Determination of Optimal Weight-Based Enoxaparin Dosing and Associated Clinical Factors for Achieving Therapeutic Anti-Xa Assays for Deep Venous Thrombosis Prophylaxis

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BACKGROUND: Previous studies have evaluated dose-to-weight ratios to define best practices for obtaining therapeutic anti-Xa assays for enoxaparin venous thromboembolism (VTE) prophylaxis. These studies have not examined relationships among dosing, patient characteristics, and therapeutic assays. This study examines factors associated with therapeutic assays and enoxaparin prophylaxis.

STUDY DESIGN: This is a retrospective review of patients admitted to a Level 1 trauma center between March 2016 and June 2018. Prophylaxis was managed according to the trauma service's enoxaparin VTE prophylaxis protocol, which targets anti-Xa concentrations of 0.2 to 0.5 IU/mL. Assays were divided into sub-therapeutic, therapeutic, and super-therapeutic groups to determine factors associated with therapeutic concentrations.

RESULTS: Overall, 623 patients (634 total anti-Xa assays) were identified during the study period. Patients with sub-therapeutic (n = 35) and therapeutic (n = 536) assays did not differ. Significant differences were identified between patients with therapeutic and super-therapeutic assays (n = 63). Receiver operating characteristic curve analysis was used to determine that the optimal cutoff for the dose-to-weight ratio was 0.4 mg/kg/dose (area under the curve 0.78; 95% CI 0.73 to 0.84; $p < 0.001$) differentiating therapeutic and super-therapeutic assays. Logistic regression revealed male sex, doses of 0.31 to 0.4 mg/kg, and creatinine clearance > 90 mL/min were independently associated with therapeutic assays. The combined effect of these 3 variables showed that therapeutic assays were 13.76 times more likely to occur (OR 13.76; 95% CI 3.43 to 56.96; $p < 0.001$).

CONCLUSIONS: These data demonstrate that a dose of 0.4 mg/kg predicts a therapeutic anti-Xa level. When regimens of 0.31 to 0.4 mg/kg/dose are administered in males with a creatinine clearance >90 mL/min therapeutic results are 13.76 times more likely, suggesting that monitoring with anti-Xa assays might be unnecessary in this subgroup. Additional prospective study of these findings is warranted. (J Am Coll Surg 2019;229:295−304. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Patients admitted with traumatic injuries are known to be an especially high-risk population for the development of deep venous thrombosis (DVT) and venous thromboembolic events.[1-3] Despite the recognition of the importance of prophylaxis of venous thromboembolism (VTE) in trauma patients, published data from our

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Abbreviations and Acronyms
AUC = area under the curve
CrCl = creatinine clearance
DVT = deep venous thrombosis
ROC = receiver operating characteristic curve analysis
SQ = subcutaneous
VTE = venous thromboembolic event

institution and others suggest that current recommended dosing regimens of enoxaparin can fail to provide adequate protection for this very high-risk patient group, even when starting doses at the high end of the spectrum (40 mg twice daily) are used initially.[4-7] Consequently, protocols have been developed using anti-Xa levels to guide enoxaparin dosing into the therapeutic range. Typically, these protocols start with a standard weight-modified dose and then measure steady-state anti-Xa levels after 3 doses, at which time the dose is titrated up or down, depending on the results.[5] With such a strategy, the clinician might be unaware that the patient is sub-therapeutic and therefore at risk for VTE, or super-therapeutic and at elevated risk of bleeding complications, for a minimum of 36 to 48 hours after institution of prophylaxis. In addition, the time to documentation of a therapeutic anti-Xa level is extended by 36 to 48 hours after each titration up or down.

Although this approach has been demonstrated to reduce the incidence of VTE, the optimal strategy for enoxaparin administration and attaining consistently therapeutic anti-Xa levels remains elusive.[4-6] In addition, the patient factors and clinical scenarios predictive of therapeutic anti-Xa levels have yet to be identified.[7] Identification of the most appropriate initial dosing strategy and recognition of clinical variables that can predict the likelihood of achieving a therapeutic anti-Xa level would be a welcome addition to the trauma literature. Such findings would aid clinicians in developing dosing strategies for enoxaparin that would maximize the likelihood of therapeutic benefit in reducing VTE, and minimize the likelihood of bleeding complications.

