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Dose Adjusting Enoxaparin is Necessary to Achieve Adequate Venous Thromboembolism Prophylaxis in Trauma Patients

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Abstract

Background—Standard venous thromboembolism (VTE) prophylaxis with enoxaparin results in inadequate protection in certain patients, with sub-therapeutic plasma anti-Xa levels associated with elevated VTE rates. We hypothesized that many trauma patients would be sub-therapeutic on the standard prophylactic dose of enoxaparin. Our goal was to adjust the enoxaparin dose to achieve target anti-Xa levels to take advantage of the drug based on its pharmacologic properties.

Methods—Patients admitted to the trauma service were included if they received at least 3 doses of prophylactic enoxaparin and underwent at least 2 screening venous duplex. Peak plasma anti-Xa levels 0.2 IU/ml were considered low and the dose was increased by 10mg bid until adequate anti-Xa levels were obtained. A strict screening venous duplex protocol was followed. Patients were excluded if they were diagnosed with a DVT prior to beginning enoxaparin or did not have correctly timed anti-Xa levels.

Results—Sixty-one trauma patients met inclusion criteria. There were 3 patients diagnosed with VTE (4.9%). Patients had a mean age of 45.9 years and were predominantly male (70.5%). Of the 61 patients, 18 (29.5%) had therapeutic anti-Xa levels on standard enoxaparin 30mg bid. Compared to patients who had therapeutic anti-Xa levels on enoxaparin 30mg bid, the 43 patients

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(70.5%) who were sub-therapeutic were more likely to be male, have larger body weight, and larger body surface area. There were no significant bleeding events in the group that received an enoxaparin dose adjustment.

Conclusions—A majority of patients had sub-therapeutic anti-Xa levels while on enoxaparin 30mg bid suggesting inadequate VTE prophylaxis. The need for routine use of a higher dose of prophylactic enoxaparin in trauma patients and the effects of routinely dose adjusting enoxaparin on VTE rates should be the study of future prospective, randomized trials.

Background

Venous thromboembolic disease (VTE) continues to be a frequent complication during admission due to traumatic injury despite increased awareness, screening, and prophylaxis. Deep venous thrombosis (DVT) affects between 3 to 44% of patients admitted to the trauma service in modern series, with diagnosed DVT rates altered by the screening strategy employed(1-6). Several characteristics have been identified which place trauma patients at even greater risk based on both patient characteristics and injury pattern(7, 8). In the absence of DVT prophylaxis, the incidence of DVT approaches 60%, further highlighting the importance of aggressive VTE prophylaxis in trauma patients(9).

Initial strategies to prevent DVT in trauma patients focused on mechanical prophylaxis with intermittent compression devices and pharmacologic prophylaxis with low dose unfractionated heparin(4, 5). A study by Geerts et al. found that Low Molecular Weight Heparin (LMWH) was superior to low dose unfractionated heparin in preventing VTE in patients following major trauma, thus defining the modern strategy for pharmacologic DVT prophylaxis(2). Current recommendations from the American College of Chest Physicians include the use of LMWH for DVT prophylaxis in trauma patients unless contraindicated due to high risk of bleeding(10).

Enoxaparin is the LMWH that is routinely chosen for pharmacologic DVT prophylaxis, with the standard dose of 30mg twice daily (bid) used in most trauma patients. Enoxaparin exerts its major anticoagulant effect through its interaction with antithrombin III which inactivates downstream coagulation factors. Enoxaparin inactivates plasma factor Xa to a greater degree than unfractionated heparin. While standard coagulation studies such as the prothrombin time (PT) or partial thromboplastin time (PTT) are not altered by enoxaparin, plasma anti-Factor Xa (anti-Xa) levels can be used to monitor its efficacy(11). Enoxaparin is attractive due to its twice daily dosing and its predictable bioavailability eliminates the need to routinely measure its efficacy. While the 30mg bid dose of enoxaparin is recognized as the standard prophylactic dose for most patients, there is a sub-group of patients that require measurement of plasma anti-Xa levels due to unpredictable bioavailability, including those with renal insufficiency and the morbidly obese(12, 13).

