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ORIGINAL ARTICLE

Dalteparin versus Enoxaparin for the prevention of venous thromboembolic events in trauma patients

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Abstract
Background The use of low-molecular-weight heparin (LMWH) for the chemoprophylaxis of venous thromboembolism (VTE) in trauma patients is supported by Level-1 evidence. Because Enoxaparin was the agent used in the majority of studies for establishing the efficacy of LMWH in VTE, it remains unclear if Dalteparin provides an equivalent effect.
Objective To compare Dalteparin to Enoxaparin and investigate their equivalence as VTE prophylaxis in trauma.
Patients/setting Trauma patients receiving VTE chemoprophylaxis in the Surgical Intensive Care Unit of a Level-1 Trauma Center from 2009 (Enoxaparin) to 2010 (Dalteparin) were included.
Measurements The primary outcome was the incidence of clinically significant VTE. Secondary outcomes included heparin-induced thrombocytopenia (HIT), major bleeding, and drug acquisition cost savings. Equivalence margins were set between −5 and 5 %.
Main results A total of 610 patient records (277 Enoxaparin, 333 Dalteparin) were reviewed. The two study groups did not differ significantly: blunt trauma 67 vs. 62 %, $p = 0.27$; mean Injury Severity Score (ISS) 17 ± 10 vs. 16 ± 10, $p = 0.34$; Acute Physiology and Chronic Health Evaluation (APACHE) II score 17 ± 9 vs. 17 ± 10, $p = 0.76$; time to first dose of LMWH 69 ± 98 vs. 65 ± 67 h, $p = 0.57$). The rates of deep venous thrombosis (DVT) (3.2 vs. 3.3 %, $p = 1.00$), pulmonary emboli (PE) (1.8 vs. 1.2 %, $p = 0.74$), and overall VTE (5.1 vs. 4.5 %, $p = 0.85$) did not differ. The absolute difference in the incidence of overall VTE was 0.5 % [95 % confidence interval (CI): −2.9, 4.0 %, $p = 0.85$]. The 95 % CI was within the predefined equivalence margins. There were no significant differences in the frequency of HIT or major bleeding. The total year-on-year cost savings, achieved with 277 patients during the switch to Dalteparin, was estimated to be $107,778.
Conclusions Dalteparin is equivalent to Enoxaparin in terms of VTE in trauma patients and can be safely used in this population, with no increase in complications and significant cost savings.

Keywords Trauma · Low-molecular-weight heparin · Deep venous thrombosis · Pulmonary embolism · Venous thromboembolism prophylaxis · Cost savings

Introduction

Venous thromboembolism (VTE) events occur frequently among trauma patients and there is extensive Level-1 evidence recommending the use of low-molecular-weight heparin (LMWH) as VTE prophylaxis in this population [1–4]. The majority of studies to date have compared the safety and efficacy of LMWH to unfractionated heparin (UFH). These studies have concluded that LMWH is superior to UFH for VTE prophylaxis, especially in orthopedic and spinal cord injury [5–7]. However, the current guidelines do not recommend a specific type of LMWH, and few studies have compared the safety and

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efficacy of different LMWH regimens in the trauma patient population.

In 1999, the TIFDED Study Group compared the LWMHs danaparoid, Enoxaparin, and Dalteparin in patients undergoing hip fracture surgery and found no statistically significant difference in safety or efficacy between these agents [8]. A more recent study in 2007 examined the utility of Dalteparin versus Enoxaparin for VTE prophylaxis in acute spinal cord injury and major orthopedic trauma [9]. Although the study was not sufficiently powered to make any definite conclusions, Dalteparin was not found to be clinically non-inferior to Enoxaparin in high-risk patients (acute spinal cord injury, major orthopedic trauma). The authors went on to recommend Enoxaparin in this patient population until an adequately powered, prospective, non-inferiority trial is performed. Other studies have looked at these two drugs in other sub-populations, with mixed results [8, 10].

The purpose of our study was to compare the incidence of VTE among trauma patients between those receiving prophylactic Enoxaparin in 2009 and those receiving Dalteparin in 2010. We hypothesized that Dalteparin was biologically equivalent to Enoxaparin for the prevention of thromboembolic events in trauma patients.