As described, previous literature has demonstrated improved efficacy of VTE prophylaxis with low-molecular-weight heparin regimens that achieve anti-Xa assays of 0.2 to 0.5 IU.mL.[4-6] Accordingly, in the current study, we attempt to define the optimum and specific weight-based dosing regimen for enoxaparin in trauma patients guided by anti-Xa assays. In addition, we examine patient factors and clinical circumstances associated with achieving therapeutic anti-Xa levels. Consequently, we aim to identify strategies through which the efficacy of VTE prophylaxis with enoxaparin can be enhanced, while preventing potential untoward effects associated with sub- or super-therapeutic anti-Xa assays.

METHODS

This was a retrospective cohort study conducted on patients admitted to the Level 1 trauma center at Charleston Area Medical Center between March 2016 and June 2018. Patients included in this study followed the trauma service's enoxaparin VTE prophylaxis protocol. The enoxaparin protocol was instituted in October 2015 as a quality improvement project focused on improving trauma patient outcomes through pharmacologic prevention of VTEs.

The protocol was carried out as follows: Patients without contraindications received an initial dose of enoxaparin based on their weight. Enoxaparin 30 mg administered subcutaneously (SQ) every 12 hours was ordered if the patient's weight was <100 kg, and 40 mg SQ every 12 hours when weight was ≥100 kg. Dose administrations were scheduled for noon and midnight. Anti-Xa levels were checked at 4 AM after the midnight administration of the third dose. If a sub-therapeutic anti-Xa level was reported (<0.2 IU/mL), each scheduled dose of enoxaparin was increased by 20%. If a super-therapeutic anti-Xa level was reported (>0.5 IU/mL), the scheduled dose of enoxaparin was decreased by 20%. Adjusted doses were rounded to the nearest 0 mg. After each dosing adjustment, anti-Xa levels were obtained following the same process and the dose was then adjusted again if needed. This process was repeated until a therapeutic anti-Xa level for prophylaxis (0.2 to 0.5 IU/mL) was achieved. For a patient whose initial 30 mg SQ every 12 hours or 40 mg SQ every 12 hours regimen resulted in a super-therapeutic anti-Xa level, the dosing frequency was reduced to once daily and no additional anti-Xa levels were obtained.

Enoxaparin VTE prophylaxis protocol was contraindicated and therefore not performed in patients with renal insufficiency (creatinine clearance [CrCL] <30 mL/min), thrombocytopenia <50,000/μL, or the presence of injuries or clinical conditions outlined in the service's VTE Prophylaxis Algorithm (Fig. 1). Anti-Xa levels for monitoring enoxaparin were designated as "Lovenox Heparin Assays" by laboratory services at the study institution and are accordingly referenced in the protocol presented in Figure 2.

After approval by the Charleston Area Medical Center/West Virginia University Charleston IRB this retrospective study was performed using the trauma registry database supplemented by chart review using the electronic medical record at the study institution. Patients were divided into 3 groups