Recent research has challenged the notion that standard dose of enoxaparin results in adequate prophylaxis in trauma patients based on anti-Xa levels. Two retrospective studies have now shown that sub-therapeutic plasma anti-Xa levels are associated with increased incidence of DVT in surgical patients(14, 15). We hypothesized that many trauma patients would be sub-therapeutic on the standard 30mg bid dose of enoxaparin. Further, we adjusted

the enoxaparin dose to achieve 'optimal' anti-Xa levels with the goal of taking advantage of the full effect of the drug based on its pharmacologic properties.

Methods

Patient Selection

Patients admitted between December 2010 and January 2012 at our level I academic trauma center, were prospectively enrolled to undergo measurement of plasma anti-Xa levels and enoxaparin dose adjustment to target therapeutic peak anti-Xa levels. All trauma patients were treated with a standard VTE prevention protocol which included pharmacologic prophylaxis with enoxaparin (Sanofi-aventis, Bridgewater, NJ) 30 mg bid unless contraindicated. Sequential compression devices were applied unless injuries precluded their use. Based on our standard screening protocol, lower extremity venous duplex was performed within 48 hours of admission and a second duplex was performed during the first week of admission, then weekly thereafter. Upper extremity venous duplex exams were ordered to diagnose upper extremity DVT and computed tomography angiogram of the chest was ordered to diagnose pulmonary embolism (PE) if indicated based on clinical suspicion for either DVT or PE.

Enoxaparin Dose Adjustments

Enoxaparin activity was monitored using steady state plasma anti-Xa levels. Peak anti-Xa levels were drawn 4 hours after the third dose of enoxaparin was administered. Trough levels were drawn 1 hour before the fourth dose was administered. All anti-Xa assays were run on ACL TOP™ machines (Beckman Coulter, Brea, CA) using the HemosIL™ heparin anti-Xa chromogenic assay. As the assay was only available Monday to Friday between 8 am to 4 pm, anti-Xa levels due during the night or on weekends were postponed until the assay was available. Peak anti-Xa levels were considered adequate for thromboprophylaxis if they were between 0.2-0.4 IU/ml (16, 17). If peak anti-Xa levels were below this range, the treatment team was notified and the risks versus benefits of enoxaparin dosing changes were discussed. Generally, patients received an enoxaparin dose increase of 10 mg twice daily; however, depending on clinician judgment, no dose adjustment or larger dose adjustments were occasionally applied. If patients required an enoxaparin dose increase, further anti-Xa levels were drawn and further dose adjustments were recommended based on subsequent anti-Xa levels.

Patients were included in the analysis if they had at least one set of properly timed anti-Xa peak and trough levels. Patients were also required to have a baseline venous duplex screening exam within 48 hours of admission and at least one follow-up venous duplex exam after the initiation of enoxaparin prophylaxis. Exclusion criteria included minors, pregnant women, and patients with renal dysfunction (Creatinine clearance < 30ml/min) or on renal replacement therapy. Patients were also excluded if there was a contraindication to pharmacologic DVT prophylaxis, they were diagnosed with a DVT prior to beginning enoxaparin, or they required therapeutic anti-coagulation for any reason. Patients missing screening venous duplex exams or those with improperly timed anti-Xa levels were also excluded.

Patient Data Collection

We analyzed demographic data including age, gender, height, weight, body mass index (BMI), body surface area (BSA) and serum creatinine. To evaluate severity of injury, injury severity score, injury mechanism, specific injuries, ventilator days, hospital and ICU length of stay were also collected. Anti-Xa peak and trough levels, administered enoxaparin doses, and outcomes of screening venous duplex studies were also collected. The primary objective of this study was to determine the rate of patients with therapeutic plasma anti-Xa levels on the standard dose of enoxaparin 30mg bid. Secondly, we measured the occurrence of and VTE including upper extremity DVT, lower extremity DVT, and pulmonary embolism in addition to the number of patients requiring dose adjustment of enoxaparin and the degree of dose adjustment required to reach adequate anti-Xa levels. This study was approved by the Institutional Review Board at the University of California, San Diego.

Statistical Analysis

Data are presented as the mean $\pm$ standard deviation (SD) or the raw percentage score. Statistical analysis was performed using Students t-test for continuous data and Chi square test for categorical data. A p value < 0.05 was considered statistically significant.

