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Utility of Once-Daily Dose of Low-Molecular-Weight Heparin to Prevent Venous Thromboembolism in Multisystem Trauma Patients

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Abstract

Introduction: Venous thromboembolism is a preventable cause of death in the severely injured patient. Low-molecular-weight heparins (LMWHs) have been recommended as effective, safe prophylactic agents. However, LMWH use remains controversial in patients at risk for bleeding, those with traumatic brain injury, and those undergoing multiple invasive or operative procedures. We hypothesized that a protocol utilizing once-daily LMWH prophylaxis in high-risk trauma patients, regardless of the need for invasive procedures, is feasible, safe, and effective.

Methods: From August 1998 to August 2000, all patients admitted to our American College of Surgeons-verified Level I trauma facility following injury were evaluated for deep venous thrombosis (DVT) risk and prospectively followed. Patients at high risk for DVT, including those with stable intracranial injuries, were placed on our institutional protocol and prospectively followed. Patients on the protocol received daily injections of the LMWH, dalteparin; DVT screening was performed with duplex ultrasonography within 48 hours of admission and after 7 to 10 days after injury. Regimen compliance, bleeding complications, DVT rates, and pulmonary embolus (PE) rates were analyzed.

Results: During the 2-year study period, 6247 trauma patients were admitted; 743 were considered at high risk for DVT. Most of the patients were men (72%), with a mean age of 38.7 years (range 15–89 years) and a mean injury severity score (ISS) of 19.5. Compliance with the daily regimen was maintained in 74% of patients. DVT was detected in 3.9% and PE in 0.8%. The wound complications rate was 2.7%, and the need for unexplained transfusions was 3%. There were no exacerbations of head injury following dalteparin initiation due to bleeding. There were 16 patient deaths; none was caused by PE or late hemorrhage.

Conclusions: Once-daily dosing of prophylactic LMWH dalteparin is feasible, safe, and effective in high-risk trauma patients. Our protocol allows one to ''operate through'' systemic prophylaxis and ensures timely prophylaxis for brain-injured and multisystem trauma patients.

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Venous thromboembolism (VTE), a preventable cause of death in trauma patients, remains a major

source of morbidity and resource expenditure.[1] Multiple studies have demonstrated the efficacy of deep venous thrombosis (DVT) prophylaxis, but the optimal therapeutic regimen is still being debated.[1–11] Low-molecular-weight heparins (LMWHs) have been recommended for multisystem-injured patients to prevent DVT,[1,2,12–14] but there is concern about an increased risk of bleeding, particularly in injured patients with intracranial hemorrhage, spinal cord injury, major solid organ injuries, and complex pelvis fractures.[15] As such, practitioners may not dose patients appropriately despite clear practice guidelines.[16] Additionally, the safety of performing invasive procedures while receiving LMWH is debated.[17] The purposes of this study were to investigate (1) the safety of once-daily dosing of LMWH in patients with traumatic brain injury and those undergoing invasive procedures, (2) the compliance of once-daily dosing of LMWH in severely injured patients, and (3) the VTE rate in this multisystem trauma patient population with this dosing regimen.

MATERIALS AND METHODS

Patients

From August 1998 to August 2000, all patients sustaining traumatic injury requiring admission to Denver Health Medical Center were evaluated and followed prospectively. Denver Health Medical Center (DHMC) is an American College of Surgeons-verified, state-designated Level 1 trauma center with approximately 3400 trauma admissions per year. Acutely injured patients 18 years of age or older were considered candidates for the prospective study. Patients currently receiving treatment for DVT, those with a diagnosis of DVT prior to LMWH administration, those already systemically anticoagulated, or those undergoing placement of an inferior vena cava filter were excluded. LMWH prophylaxis was initiated once patients were hemodynamically stable (supported by no vasoactive agents, a resolving base deficit, and no need for aggressive fluid resuscitation or ongoing blood product transfusions), without evidence of continued hemorrhage; such trauma resuscitation is often complete by the morning following admission, and dalteparin was initiated at the next dosing time. In patients with intracranial hemorrhage, close clinical monitoring and repeat head computed tomography (CT) scanning 12 to 24 hours after injury were performed; prophylaxis was initiated if there was no evidence of active or increased intracranial hemorrhage on repeat CT scan. Similarly, spine patients were evaluated by the spine/neurosurgery team and started on prophylaxis when the criteria were fulfilled. Patients with epidural analgesia did not start LMWH prophylaxis until the epidural catheter was removed.

Table 1.
Patients at high risk for DVT

CNS injury with GCS < 8
Complex spine fractures
Previous DVT history
Morbid obesity
Prolonged immobilization > 5 days
Multisystem injury (ISS > 14)
Quadriplegia/paraplegia
Complex long-bone, acetabular, or pelvic fracture

CNS: central nervous system; GCS: Glasgow Coma Score; DVT: deep venous thrombosis; ISS: Injury Severity Score.