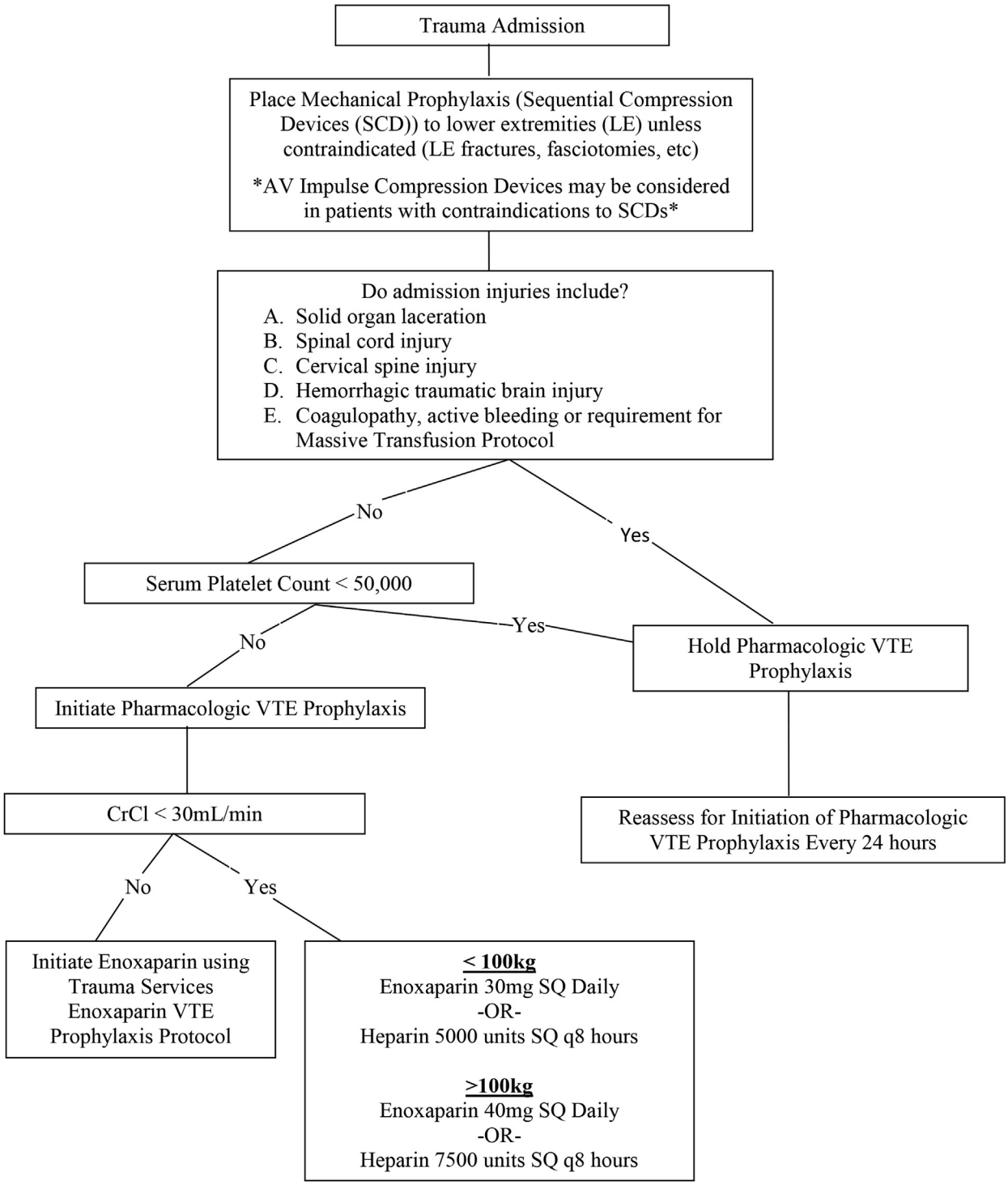

Figure 1. Trauma services venous thromboembolism (VTE) prophylaxis algorithm. CrCl, creatinine clearance; SQ, subcutaneous.

based on their initial anti-Xa level for prophylaxis: therapeutic (anti-Xa level between 0.2 and 0.5 IU/mL); super-therapeutic (anti-Xa level >0.5 IU/mL); and sub-therapeutic (anti-Xa level <0.2 IU/mL). Variables that were prospectively collected by the trauma registrars included age, sex, pre-existing conditions, presenting injuries, incidence of ICU admission, ICU and hospital length of stay, Injury Severity Score, and blood products administered at the hospital.

1. Enoxaparin-Initial dosing scheduled at 12:00 and 00:00
   - <100 kg → 30mg SQ BID or >100 kg → 40mg SQ BID
2. Check an anti-Xa level (Lovenox Heparin Assay) after 3rd or 4th dose (with a.m. labs)
   - If sub-therapeutic (<0.2 IU/mL) → Increase each dose by 20% (each dose rounded to the nearest zero)
   - If super-therapeutic (>0.5 IU/mL) → Decrease each dose by 20% (each dose rounded to the nearest zero)

   ➢ Initial (starting) Q12 hour regimens should be changed to once daily regimens

   – <100 kg → 30mg SQ qday or >100kg → 40mg SQ qday
3. After each dosing change (BID regimens only), repeat anti-Xa level (Lovenox Heparin Assay) after the 3rd/4th dose and adjust accordingly as outlined above
4. Protocol management is contraindicated for any of the following reasons:
   - Renal insufficiency (CrCl <30 mL/min), thrombocytopenia <50, 000, or trauma team decision

Figure 2. Trauma services enoxaparin venous thromboembolism prophylaxis protocol. CrCl, creatinine clearance; SQ, subcutaneous.

