaxis were used instead of the permanent prophylactic vena caval filter. Enoxaparin therapy, if definitively proven to be a safe form of prophylaxis in patients with IHI, might provide a viable alternative to the more permanent vena caval filter and its potential long-term complications.

The risk of PE in the general neurosurgical population is as high as 5%, with mortality ranging from 9% to 50%.\(^19\) Despite these sobering statistics, a reluctance to use anticoagulant agents in these high-risk patients because of the perceived possible catastrophic consequences of hemorrhage within the cranium or spinal canal still exists.\(^12,19\) It was speculated as early as 1994\(^19\) that low-molecular-weight heparin agents would eventually supplant the role of low-dose unfractionated heparin and other forms of prophylaxis for VTE in the neurosurgical patient population. To our knowledge, there have been only 2 randomized studies\(^14,15\) looking at the safety and efficacy of enoxaparin use in elective neurosurgical patients. These studies provided conflicting conclusions, and presently there are no randomized studies in patients with IHI.

The results of the present study suggest that enoxaparin therapy, when started 24 hours after hospital admission or craniotomy for IHI, provides safe VTE prophylaxis for most head-injured patients. These results also provide support for further investigation into the safety of enoxaparin prophylaxis in patients with IHI. If the findings of this study are confirmed in a much larger group of patients or in the setting of a randomized, multicenter trial, then the incidence of VTE in multitrauma patients with IHI may be significantly reduced without the need for vena caval filter insertion.
REFERENCES


DISCUSSION

Gail T. Tominaga, MD, Honolulu, Hawaii: Venous thromboembolism is a common life-threatening complication of major trauma. With prophylaxis, patients with multisystem or major trauma have a risk for DVT that exceeds 50%, and fatal PE occurs in approximately 0.4% to 2.0%.

Routine thromboprophylaxis in trauma patients was first recommended over 50 years ago by Bauer. Unfortunately, there are few prospective randomized trials of prophylaxis in major trauma patients. Research in this area has been limited because of the inherent heterogeneity of the trauma population. Previous studies using low-dose heparin or low-molecular-weight heparin have excluded head-injured patients. The possibility of exacerbating intracranial hemorrhage with heparin products has made surgeons reluctant to use them.

Dickinson et al demonstrated an increased incidence of postoperative intracranial hemorrhage when enoxaparin was initiated preoperatively for DVT prophylaxis in elective neurosurgical patients with brain tumors. In addition, heparin-induced thrombocytopenia is a potential concern with the use of heparin preparations. The rate of thrombocytopenia with prophylactic heparin is 1% to 5%. Low-molecular-weight heparins are much less likely to produce heparin-induced thrombocytopenia than unfractionated heparin but still can pose a problem in multisystem-injured patients.

Current contraindications to early initiation of low-molecular-weight heparin include intracranial bleeding, incomplete spinal cord injury associated with paraspinal hematoma, ongoing uncontrolled bleeding, and uncorrected coagulopathy.

Dr Norwood’s group has previously reported on 118 trauma patients who received enoxaparin DVT prophylaxis. Their study included 55 blunt head–injured patients with intracranial hemorrhage. They reported no bleeding complications in this subgroup.

The current study by Dr Norwood and colleagues reports on 177 trauma patients with intracranial hemorrhagic injuries. Patients received enoxaparin at the standard dose of 30 mg subcutaneously every 12 hours starting approximately 24 hours following admission. Enoxaparin administration was delayed until 72 hours following admission in patients with splenic injuries who were managed nonoperatively. All patients had head CT scans performed on admission and at 24 hours. They excluded patients for coagulopathy, heparin allergy, expected brain death or discharge within 48 hours, and age less than 14.

Enoxaparin was continued throughout hospitalization unless one of the exclusion criteria or bleeding complications developed. After the first 22 patients, the study protocol was modified so that heparin was delayed 24 hours following initial and subsequent craniotomies. The bleeding rate in this study was reported at 4% and is similar to that seen in previous reports of enoxaparin use in neurosurgical patients, which is reported at 2.7%. This study suggests that enoxaparin is safe to use in the head-injured trauma patient with hemorrhagic injuries noted on CT scan. I agree with the authors that a prospective randomized trial comparing enoxaparin to a control group is needed.