Results

Study Patient Characteristics

There were 164 patients screened with a plasma anti-Xa level during the course of the study. Of those, 103 patients were excluded due to either improperly timed anti-Xa levels, they did not undergo at least 2 screening lower extremity duplex, or they required therapeutic anticoagulation (Figure 1). There were 61 patients included in the study with a mean age of 45.9 years (Table 1). Patients were predominantly male (70.5%) and admitted after blunt injury (88.5%). The average ISS was 24.0 ± 10.9 with an average ICU LOS of 9.2 ± 10.2 and hospital LOS of 21.9 ± 17.2 . Three patients (4.9%) had VTE, including 2 DVT (3.3%) and 1 pulmonary embolism (1.6%). There were no deaths in the 61 patients included in the study.

Patients Sub-therapeutic on Standard Prophylactic Dose Enoxaparin

Of the 61 patients enrolled in this study, there were 18 (29.5%) patients with therapeutic peak plasma anti-Xa levels on the standard 30mg bid dose of prophylactic enoxaparin. There were 43 (70.5%) patients who had sub-therapeutic peak anti-Xa levels (< 0.2 IU/ml). Patients who were therapeutic on standard prophylactic dose enoxaparin are compared to those who were sub-therapeutic (Table 2). There was no difference based on injury severity or the location of injury. Patients who were sub-therapeutic on the standard dose of prophylactic enoxaparin were more likely to be male. Patients with sub-therapeutic peak anti-Xa levels were also more likely to have larger body mass, with significantly higher weight and body surface area compared to those with therapeutic peak anti-Xa levels. There was also a trend toward higher BMI in patients who were sub-therapeutic, however, this did not reach statistical significance ($p=0.0558$). Trough plasma anti-Xa levels did not correlate well with peak anti-Xa levels. There were only 5 patients who had both therapeutic peak and

trough anti-Xa levels, while there were no patients in the sub-therapeutic peak anti-Xa group who had therapeutic trough anti-Xa levels.

Patients Diagnosed with VTE

The overall VTE rate in this study was 4.9%. The patients diagnosed with VTE in this study are described in Table 3. There were 2 patients with therapeutic peak anti-Xa levels who developed a DVT. Each patient underwent an upper extremity duplex based on clinical suspicion due to arm swelling and was diagnosed with an upper extremity DVT. The DVT in each of these individuals was a non-occlusive thrombus associated with a central venous catheter. There was 1 pulmonary embolism in the group of patients who initially had a sub-therapeutic peak anti-Xa level. This patient underwent a CT angiogram of the chest based on the presence of tachycardia associated with decreased oxygen saturations. While the patient's initial peak anti-Xa level was sub-therapeutic, he was diagnosed with pulmonary embolism on the same day his initial peak anti-Xa level was drawn, and therefore did not undergo an enoxaparin dose adjustment.

Patients Treated with Enoxaparin Dose Adjustment

Of the 45 patients who initially had a sub-therapeutic peak anti-Xa level, there were 27 patients who remained in the hospital and received an enoxaparin dose adjustment. The remaining 16 patients were discharged before an enoxaparin dose increase was performed. The patients that received an enoxaparin dose adjustment are described in Table 4. There were 22 patients treated with a final prophylactic enoxaparin dose of 40mg bid, 4 patients treated with 50mg bid, and 1 patients treated with 60mg bid. There were no episodes of VTE in the 27 patients that received an enoxaparin dose adjustment. No clinically significant bleeding complications occurred in the cohort of patients that were treated with increased doses of enoxaparin.

Discussion

VTE is a source of significant morbidity and mortality in patients admitted following trauma. Recent studies in surgical intensive care unit (ICU) patients and burn patients have questioned whether the currently recommend standard prophylactic dose of enoxaparin (30mg bid) provides adequate VTE prophylaxis in injured patients(14, 15, 18). The goal of this study was to prospectively determine whether trauma patients were receiving adequate VTE prophylaxis with enoxaparin 30mg bid based on plasma anti-Xa levels. We employed a strategy to intervene in patients with sub-therapeutic VTE prophylaxis by increasing the enoxaparin dose with the goal of achieving the appropriate target prophylactic plasma anti-Xa levels.