Methods

This is a retrospective cohort study of critically ill trauma patients receiving prophylactic anticoagulation therapy. After institutional review board approval, a review of the institutional trauma registry and the Surgical Intensive Care Unit (SICU) database at the Los Angeles County + University of Southern California (LAC + USC) Medical Center from January 2009 through December 2010 was performed. The study population consisted of two groups defined by the two time periods; those treated in 2009 during which Enoxaparin was used and those treated in 2010 during which Dalteparin was used. This grouping was the result of the institutional formulary change in LMWH prophylaxis from Enoxaparin to Dalteparin in 2010. With the exception of the change in VTE prophylaxis, there were no significant practice changes at the institution. Clinical personnel were notified of the formulary change, and inpatients were transitioned over a 2-week period. Patients who received both drugs were excluded from the analysis.

Study population

All adult trauma patients admitted to the SICU during the study period were included in the analysis. Patients were excluded if they had any of the following: age below 16 years, pregnancy or patients within the immediate post-partum period, presence of malignancy and/or use of chemotherapeutic agents, long-term use of steroids or estrogen therapy, a history of recent VTE in the preceding year, a history suggestive of myelodysplastic or procoagulation syndromes, and the use of any confounding anticoagulation other than the drugs being investigated.

Chart review was performed to elicit the patient history and also determine the clinical course. Demographic data such as age, gender, injury mechanism, admission vital signs, and laboratory findings were collected. The primary outcome was the occurrence of VTEs while on anticoagulation. This was determined from positive findings on lower extremity Doppler ultrasound (DUS) for deep venous thrombosis (DVT) or computed tomography pulmonary angiography (CT-PA) or ventilation–perfusion (V/Q) scans for pulmonary emboli (PE). The incidence of VTE in either study group was documented.

The frequency of major bleeding episodes while on anticoagulants was also noted. Major bleeding was defined as the following: bleeding resulting in death or reoperation; any intracranial, perispinal, intraocular, or retroperitoneal bleeding; any overt bleeding resulting in acute hemodynamic instability (systolic blood pressure <90 mmHg or mean arterial pressure <60 mmHg requiring fluid boluses or vasopressors); a decrease in hemoglobin of at least 2 g/L, or requiring a transfusion of at least two units of packed red blood cells.

The incidence of heparin-induced thrombocytopenia (HIT) was also monitored in both populations. Patients developing thrombocytopenia with or without clinical evidence of thrombosis were screened using the HIT panel, and those with a positive HIT panel screen were subjected to confirmatory testing using the serotonin assay. Alternative anticoagulation using direct thrombin inhibitors was provided for all suspected cases until confirmation.

Setting

The LAC + USC Medical Center is an American College of Surgeons verified Level-1 Trauma Center, managing about 5,000 trauma admissions annually. Per-protocol, all patients admitted to the ICU following trauma receive prophylactic anticoagulation with LMWH throughout their ICU stay until they were ambulatory or no other indication for DVT prophylaxis is required. In addition, intermittent pneumatic compression devices are used in all trauma patients except when contraindicated by inaccessible lower limbs or extremities with vascular compromise. Prophylaxis was used with caution in patients with intracranial hemorrhage, and only when the bleeding was judged to be stable by the neurosurgical consultant.

The role of routine screening for asymptomatic DVT is somewhat controversial and practices vary widely among different centers. Although some studies suggest that routine duplex ultrasound in high-risk trauma patients might provide benefit from early detection, others have found that routine scanning is not cost-effective [11–13]. In fact, current guidelines do not support this practice [14] and the practice in our institution is not to screen routinely for lower extremity DVT on admission. Throughout the duration of this study, Enoxaparin was administered at a dose of 30 mg SC twice daily, while Dalteparin was given at a dost of 5,000 units SC once daily.

Cost analysis

The cost for each drug was estimated using the acquisition cost in the corresponding year. No additional consideration was made for renal or weight adjustments, cost of drug reconstitution by the in-house pharmacy, administration charges, or therapeutic interventions for VTE.

Statistical analysis

Using a minimum clinically important difference (MCID) of 5 %, the sample size was estimated to be 220 patients per arm (power = 80 %, alpha = 0.05). Univariate analysis was performed to compare the demographic and clinical characteristics between the two groups of patients. Selected continuous variables were dichotomized using clinically relevant cut-points: age ($\geq$55 vs. <55 years); systolic blood pressure on admission (<90 vs. $\geq$90 mmHg); Glasgow Coma Scale (GCS) score ($\leq$8 vs. >8). Normality testing was performed on continuous variables using the Shapiro–Wilk test. Comparisons of continuous variables were made using the Student *t*-test or Mann–Whitney *U*-test where applicable, while differences in proportions were made using Pearson's χ^2 test or the two-sided Fisher's exact test when appropriate.