Drug Regimen

Patients determined to be at high risk for DVT, based on previously reported and verified conditions (Table 1), comprised the study population.[11] Patients underwent intermittent pneumatic compression of the lower extremities (except when it was precluded by injury to an extremity) and subcutaneous injection of the LMWH dalteparin sodium (Fragmin; Pharmacia, Bridgewater, NJ, USA) 5000 units once daily. Dalteparin dosing was continued throughout the hospital stay until discharge or until patients could ambulate independently. The dose was appropriately adjusted for patients with renal insufficiency or failure. Once LMWH prophylaxis was started, it was continued daily despite the need for return trips to the operating room or invasive procedures in the surgical intensive care unit (SICU) or interventional radiology suite.

DVT Screening

Initial screening for DVT was performed using duplex ultrasonography (US) within 48 hours of admission (prior to LMWH administration), and follow-up US was performed between 7 and 10 days postinjury. US was performed by qualified, licensed US technologists from the Department of Radiology using an ATL all-digital broadband hDI-5000 ultrasound device (Philips Medical Systems, Bothell, WA, USA). Bilateral lower extremities were assessed from the femoral head to the popliteal fossa. Diagnosis of a DVT was based on the lack of normal venous compressibility and the lack of normal Doppler

flow detection. If at any time a patient manifested clinical evidence of DVT, a US examination was performed.

Treatment Outcomes

Patients were considered to have failed prophylaxis if they had a DVT documented by US 7 to 10 days after the injury or if the US performed for clinical symptoms was positive for DVT. These patients then received appropriate anticoagulation for treatment of their DVT. Patients with clinical symptoms of PE, including increased ventilatory requirements, a drop in oxygen saturation, or an increased A-a gradient, were evaluated using pulmonary angiography or helical CT scanning. The cause of any patient's death was identified from autopsy reports, which included inspection of the pulmonary vasculature.

To evaluate the safety and feasibility of LMWH, compliance with the prophylaxis regimen and patient morbidity were analyzed. Noncompliance was defined as missing a single dose of dalteparin for any reason. Bleeding was monitored by daily wound inspection, daily monitoring of the hemoglobin value, and evaluation of the etiology of and need for transfusions. Clinically relevant bleeding, the primary measure of safety, was defined ''as expected'' (related to the original injury or surgical intervention) or ''unexpected.'' The need for and the etiology of all transfusions were determined by a committee that included a trauma surgeon, an orthopedic surgeon, and a neurosurgeon; all committee members were blinded to the identity of the patient. Wound drainage was similarly categorized, with unexpected drainage defined as persistent wound drainage 72 hours after full wound closure. Patients with closed head injury underwent noncontrast head CT 7 to 10 days after injury to ensure that there was no new intracranial hemorrhage.

Additional patient data, including demographics, associated injuries, Injury Severity Score (ISS), ventilation status, length of stay in the intensive care unit, and non-VTE complications, were obtained through our trauma registry. The Colorado Multi-institutional Review Board approved this study with waiver of consent.

RESULTS

During the 2-year study period, there were 6247 trauma admissions; 743 patients were considered at high risk for DVT and received daily dosing of the LMWH dalteparin. Most of the patients were men (72%), with a mean age of 38.7 years (range 15–89 years), a mean ISS of 19.5 (range 1–75), and a mean Glasgow Coma Scale score of 13.4 (range 3–15) (Table 2). Most of the patient injury mechanisms were blunt trauma (93%), with motor vehicle collisions predominating (71%) (Table 3). Patients were multiply injured, with 64% sustaining fractures of the pelvis or a lower extremity long bone; 43% had spinal or intracranial injuries, 30% had thoracic injuries, and 15% had intraabdominal injuries (Table 3).

Dalteparin was initiated a mean of 3.3 days after admission. Compliance with the daily regimen was maintained in 74% of patients. Patients underwent a mean of 5.0 (range 1–42) invasive procedures during their hospital stay. The mean SICU stay was 8.0 days

Table 2.
Patient demographic data

Study Data	Mean	Range
Age (years)	38.69	15–89
Total length of stay (days)	14.38	1–96
Time in SICU (days)	8.08	0–96
Time on ventilator (days)	4.59	0–81
Blood products received in initial 48 hours (units)	2.82	0–82
Blood products received after 48 hours (units)	1.75	0–70
Total blood received (units)	4.58	0–16
GCS	13.4	3–15
ISS	19.5	1–75
No. of surgical procedures during stay	4.99	1–42
Total doses of dalteparin received	9.19	1–76
Delay before first dose of dalteparin administered (days)	3.28	0–29