We found that 70.5% of patients enrolled did not achieve the target prophylactic peak plasma anti-Xa levels on enoxaparin 30mg bid, suggesting that the current prophylactic dosing regimen is inadequate for trauma patients. We found that males were more likely than females to have sub-therapeutic anti-Xa levels. We also found that patients with increased body mass were more likely have sub-therapeutic anti-Xa levels. Body weight and body surface area were significantly increased in the sub-therapeutic group with a similar

trend for body mass index (BMI). There was no difference in achieving target anti-Xa levels based on age, injury severity, injury pattern, or hospital length of stay.

Morbid obesity has previously been recognized as an indication to monitor plasma anti-Xa levels as those patients may not achieve adequate prophylaxis on standard doses(17). A recent study by Ludwig et al., utilized a weight based dosing protocol of enoxaparin in morbidly obese surgical ICU patients to successfully achieve adequate anti-Xa levels with no significant bleeding complications(19). The majority of the patients that were sub-therapeutic on standard dose enoxaparin in this study were not morbidly obese, with a mean BMI of 28.7. This suggests that considering enoxaparin dose adjustment only for the morbidly obese may be inadequate. This was supported in a study of anti-Xa levels in acutely burned patients where body weight correlated with final enoxaparin dose(20).

Major injury is known to induce a hypercoagulable state which is characterized by alterations in thrombin generation and its regulation(21). Due to this pro-thrombotic state, VTE prophylaxis is recognized as an important component in the care of the injured patient to limit DVT and pulmonary embolism and their acute and long-term sequelae(22, 23). Current consensus recommendations state that trauma patients should be treated with low molecular weight heparin if no contraindication exists(8, 10, 24). In addition to pharmacologic prophylaxis against VTE, screening strategies are important to diagnose occult DVT and limit the risk of pulmonary embolism. Despite the recognized importance of screening for DVT in asymptomatic trauma patients, duplex screening protocols vary widely across trauma centers in the United States, with more aggressive screening protocols associated with higher DVT rates(1, 25).

A study by Malinoski et al. evaluated plasma anti-Xa levels on 54 surgical and trauma patients in the surgical ICU. They found that 50% of patients were sub-therapeutic based on a trough anti-Xa level < 0.1 IU/ml. In that study the authors measured trough levels after the 3rd dose of enoxaparin and utilized a similar DVT screening protocol as used in our study. They found that patients with sub-therapeutic trough levels were more likely to develop a DVT compared to those who were therapeutic (37% vs. 11%). They also found that patients with trough levels in the therapeutic range also had mean peak anti-Xa levels in the therapeutic range. The optimal method of measuring the efficacy of enoxaparin treatment is a subject of some debate with many experts recommending titrating enoxaparin dosing based on peak anti-Xa levels(17, 26). While we stratified patients in this study based on peak anti-Xa levels, we measured trough anti-Xa levels as well. We found a poor correlation between peak and trough levels, however, found only 5 patients with therapeutic trough anti-Xa levels.

Van et al. compared thromboelastography (TEG) and anti-Xa levels in a mixed population of general surgery and trauma patients admitted to the surgical ICU in an attempt to predict which patients treated with enoxaparin would develop DVT(15). They found that the TEG "R time", a measure of the time to initial clot formation, was shorter in patients with DVT compared to those without DVT. They found no difference in anti-Xa levels between those with DVT and without DVT, however the timing of anti-Xa measurement in that study and whether the sample was a true peak or trough level is unclear. In addition, the enoxaparin

dose differed among patients and the timing of the lower extremity venous duplex studies were not specified making the diagnosis of DVT in each group difficult to interpret.

We evaluated the occurrence of DVT between those patients who had initial plasma anti-Xa levels in the appropriate prophylactic range with those patients that were sub-therapeutic; however, this study was neither designed nor powered to compare DVT rates between groups. In addition, all patients in this study were undergoing measurement of anti-Xa levels to assess the efficacy of VTE prophylaxis, with enoxaparin dose adjustments as indicated for those falling below the goal prophylactic anti-Xa level. As such, there was no control group in this study that was truly undergoing the standard of care which is enoxaparin 30mg bid with no measurement of anti-Xa levels. We identified 3 patients with VTE in this study, including 2 DVT and 1 PE. Both patients with DVT had therapeutic anti-Xa levels and developed upper extremity non-occlusive thrombus that was associated with a central venous catheter, which appear to have a different natural history compared to lower extremity DVT(27). Interestingly, there was no lower extremity DVT diagnosed in our study population despite aggressive lower extremity duplex screening.

