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Weight-based enoxaparin dosing and deep vein thrombosis in hospitalized trauma patients: A double-blind, randomized, pilot study☆

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ABSTRACT

Background: Venous thromboembolism is a cause of morbidity and mortality in trauma patients. Chemoprophylaxis with low-molecular-weight heparin at a standardized dose is recommended. Conventional chemoprophylaxis may be inadequate. We hypothesized that a weight-adjusted enoxaparin prophylaxis regimen would reduce the frequency of venous thromboembolism in hospitalized trauma patients and at 90-day follow-up.

Methods: This prospective, randomized pilot study enrolled adult patients admitted to a level 1 trauma center between July 2013 and January 2015. Subjects were randomized to receive either standard (30 mg subcutaneously every 12 hours) or weight-based (0.5mg/kg subcutaneously every 12 hours) enoxaparin. Surveillance duplex ultrasound for lower extremity deep vein thrombosis was performed on hospital days 1, 3, and 7, and weekly thereafter. The primary outcome was deep vein thrombosis during hospitalization. Secondary outcomes included venous thromboembolism at 90 days and significant bleeding events.

Results: Two hundred thirty-four (124 standard, 110 weight-based) subjects were enrolled. There was no difference between standard and weight-based regarding age, body mass index, percentage female gender, injury severity score, or percentage that had surgery. There was a trend toward less in-hospital deep vein thrombosis in weight-based (12 [9.7%] standard vs 4 [3.6%] weight-based, $P = .075$). At 90 days, there was no difference in venous thromboembolism (12 [9.7%] standard vs 6 [5.5%] weight-based, $P = .34$). There was 1 bleeding event, which occurred in a standard subject.

Conclusion: Weight-based enoxaparin dosing for venous thromboembolism chemoprophylaxis in trauma patients may provide better protection against venous thromboembolism than standard. A definitive study is necessary to determine whether weight-based dosing is superior to standard.

Venous thromboembolism (VTE), composed of deep vein thrombosis (DVT) and pulmonary embolism (PE), is responsible for an economic impact of up to $69 billion annually in the United States, and is linked to over one-half million hospitalizations.[1] VTE frequently complicates the care and clinical course of trauma patients, and is a major cause of morbidity and late mortality. Risk factors including age, obesity, and improved trauma survival contribute to high VTE rates in this patient population. Although trauma-associated VTE is potentially preventable, the majority of trauma patients are already receiving standard prophylaxis[2-4] when diagnosed with VTE. Therefore, although prevention of VTE is crucial, the optimal regimen for VTE prophylaxis remains uncertain.

Pharmacologic agents, particularly heparinoids, are the cornerstone of VTE prophylaxis; yet the evidence informing the dosing of these agents in trauma patients is limited. Although a standard fixed dose of heparinoid has been recommended,[5] recent studies

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suggest that this one-size-fits-all approach may not be adequate to prevent VTE in all injured patients, perhaps in part because insufficient drug levels are attained in overweight and obese patients.[6-8]

The purpose of this pilot study was to determine the feasibility, and inform the power estimates for, a definitive trial to assess the efficacy of a weight-adjusted regimen of enoxaparin in all high-risk trauma patients regardless of body mass index (BMI). We hypothesized that weight-based (WB) dosing of enoxaparin (0.5 mg/kg subcutaneously [SQ] twice daily) would reduce the rate of VTE, without increasing the incidence of bleeding complications, as compared to standard (ST) fixed dosing.

Methods

Between July 2013 and January 2015, we conducted a randomized, double-blind, controlled pilot trial comparing WB versus ST dosing of enoxaparin in patients admitted to the trauma service at Intermountain Medical Center, an American College of Surgeons verified level 1 trauma center, with approximately 3,500 trauma activations annually. We randomized consecutive eligible patients to either ST (enoxaparin 30 mg SQ every 12 hours) or WB (enoxaparin 0.5 mg/kg SQ every 12 hours) pharmacologic prophylaxis. Actual body weight on hospital admission was used for the WB dosing. Eligible patients were those admitted to the trauma service who were at least 18 years old weighing 60 kg or greater, met institutional criteria for high-risk for VTE (1 or more of: BMI >30 kg/m^2, age >40 years, spine fracture, pelvis or lower extremity fracture, hemorrhagic shock defined as systolic blood pressure <90 mmHg, moderate or severe head injury defined as Glasgow Coma Score <13, injury severity score [ISS] >9), and who provided written informed consent. Patients were approached within 48 hours of admission, and proxies or relatives could be used for consent. Exclusion criteria included injury causing, or at risk to cause, significant bleeding (solid organ injury defined as adjusted injury scale ≥ 3 or any intracranial hemorrhage); acute or chronic renal insufficiency (glomerular filtration rate <30 mL/min); thrombocytopenia (platelet count <100 K/μL); sensitivity to heparin or history of heparin-induced thrombocytopenia; pregnancy or breast feeding; hemorrhagic cerebral vascular event within the preceding 3 months; baseline coagulopathy (international normalized ratio >1.4); baseline therapeutic anticoagulation; use of aspirin ≥ 325 mg daily; life expectancy <1 month; and hospitalization for >72 hours prior to randomization; more than a single dose of prophylactic heparin was administered prior to screening. Eligible patients were randomized by computerized random number generator, and sealed opaque envelopes were used to conceal group assignment. Clinical and study staff had no means to predict results of randomization.