SICU: surgical intensive care unit; GCS: Glasgow coma score; ISS: Injury Severity Score

Table 3.
Mechanism and etiology of patient injury

Parameter	Total no.
Mechanism	
Vehicular collisions	530 (71%)
Fall	100 (13%)
Assault	36 (5%)
Workplace	24 (3%)
Other	53 (7%)
Type of injury	
Long-bone fracture	207 (28%)
Pelvis/acetabular fracture	271 (36%)
Spinal injury	143 (19%)
Brain injury	174 (23%)
Thoracic injury	223 (30%)
Abdominal injury	115 (15%)
Other	237 (32%)

(range 1–96 days), and the mean hospital stay was 14.4 days (range 1–96 days).

Initial US screening for lower extremity DVT was performed in all 743 patients. No patient had evidence of DVT at the initial examination, which was performed within 48 hours of admission. Follow-up US examination, performed in 673 patients at 7 to 10 days revealed DVT in 26 patients (3.9%). Altogether, 70 patients were discharged prior to follow-up US; to our knowledge, none had signs or symptoms of DVT/PE. Six patients developed documented PE (0.8%), but no patient had a fatal outcome. None of the six patients had a positive US examination prior to their PE, but follow-up US to document a lower extremity source was not routinely performed.

A total of 18 patients (2.7%) had prolonged wound drainage or hematoma; none developed infection. Of the cases of prolonged drainage, six were from ilioinguinal approaches following acetabular surgery, four were from closed laparotomy wounds, three were from extremity orthopedic wounds, two followed pelvis open reduction/internal fixation, two followed free tissue transfers, and one was from a deep facial laceration. Altogether, 22 (3%) of the patients required packed red blood cell transfusions (range 1–3 units) while on dalteparin that appeared unrelated to the initial injury or surgical bleeding. No patients developed or had increased intracranial hemorrhage following the initiation of dalteparin. During the patient's acute hospitalization, there were 16 deaths in the study population (2.1%). No deaths were attributed to dalteparin-related bleeding complications or PE based on review of death reports and results of autopsies, which were performed in all 16 patients.

DISCUSSION

Severely injured patients have the highest risk of proximal DVT and subsequent PE, with significant attendant morbidity and mortality, owing to the combination of endothelial injury, variable coagulable states, and venous stasis.[15,18,19] There is a wide range of DVT rates in trauma patients, from 2.4% to 90.0%,[1,2,10,12,13,15,20,21] whereas reported PE rates range from 0% to 22% with 1% to 2% fatal PE.[2,10–13,15,18,20] Multiple studies have investigated the optimal method of prophylaxis for DVT, recognizing that DVT and PE rates are lowered in trauma patients who are treated with LMWH,[1,2,22] mechanical compression,[3,4] or inferior vena cava filters.[5–7,12] The advantages of using LMWH compared to other modalities are its ease of administration, increased efficacy, improved specificity compared to unfractionated heparin (UH), and no monitoring requirement.[1,2,11,12,23–30] The paradox of VTE prophylaxis is that any agent that decreases venous clot formation has a corresponding potential to increase bleeding in nonhemostatic or injured tissue. We hypothesized that a once-daily dosing of LMWH would increase compliance in a busy intensive care unit (ICU) setting, would be safe in patients with closed head injuries and those undergoing invasive procedures, and would provide reasonable efficacy compared to current standards.

The optimal drug choice and dosing regimen for VTE prophylaxis in the high-risk trauma patient continues to be debated. Previous studies have shown that twice-daily dosing with LMWH agents, specifically enoxaparin 30 mg is safe and efficacious.[1,22,23] Severely injured patients often require repeated trips to the operating room, and at our institution we found it impractical to discontinue chemical prophylaxis for each surgery. In a pilot study, we attempted to discontinue usage of LMWH on the day of surgery. Subsequently, we found that our patients received prophylaxis during only 33% of their hospital stay. Based on our experiences in cases in which dalteparin had inadvertently not been discontinued, we theorized that there would be no adverse effects if we "operated through" prophylaxis. By adopting the protocol of continuing prophylaxis despite the need for invasive procedures and using once-daily administration LMWH, compliance rates (defined as no missed doses of dalteparin) increased to 74%. With continued application of this protocol, including physician and nursing education, we hope to achieve 100% compliance. Although not explored in this study, additional benefits of a once-daily versus twice-daily dosing regimen may include increased patient comfort by the decreased number of needle injections and decreased cost of administration due to decreased drug, nursing, and pharmacy costs.