Since both molecules are biologically active, we hypothesized that Enoxaparin was equivalent to Dalteparin as the primary prophylaxis for VTE. The MCID between Dalteparin and Enoxaparin was established at $\pm$5 %. We calculated the 95 % confidence interval (CI) for the difference in the VTE rate between the two treatments and determined whether it lies within the MCID in order to establish equivalence. All analyses were performed using SPSS 17 for Windows (Chicago, IL).

Results

A total of 647 trauma patients were admitted to the SICU during the study period. Thirty-seven of these patients were excluded from the analysis: nine were <16 years, one was pregnant at the time of admission, 11 had previously been diagnosed with malignancy, four had a previous VTE, and 12 patients received other anticoagulation during the study period. The remaining 610 patients were subsequently included in the analysis (Fig. 1).

During the study period, the population demographic was predominantly male (82 %, 503/610), having a mean age of 38 $\pm$ 18 years, with 64 % (393 patients) admitted following blunt trauma. 277 patients were included from the first period (year 2009 on Dalteparin) and 333 patients were included in the second period (year 2010 on Enoxaparin). There were no significant differences in the patient demographics, injury pattern, admission physiology, injury severity, or duration of hospitalization (Table 1).

Overall, 74 lower extremity DUS and 63 CT-PA investigations were conducted during the 2-year study period. No significant difference in the frequency of these investigations was noted in either study arm (Table 2). Six patients developed thrombocytopenia requiring discontinuation of LMWH and the administration of Argatroban (a direct thrombin inhibitor). These patients were subsequently screened for HIT using both the HIT antibody panel and the serotonin assay. Two of these patients who had been treated using Dalteparin tested positive. This finding did not reach statistical significance (Table 3).

Major bleeding was documented in two patients receiving Enoxaparin. One of the patients was an 18-year-old man who sustained a thoracoabdominal gunshot wound with injuries to the abdominal aorta, liver, right kidney, stomach, and mesentery. He required damage control

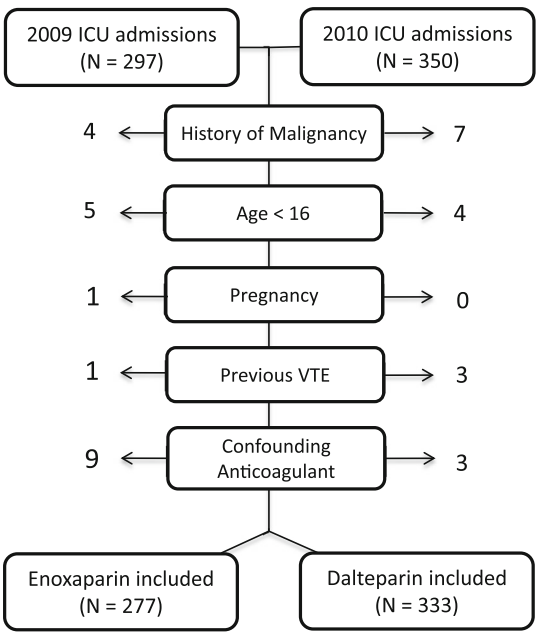

Fig. 1 CONSORT diagram describing subject allocation

Table 1 Demographic and clinical details for the trauma patients admitted to the surgical intensive care unit (SICU)

	Enoxaparin ($n = 277$)	Dalteparin ($n = 333$)	p-Value
Age (years), mean ± SD	38.6 ± 17.9	38.4 ± 18.3	0.934
Age ≥55 years	17.7 % (49/277)	16.5 % (55/333)	0.746
Gender (male)	83.0 % (230/277)	82.0 % (273/333)	0.750
Mechanism (blunt), %	66.8 % (185/277)	62.5 % (208/333)	0.271
Hypotension on admission	7.3 % (20/274)	8.8 % (29/328)	0.551
GCS ≤8	14.1 % (38/269)	13.1 % (43/327)	0.810
Hb on admission, mean ± SD	13.4 ± 1.9	13.5 ± 2.0	0.293
Admission lactate, mean ± SD	3.6 ± 2.7	3.6 ± 2.9	0.801
Admission base deficit, mean ± SD	6.0 ± 4.3	6.4 ± 4.6	0.279
APACHE II score, mean ± SD	16.6 ± 9.4	16.8 ± 9.5	0.757
Head AIS ≥3	20.6 % (57/277)	21.0 % (70/333)	0.920
Chest AIS ≥3	45.5 % (126/277)	42.3 % (141/333)	0.461
Abdomen AIS ≥3	22.0 % (61/277)	23.7 % (79/333)	0.630
Extremity AIS ≥3	35.4 % (98/277)	27.9 % (93/333)	0.054
Pelvic fracture	18.1 % (50/277)	17.4 % (58/333)	0.838
Long-bone fracture	33.9 % (94/277)	28.8 % (96/333)	0.175
Spinal cord injury	4.3 % (12/277)	4.8 % (16/333)	0.781
ISS, mean ± SD	16.6 ± 10.2	15.8 ± 9.7	0.335
ISS ≤15	52.9 % (146/276)	52.6 % (175/333)	0.935
ISS 16–25	28.3 % (78/276)	28.8 % (96/333)	0.928
ISS >25	18.8 % (52/276)	18.6 % (62/333)	1.000
Time to LMWH (h), mean ± SD, median (range)	69.1 ± 97.7, 33.0 (0–258)	65.3 ± 66.7, 49.0 (0–327)	0.573
Non-TBI LMWH (h), mean ± SD, median (range)	19.1 ± 6.2, 20.5 (0–58)	15.3 ± 3.5, 22.0 (1–59)	0.628
Ventilator days, mean ± SD	8.1 ± 8.3	8.8 ± 8.9	
ICU LOS, mean ± SD	10.3 ± 13.8	11.0 ± 11.6	0.489
Hospital LOS, mean ± SD	18.4 ± 21.3	20.0 ± 24.8	0.403