The hospital's central pharmacy provided the study enoxaparin (fixed dose or weight-adjusted dose) in identical packaging for both study arms, to ensure blinding of the patient, study staff, and the clinical team. The study drug was administered to patients during their entire hospital stay unless a contraindication arose, in which case the contraindication was documented. Continued prophylaxis at the time of discharge, if any, was at the discretion of the clinical team. Per trauma service standard, sequential compression devices were placed on bilateral lower extremities in all patients, unless contraindicated by injury. Extended prophylaxis (following hospital discharge) was prescribed at the discretion of treating clinicians, and was not directed by study protocol.

Feasibility outcomes included the number of patients screened, percentage of eligible patients consenting to participate, adherence to study protocol, and percentage of enrolled patients who could be analyzed for study outcomes.

The primary efficacy outcome measure was objectively confirmed VTE found during the index hospitalization. Asymptomatic lower extremity DVT was identified through a duplex ultrasound (DUS) screening surveillance protocol (the standard of care for all patients admitted to the trauma service) with whole-leg bilateral DUS performed within 24 hours of admission, at days 3 and 7 after admission, and weekly thereafter until hospital discharge. DUS results were available to the trauma clinicians nearly immediately after the test was performed. Symptomatic VTE workup was based on the individual case and treating provider.

Safety outcomes were death or major bleeding within 90 days from discharge, thrombocytopenia, and any other suspected adverse drug reactions. Major bleeding was determined using the criteria published by the International Society on Thrombosis and Haemostasis,[9] and included fatal bleeding; symptomatic bleeding in a critical area or organ such as intracranial, intra-abdominal, or retroperitoneal; and bleeding resulting in a hemoglobin drop of at least 20 g/L or requiring transfusion of 2 or more units of either whole blood or packed red blood cells. Thrombocytopenia was defined as a decrease in platelet count by at least 30% from baseline or a count less than 100,000 per microliter.

All clinical outcomes were ascertained by using a 90-day follow-up review of medical records. Intermountain Healthcare is an integrated health-care system with a single medical record across 22 hospitals and hundreds of outpatient clinics. If there was no 90-day information in the medical record, patients were then contacted by phone. An independent endpoint adjudication committee composed of physicians who were blinded to the treatment assignments reviewed all records.

A formal Data Safety Monitoring Board made up of physicians not part of the study team examined the data on a regular basis to evaluate patient safety. The Data Safety Monitoring Board was empowered to recommend that the principal investigator stop the study if significant safety concerns arose, primarily centered on bleeding events. The trial adhered to CONSORT reporting guidelines (Fig. 1).

The study was registered at clinicaltrials.gov (identifier *NCT01916707*) and was funded by a grant from the Intermountain Research and Medical Foundation. The Intermountain Central Institutional Review Board approved the study.

Statistical analysis

Descriptive statistics stratified by dosing strategy were performed for the whole study population as well as for a subgroup of those who had a confirmed VTE during their index hospitalization. Binomial confidence intervals (CIs) were estimated using Bayesian inference at 95% confidence with Jeffreys prior distribution.

Inferential analyses were conducted for 1 primary analysis and 3 secondary analyses of the whole population, as well as for 1 subgroup of those who had a confirmed in-hospital VTE event. The primary analysis used Fisher exact test to compare rates of in-hospital VTE between the treatment arms. The secondary analyses used Pearson χ^2 statistic to compare rates of 90-day VTE events between treatment arms, and Fisher exact tests to compare rates of 90-day major bleeding events and 90-day all-cause mortality between the treatment arms. The subgroup analysis used the bootstrapped Kolmogorov-Smirnov (KS) test to compare the discrete, ordinal distributions of days to VTE diagnosis between treatment arms among those who experienced an in-hospital VTE event. Since the time to VTE diagnosis was measured as integers in units of days, the bootstrapped KS test was used because of its ability to handle ties between comparison distributions.

Based on previous published data, we estimated that a minimum clinically important difference in event rates between the WB and ST groups would correspond to a decrease ranging between 2.1% and 3.7%. Based on this, enrollment of 1,200 total patients (600 per arm) would be sufficient to achieve 80% to