Currently we recommend screening anti-Xa levels for all trauma patients as the risk factors for having low anti-Xa levels have not been conclusively defined. The final necessary dose for patients is unknown and likely varies from individual to individual, therefore, the need to check anti-Xa levels which is the current standard method of measuring the effect of enoxaparin. Utilizing other methods to measure the effects of enoxaparin are currently being investigated (e.g. ROTEM), however, further studies are needed to determine the sensitivity and specificity of these methods and their ability to reliably measure the anticoagulant effects of enoxaparin. Based on data presented in this study, patients who are obese males should certainly be screened or even started on a higher dose of enoxaparin. Larger, randomized studies are needed to identify other populations who may also warrant closer screening with anti-Xa levels. Future studies will also be needed to determine whether dose-adjusting enoxaparin with the goal of limiting VTE is cost effective.

Limitations of our findings include the small sample size and the number of patients that were excluded due to improperly timed plasma anti-Xa levels as the test was only available on weekdays. Patients were also discharged from the hospital while undergoing titration of their enoxaparin dose; therefore, there were several patients who had sub-therapeutic anti-Xa levels initially who were discharged prior to dose adjustment and repeat anti-Xa level measurement. In addition, some patients had their dose of enoxaparin increased but were discharged prior to achieving a therapeutic peak anti-Xa level, making it difficult to determine their appropriate final enoxaparin dose. The data presented here demonstrates that most trauma patients did not reach target anti-Xa levels when receiving a dose of 30mg bid, however, the optimal dose for most patients is unclear. Finally, we are unable to compare the effects of enoxaparin dose adjustments on VTE rates as there was no control group receiving enoxaparin 30mg bid with no measurement of anti-Xa levels and no dose adjustments.

The risk of bleeding in patients with elevated anti-Xa levels is controversial. In a study of obese surgical ICU patients who were treated with weight based enoxaparin dosing and dose

adjustments to target a peak anti-Xa level 0.2-0.5 IU/ml there was minimal bleeding risk with no major bleeding events and only 1 minor bleeding event(19). Conversely, a study of patients undergoing total hip replacement found a significant increase in wound hematoma formation in patients with peak anti-Xa levels > 0.2 IU/ml(28). Importantly, in this study we found no documented episodes of clinically significant bleeding that were related to the increased enoxaparin dosing that was required to achieve the target peak anti-Xa level. A study of enoxaparin dose adjustments in burn patients also found no episodes of bleeding complications despite a median dose of 40mg every 12 hours(20).

Our data suggests that a majority of trauma patients are receiving inadequate DVT prophylaxis based on sub-therapeutic anti-Xa levels despite following the guidelines currently recommended by organizations such as the American College of Chest Physicians and the Eastern Association for the Surgery of Trauma(10, 24). Taken together with recent retrospective data demonstrating that having sub-therapeutic anti-Xa levels are associated with increased DVT rates, we consider the current recommended prophylactic dose of enoxaparin (30mg bid) to be inadequate. Whether all trauma patients, or a certain subpopulation of trauma patients, should receive a higher dose of prophylactic enoxaparin and the ability of routinely dose adjusting enoxaparin in decreasing VTE rates should be the study of future prospective, randomized trials.

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Figure 1.

Diagram of patients enrolled in study.

Table 1
Demographics of patients enrolled in study

	All Patients (n=61)
Age (yr)	45.9 ± 20.6
Gender (Male)	43 (70.5%)
Weight (kg)	82.7 ± 24.4
BMI (kg/m ²)	27.6 ± 6.9
BSA (m ²)	1.95 ± 0.38
Serum Creatinine	0.74 ± 0.30
Injury	
Blunt	54 (88.5%)
Intracranial Hemorrhage	26 (42.6%)
Spinal Fracture	28 (45.9%)
Spinal Cord Injury	2 (3.3%)
Pelvic Fracture	9 (14.8%)
Any Extremity Fracture	13 (21.3%)
Upper Extremity Fracture	4 (6.6%)
Lower Extremity Fracture	12 (19.7%)
Injury Severity Score	24.0 ± 10.9
Hospital Days	21.9 ± 17.2
ICU Days	9.2 ± 10.2
Ventilator Days	5.9 ± 8.7
Any VTE	3 (4.9%)
Pulmonary Embolism	1 (1.6%)
DVT	2 (3.3%)