Additional data extracted from the medical record included BMI, CrCl, anti-Xa levels, date and time of first enoxaparin administrations preceding anti-Xa levels, and frequency of enoxaparin. Vasopressor and diuretic exposure surrounding the drawing of an anti-Xa level was also recorded. Specifically, vasopressors infusing at the time in which anti-Xa levels were drawn and diuretics administered within the 48 hours preceding the drawing of an anti-Xa level were documented.

Descriptive analyses were performed for each variable in the study. Continuous variables were presented as means and SDs and compared by using the univariate *t*-test. Categorical variables were reported as percentages and compared using chi-square/Fisher's exact test as necessary. Receiver operating characteristic curve analysis (ROC) for area under the curve (AUC) and the Youden Index (J) were performed to determine the dose/weight ratio that discriminated between therapeutic and super-therapeutic assays. The Youden Index was calculated using the formula, J = sensitivity + specificity − 1. Based on the calculated optimal cutoff point, the dose-to-weight ratio data were then categorized to determine ranges that yielded the highest overall accuracy. Logistic regression was performed to determine whether the identified optimal dose-to-weight range remained a predictor for therapeutic assays, while controlling for all identified potential confounders present on univariate analysis. Statistical significance was set as $p \leq 0.05$. Statistical analysis was performed using SPSS, version 22.0 (IBM).

RESULTS

A total of 622 patients were included in the study, with a total of 634 assays performed. Of these, 536 assays were found to be in the therapeutic range, 63 were in the super-therapeutic range, and 35 were in the sub-therapeutic range. The relationship between dose-to-weight ratio and therapeutic levels were analyzed via ROC/AUC. The AUC analysis revealed that dose-to-weight ratio failed to significantly discriminate between

therapeutic vs sub-therapeutic assays. After this finding, no additional analyses were conducted with the sub-therapeutic group.

Receiver operating characteristic/area under the curve analysis of dose-to-weight ratio was successful in predicting therapeutic vs super-therapeutic assays with AUC 0.78 (95% CI 0.73 to 0.84; $p \leq 0.001$). The optimal cutoff point for dose-to-weight ratio was analyzed using the Youden Index to determine the dose-to-weight value that yielded the highest sensitivity and specificity for discriminating between therapeutic vs super-therapeutic assays. This revealed that a dose-to-weight ratio of 0.40 mg/kg dose showed the greatest sensitivity (66%) and specificity (80%). Based on this optimal cutoff value, the dose-to-weight ratio data was further categorized to establish a range that yielded the highest overall accuracy. A range of 0.31 to 0.40 mg/kg/dose yielded the highest overall accuracy (63%) with a sensitivity of 61% and specificity of 75% (Table 1).

Additional univariate analyses were performed comparing the therapeutic and super-therapeutic groups to determine whether specific patient or injury characteristics were associated with a therapeutic assay result (Tables 2 and 3). Patients in the therapeutic group were significantly younger (50.77 vs 61.31; $p \leq 0.001$) and had higher BMI (29.52 vs 25.58; $p < 0.001$). The 2 groups were found be significantly different with regard to CrCl; with the therapeutic group having a higher percentage of patients with CrCl >90 mL/min (65.4% vs 33.3%; $p < 0.001$). A pre-admission diagnosis of alcohol or substance use (47.6% vs 33.3%; $p = 0.032$) and the presence of a gastrointestinal injury on admission (12.9% vs 1.6%; $p = 0.006$) were significantly higher for the therapeutic group, as well.

These statistically significant differences between the 2 groups were included in a multivariate model to establish whether the previously determined optimal dose-to-weight ratio range (0.31 to 0.40 mg/kg/dose) was an independent predictor for a therapeutic assay (Table 4). Patients receiving enoxaparin prophylaxis within range of 0.31 to 0.40 mg/kg/dose were 2.6 times (OR 2.56; 95% CI 1.22 to 5.37; $p = 0.013$) more likely to achieve therapeutic assay. In addition to the dose-to-weight ratio range, male sex and CrCl of >90 mL/min increased the likelihood of reaching therapeutic range by 3 times (OR 2.98; 95% CI 1.48 to 5.99; $p = 0.002$) and 10 times (OR 10.32; 95% CI 1.75 to 61.02; $p = 0.010$), respectively (Table 4). Additional analysis was conducted to determine the odds of achieving therapeutic assays when all the 3 positively related independent factors were present (male, CrCl > 90 mL/min and dose-to-weight 0.31 to 0.40 mg/kg/dose). These data revealed that when patients met this criterion, they were almost 14 times (OR 13.76; 95% CI 3.32 to 56.96; $p < 0.001$) more likely to reach therapeutic levels at the specified dosing range of 0.31 to 0.4 mg/kg/dose (Table 5).