My questions for the authors are as follows: There were 4 patients out of 177 who were excluded due to coagulopathy in this study. This seems a bit low for seriously head-injured patients. What was your criterion for coagulopathy? What was your incidence of heparin-induced thrombocytopenia, and was enoxaparin stopped on any patient because of heparin-induced thrombocytopenia?

Enoxaparin was delayed in patients who had craniotomies or cranioplasties and in patients undergoing nonoperative splenic injury management. Was enoxaparin administration delayed in patients who had ventriculostomies or ICP monitors placed? Did patients with major liver injuries, major pelvic hematomas, or exploratory laparotomies have a delay in enoxaparin administration?

Finally, how did you get your neurosurgeons to agree to start their enoxaparin administration so early after the time of injury?
rable group available in the literature. We don't really know what bleeding rate to expect after 24 hours in severely head-injured trauma patients.

Also, the focus was not lower-extremity DVT, but again the 1.9% rate that you reported is amazingly low. However, in at least a third of your patients, the diagnosis would have been made only based on clinical findings since you only did color flow Doppler on about two thirds of the patients. So, although the numbers in your paper strongly suggest that it is pretty safe to use enoxaparin and the DVT rate is low, it is not clear about the efficacy.

Also, I wonder if you had done a third CT scan routinely, maybe at 48 or 72 hours, you would have known more about what was going on in the head, possibly uncovering additional rebleeding.

I agree with both your own suggestion and Dr Tominaga's that this needs to be subjected to a randomized trial. Have you looked at that? Have you any idea how large a trial that would take? Do you think the addition of additional head CT scans and routine serial look for DVT with color flow Doppler would be reasonable?

J. David Richardson, MD, Louisville, Ky: Philosophically, we are trying to prevent a fairly low-event disastrous outcome, ie, death from pulmonary embolus. You are substituting a prophylactic measure, which has a potential risk for a disastrous outcome, albeit small. Granted, 4% increased bleeding may be low, but if 1 patient out of every 100 dies or has a worsened outcome, is our risk-benefit worth it? How do you answer that in terms of those who would question what you're doing? Do you continue these patients on Coumadin or some other type of anti-coagulant after discharge?

Dr Norwood: I would like to thank Dr Tominaga for flying halfway around the world to discuss this paper. She arrived at midnight last night and has to leave in about an hour, so I appreciate her being here.

In answer to your questions, we used the usual parameters for coagulopathy. If the patient's prothrombin time was elevated more than 2 seconds, we did not enter them in the study until the PT was corrected. We also eliminated those patients with elevated PTT or platelet counts less than 60,000. We had no patients in our study group who developed heparin-induced thrombocytopenia, but we did have 3 patients during the study period who were not study patients but developed this problem and enoxaparin was discontinued.

We did not withhold prophylaxis for ventriculostomies. We had about 20 patients with liver injuries, retroperitoneal injuries, or pelvic fractures, and all of these patients were prophylaxed at 24 hours.

The reason we withheld prophylaxis in the patient with splenic injuries until 72 hours was because in our previous study, 2 out of 12 patients with spleen injuries bled; so we arbitrarily decided to wait 72 hours in these patients.

How did we get the neurosurgeons to agree to this? We were very fortunate because the neurosurgeons were somewhat familiar with using this drug in their aneurysm patients. We began by cautiously using enoxaparin in our multiply-injured patients, including some with brain injuries. After accumulating 55 patients, we convinced them that enoxaparin could be safely used when applied in a careful, prospective fashion.

Dr Berne, I agree that a 4% bleeding complication rate is low, and I believe that the actual rate is even lower. We will continue to collect patients. In answer to your question about how many patients would be needed to do a prospective randomized study, again, the only data available is in elective neurosurgery patients. I believe that we would need about 139 patients in each arm to do that study.

In answer to your question about a third CT, most patients did have a third CT, and may have several more prior to discharge. We did 468 scans in 150 patients.

Dr Richardson, I appreciate your concerns. All I can say is that we are extremely careful with prophylaxing these patients. We have rounds every morning with the neurosurgeon who is assigned to the trauma service and discuss these patients to make sure that everyone is in agreement with the plan to prophylax the patients with enoxaparin.

Concerning prophylaxis after discharge, we have a disclaimer on our discharge instruction sheet saying that the question of DVT is unanswered, and we recommend that they all take aspirin until ambulatory unless they are on another anti-coagulant for other reasons.