Table 2
Comparison of patients therapeutic on 30mg bid of enoxaparin with those non-therapeutic

	Therapeutic (n=18)	Sub-Therapeutic (n=43)	P value
Age (yr)	52.1 ± 22.5	43.3 ± 19.4	0.1287
Gender (Male)	7 (38.9%)	36 (83.7%)	0.0013 *
Injury			
Blunt	18 (100%)	36 (83.7%)	0.0935
Intracranial Hemorrhage	9 (50.0%)	17 (39.5%)	0.5723
Spinal Fracture	11 (61.1%)	17 (39.5%)	0.1624
Spinal Cord Injury	2 (11.1%)	0	0.0836
Pelvic Fracture	2 (11.1%)	7 (16.3%)	0.7131
Any Extremity Fracture	3 (16.7%)	10 (23.3%)	0.7372
Upper Extremity Fracture	1 (5.6%)	3 (7.0%)	1.000
Lower Extremity Fracture	3 (16.7%)	9 (20.9%)	1.000
Weight (kg)	70.5 ± 15.7	87.5 ± 25.7	0.0117 *
Body Mass Index (kg/m ²)	25.0 ± 5.5	28.7 ± 7.2	0.0558
Body Surface Area (m ²)	1.80 ± 0.23	2.05 ± 0.32	0.0040 *
Serum Creatinine	0.74 ± 0.30	0.74 ± 0.30	1.000
Mean Initial Peak anti-Xa	0.27 ± 0.09	0.10 ± 0.05	<0.0001 *
Mean Initial Trough anti-Xa	0.07 ± 0.06	0.02 ± 0.03	0.0001 *
Trough anti-Xa > 0.1 IU/ml	5 (27.8%)	0	0.0014 *
Injury Severity Score	27.6 ± 11.0	22.4 ± 10.6	0.0891
Hospital Days	22.3 ± 10.4	21.6 ± 19.5	0.8864
ICU Days	11.2 ± 9.2	8.4 ± 10.6	0.3329
Ventilator Days	6.4 ± 7.2	5.6 ± 9.4	0.7478
Mortality	0	0	
Any VTE	2 (11.1%)	1 (2.3%)	0.2055
Pulmonary Embolism	0	1 (2.3%)	1.000
DVT	2 (11.1%)	0	0.0836

*
p<0.05

Table 3
Episodes of VTE in study population

Patient	Height/Weight	Enoxaparin dose & Anti-Xa level	Type of VTE	Notes
70 y/o male	Wt: 88.3 kg Ht: 162 cm BMI: 33.6 kg/m ²	30 mg bid Peak: 0.05	Pulmonary embolism	PE diagnosed prior to dose adjustment
21 y/o male	Wt: 89 kg Ht: 183 cm BMI: 26.5 kg/m ²	30 mg bid Peak: 0.24	Non-occlusive upper extremity clot	Associated with central line
23 y/o male	Wt: 68.8 kg Ht: 170 cm BMI: 23.8 kg/m ²	30 mg bid Peak: 0.25	Non-occlusive upper extremity clot	Associated with central line

Table 4
Patients receiving enoxaparin dose adjustment

	Patients (n=27)
Age (yr)	40.5 ± 18.2
Gender (Male)	24 (88.9%)
Weight (kg)	92.1 ± 30.7
BMI (kg/m ²)	29.0 ± 7.9
BSA (m ²)	1.95 ± 0.38
Serum Creatinine	0.80 ± 0.33
Maximum Lovenox Dose	
40mg bid	22 (81.5%)
50mg bid	4 (14.8%)
60mg bid	1 (3.7%)
Injury	
Blunt	23 (85.2%)
Traumatic Brain Injury	11 (40.7%)
Spinal Fracture	11 (40.7%)
Spinal Cord Injury	0
Pelvic Fracture	6 (22.2%)
Any Extremity Fracture	8 (29.6%)
Upper Extremity Fracture	2 (7.4%)
Lower Extremity Fracture	7 (25.9%)
Injury Severity Score	22.9 ± 10.2
Hospital Days	26.1 ± 22.2
ICU Days	8.8 ± 9.6
Ventilator Days	5.5 ± 8.8
Any VTE	0
Pulmonary Embolism	0
DVT	0
Significant Bleeding Events	0