Bleeding complications are difficult to assess in trauma patients because of the heterogeneity of the population and the presence of bleeding from multiple injury sites. Two methods have been used in previous studies to assess bleeding complications: the bleeding index, used following elective hip arthroplasty, and committee adjudication.[1] The bleeding index may not be an accurate measurement in trauma patients with hemorrhage prior to LMWH administration. Therefore we chose committee adjudication to evaluate bleeding complications. The blinded committee of an orthopedic surgeon, neurosurgeon, and trauma surgeon evaluated all patient cases for two indices of bleeding complications: wound

complications and transfusions unexplained by injury or surgery. Only 2.7% of patients had prolonged wound drainage or significant hematoma requiring operative intervention. Although we attributed this to a complication of dalteparin, this may overestimate the impact of LMWH on bleeding complications. Similarly, as is true of any subjective evaluation, underestimation of the contribution of dalteparin to the patient's need for transfusion cannot be excluded.

Three percent of patients received red blood cell transfusions that did not appear related to initial injury or operative intervention. The need for transfusion was determined by the patient's attending surgeon; although guidelines for appropriate transfusion based on hemoglobin counts exist,[31] we cannot ensure that all of the attending physicians adhered to these guidelines. Therefore, the absolute hemoglobin level that triggered transfusion may be different in each case. Additionally, patients in the ICU may lose a significant amount of blood volume from daily blood draws for laboratory tests. Again, this points to a possible overestimation of unexplained transfusions, which we considered bleeding complications of dalteparin. No deaths in our study were due to bleeding complications following the initiation of LMWH. We believe that our rate of bleeding complications is similar to those in previous studies[1] and are reasonable given the 1% to 2% incidence of fatal PE without prophylaxis in this population.[18]

Patients with traumatic brain injury may be particularly susceptible to complications caused by VTE prophylaxis.[32,33] There was no evidence of new or increased intracranial hemorrhage following initiation of dalteparin prophylaxis in our population. We currently repeat a head CT scan within 12 to 24 hours after injury prior to starting LMWH. Our results indicate that dalteparin can be safely used following traumatic brain injury in the absence of active intracranial hemorrhage.

The DVT rate in our series compares favorably with those from prior studies in trauma patients. Using a once-daily dosing regimen of dalteparin, DVT was detected in 3.9% of patients and PE in 0.8% of patients. Geerts et al. found a 6% rate of proximal DVT in 344 patients treated with twice-daily enoxaparin.[1] With a similar dosing regimen of enoxaparin, Norwood et al. treated 118 patients and detected DVT in 2% of patients.[23] Likewise, Schwarcz et al. examined 241 patients treated with twice-daily dosing of enoxaparin and found 2% to have DVT.[22] Our study evaluated more than twice the number of patients as in these previous studies and, to our knowledge, is the first report on the efficacy of once-daily dalteparin in a multisystem trauma population.

We recognize that this is a single institution's experience. Although providing a control group would be ideal, we did not believe it ethical to withhold DVT prophylaxis in this patient population. We also did not think that choosing an LMWH with twice-daily administration—the only regimen with proven decreases in DVT and PE rates—was viable in our institution because of the low compliance rates. Therefore, our dosing regimen may be criticized for lack of a comparative group. Similarly, without such a control, our efficacy is based on prior reports; our study showed similar rates of DVT/PE, although strict population matching remains limited by such an approach. Our standard technique for DVT screening is duplex US. Although venography is considered the gold standard for diagnosing DVT, in experienced hands the sensitivity of duplex US is 92% to 95%, and the specificity is 97% to 100%.[34] One drawback, however, is that US may underestimate the DVT rate because of its inability to examine pelvic veins. We believe that venography does not lend itself to severely injured patients. Many of these patients are extremely labile; and unnecessary dye loads, with the risk of impending renal failure in the face of incipient multisystem organ failure, cannot be justified. Duplex US can be performed at the bedside without deleterious effect on the patient. An additional limitation of the study is the timing of the second duplex; although the timing of the follow-up US was determined prior to initiation of the study to establish a reasonable interval from that performed at admission and entry into the study, the average hospital stay was several days longer than the predetermined time interval. With up to 50% of DVTs occurring after the first week of hospitalization, early screening may miss such occurrences. As such, patients with prolonged hospitalizations and asymptomatic DVTs would be underestimated by this approach.

CONCLUSIONS

In our experience, once-daily LMWH prophylaxis for DVT in severely injured patients is safe, feasible, and efficacious. Dalteparin administered in a convenient once-daily dosing regimen had similar safety and efficacy results compared to previous studies utilizing twice-daily enoxaparin. In addition, the once-daily dosing schedule, administered regardless of the need for invasive procedures, resulted in increased compliance compared to a pilot study at our institution in which LMWH was discontinued on the day of surgery. Our protocol allows one to ''operate through'' systemic prophylaxis and ensures

timely prophylaxis for brain-injured and multisystem-trauma patients. Future prospective randomized studies should be performed to validate these findings.

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