SD standard deviation, *GCS* Glasgow Coma Scale, *APACHE* Acute Physiology and Chronic Health Evaluation, *AIS* Abbreviated Injury Score, *ISS* Injury Severity Score, *LMWH* low-molecular-weight heparin, *TBI* traumatic brain injury, *LOS* length of stay

Table 2 Investigations performed

	All	Enoxaparin ($n = 277$)	Dalteparin ($n = 333$)	Difference (95 % CI)	p-Value
LE-DUS	17.5 % (107/610)	17.7 % (49/277)	17.4 % (58/333)	0.3 (−5.8, 6.4)	1.000
CT-PA	10.3 % (63/610)	9.0 % (25/277)	11.4 % (38/333)	−2.4 (−7.3, 2.5)	0.353

LE-DUS lower extremity Doppler ultrasound, *CT-PA* computed tomography pulmonary angiography

Table 3 Complications of anticoagulant use

	Enoxaparin ($n = 277$)	Dalteparin ($n = 333$)	Difference (95 % CI)	p-Value
Thrombocytopenia	0.7 % (2/277)	1.2 % (4/333)	−0.5 (−2.1, 1.1)	0.694
HIT	0	0.6 % (2/333)	−0.6 (−1.5, 0.3)	0.503
Major bleeding	0.7 % (2/277)	0	0.7 (−0.2,1.6)	0.206

HIT heparin-induced thrombocytopenia

surgery with multiple trips to the operating room. His prolonged ICU course was complicated by sepsis, acute kidney injury, and acute respiratory failure, and he expired 19 days after admission due to massive hemorrhage from aortic rupture. Of note, this patient did not receive LMWH until day 15 of his admission and his death was likely

Table 4 Venous thromboembolic events in the study period

	Enoxaparin	Dalteparin	Difference (95 % CI)	*p*-Value
Lower extremity DVT	3.2 % (9/277)	3.3 % (11/333)	1.2 (−2.1, 4.4)	1.000
Pulmonary embolus	1.8 % (5/277)	1.2 % (4/333)	0.6 (−1.3, 2.5)	0.738
Any VTE	5.1 % (14/277)	4.5 % (15/333)	0.5 (−2.9, 4.0)	0.849
Any VTE (TBI patients)	8.8 % (5/57)	5.7 % (4/70)	3.1 (−4.7, 10.9)	0.508
Any VTE (non-TBI patients)	4.1 % (9/220)	4.2 % (11/263)	−0.1 (−3.1, 2.9)	0.920

DVT deep venous thrombosis, *VTE* venous thromboembolism, *TBI* traumatic brain injury

unrelated to the initiation of VTE prophylaxis. The other patient with major bleeding was an 82-year-old woman who sustained a closed pelvic fracture following a motor vehicle collision. She had a small pelvic hematoma, which was initially concerning for extravasation, but was managed non-operatively with packed red blood cell transfusions. LMWH was started on hospital day 3 but held on hospital day 5 for a slight decrease in her hemoglobin level. She was subsequently transfused with two additional units of packed red blood cells. LMWH was commenced on hospital day 10 with no further complications.

There were 29 VTEs documented during the study period. Twenty of these were DVTs, while nine were PEs. There was no statistically significant difference in the incidence of DVT or PE between the two LMWH groups. The overall incidence of VTE while using Enoxaparin was 5.1 %, and it was 4.5 % when Dalteparin was instituted. The absolute difference in the incidence of VTE was 0.5 % (95 % CI: −2.9, 4.0 %). The 95 % CI for lower extremity DVT and for pulmonary embolus was also within the MCID required to establish equivalence (Table 4). The estimated total cost savings with the switch from Enoxaparin to Dalteparin, achieved with 277 patients was $107,778.

Discussion

The rate of symptomatic DVT or PE among trauma patients receiving prophylactic anticoagulation, especially those with orthopedic and acute spinal cord injury, has been found to range from 1.0 to 7.6 % [15–19]. Prolonged periods of immobilization, ongoing pro-inflammatory states, and the frequent occurrence of long-bone fractures place this patient population at extremely high risk for developing VTE. The use of pharmacologic prophylaxis for VTE is a level 1 recommendation in such high-risk patient populations [2–4, 20].

The most commonly used pharmacologic agents in these high-risk patients include unfractionated and LMWH. Heparin is a naturally occurring glycosaminoglycan, which exerts its effect by binding to antithrombin III and forming a ternary complex consisting of antithrombin (AT), heparin, and thrombin, which leads to the inactivation of thrombin and factor Xa. LMWHs, on the other hand, are synthetic derivatives of heparin that bind indirectly to AT and accelerate the inhibition of thrombin and activated factor X. Advantages of the use of LMWH include superior pharmacokinetic properties such as increased bioavailability, less frequent dosing, and decreased incidence of HIT compared to UFH [21–23]. Dalteparin and Enoxaparin both have different biochemical and pharmacologic profiles. The volume of distribution, half-life, and anti-Xa and anti-IIa activity of both molecules also vary significantly [24]. Despite the lower efficacy of LMWH in inactivating factor II, Dalteparin has demonstrated higher anti-II activity, and might have a theoretical advantage in the prophylaxis of VTE. Conversely, Enoxaparin has a better anti-Xa profile, which may negate some of the benefit conferred by the anti-IIa activity of Dalteparin.

Among trauma patients with severe orthopedic, spinal fractures and spinal cord injury, LMWH has been found to reduce the risk of symptomatic VTE by up to 43 % [6]. Despite the evidence supporting the use of LMWH in high-risk populations however, there is little data to support the use of one type of LMWH over another. Previous studies found Dalteparin to be safe but failed to demonstrate a significant difference in the VTE rate or complications compared to Enoxaparin in patients with TBI [10] or spinal cord injury [21]. Slavik et al. [9] studied both drugs in major orthopedic and acute spinal cord injury patients, but their study was underpowered and the results remain inconclusive.

Our results show that there is no statistically significant difference in the incidence of DVT or PE in patients receiving prophylactic doses of either Enoxaparin or Dalteparin, which is similar to the results of prior studies [9, 10, 21]. Few studies [6, 25] have examined the incidence of hemorrhagic complications associated with pharmacologic VTE prophylaxis and found this to be relatively low (<2 %). Our study demonstrated a very low bleeding rate (0.7 vs. 0 % in the Enoxaparin and Dalteparin groups, respectively), which is consistent with the published literature. HIT has a much lower incidence in patients receiving LMWH prophylaxis [22, 23] when compared to UFH, but

there are no specific studies documenting the incidence in an LMWH cohort. In our population, the incidence of thrombocytopenia and HIT was slightly higher but not statistically significant in the Dalteparin group (1.2 vs. 0.7 % and 0.6 vs. 0 %, respectively). However, this study was not powered to detect these differences and the clinical relevance is uncertain. The estimated cost savings reported over the study period would be reproducible at any North American institution, since the doses used at our institution are the recommended regimes for either drug as approved by the Food and Drug Administration (FDA).

The major limitation of our study is its retrospective design. Despite the relatively large sample size, it was based on a consecutive sample of only 12 months of data for each pharmacologic agent. A larger sample size could increase the power and precision of this study. Nevertheless, our study is one of the largest to date comparing the safety and efficacy of two different LMWH regimens in trauma patients. Within the confines of an equivalency design, this study was adequately powered to conclude that Dalteparin and Enoxaparin are equivalent for VTE prophylaxis after trauma. Our results show that the use of either pharmacologic agent in the trauma population is safe, without an increased risk of side effects. Further research should include a controlled clinical trial with the random allocation of pharmacologic agents to limit bias and more accurately determine the causality of adverse events. Future studies might also compare different doses of Enoxaparin and Dalteparin and examine the effects of various combinations of pharmacologic and mechanical prophylaxis in this particular patient population.

Conflict of interest We confirm that the manuscript has been read and approved by all the named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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