A final multivariate analysis was performed to investigate the differences between males and females and the observed relationship between male sex and therapeutic assays. A higher percentage of males had CrCl >90 mL/min (76.1% vs 43.5%; $p < 0.001$) and received enoxaparin prophylaxis in the optimal dose-to-weight range (67.6% vs 43.3%; $p < 0.001$) than females in the study population, suggesting that these might simply be acting as surrogates for male sex in the series (Table 6). No other significant differences were established between male and female patient groups.

DISCUSSION

Enoxaparin remains the preferred agent for VTE prophylaxis in trauma.[1] The most commonly used regimen and the regimen most endorsed in published clinical guidelines is that of 30 mg administered twice daily.[1,8,9] Recent literature has raised concerns, however, that the recommended dosing regimen might not protect all patients equally.[2,4-6] This problem is significant, as previously published literature has demonstrated that conventional recommended prophylactic dosing schedules can result in as much as 89.3% of assays falling within the sub-therapeutic range.[4] Anti-Xa assays are readily available and are in use at our institution and others, however, consensus is lacking on their routine usage. Their clinical utility lies in the theory that sub-therapeutic administration, as evidenced by anti-

Table 1. Accuracy Estimation of Enoxaparin Prophylaxis Dose-to-Weight Ratio for Therapeutic vs Super-Therapeutic Assays

Dose-to-weight range, mg/kg	TP	FP	TN	FN	Total, n	Sensitivity	Specificity	Accuracy	PPV	NPV
.21 to .30	36	0	63	500	599	6.7	100.0	17	100.0	11.2
.31 to .40	329	16	47	207	599	61.4	74.6	63	95.4	18.5
.41 to .50	129	22	41	407	599	24.1	65.1	28	85.4	9.2
.51 to .60	30	18	45	506	599	5.6	71.4	13	62.5	8.2
.61 to .70	9	5	58	527	599	1.7	92.1	11	64.3	9.9

FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TP, true positive; TN, true negative.

Table 2. Patient Characteristics

Characteristic	Therapeutic (n = 536)	Super-therapeutic (n = 63)	p Value
Age, y, mean ± SD	50.77 ± 19.74	61.31 ± 20.45	<0.001*
Sex, n (%)			<0.001*
Male	336 (62.7)	16 (25.4)	
Female	200 (37.3)	47 (74.6)	
Injury Severity Score, mean ± SD	13.52 ± 8.13	12.71 ± 8.25	0.460
BMI, kg/m^2, mean ± SD	29.52 ± 8.92	25.58 ± 5.58	<0.001*
Dose/weight, 0.31–0.40 mg/kg/dose, n (%)	329 (61.4)	16 (25.4)	<0.001*
Blood product, n (%)	165 (30.8)	13 (20.6)	0.095
Serum creatinine, mg/dL, mean ± SD	0.76 ± 0.24	0.78 ± 0.24	0.546
Creatinine clearance, n (%)			0.0001*
<30 mL/min	3 (0.6)	4 (6.7)	
30–90 mL/min	177 (34.0)	36 (60.0)	
>90 mL/min	340 (65.4)	20 (33.3)	
Diuretic, n (%)	61 (11.4)	4 (6.3)	0.287
Vasopressor, n (%)	16 (3.0)	0 (0.0)	0.397
ICU admission, n (%)	353 (65.9)	37 (58.7)	0.261
ICU stay, d, mean ± SD	7.30 ± 7.40	5.86 ± 5.77	0.254
Hospital stay, d, mean ± SD	11.64 ± 9.46	10.35 ± 7.69	0.297
Comorbidity, n (%)			
Neurologic	54 (10.1)	11 (17.5)	0.075
Hematologic	38 (7.1)	6 (9.5)	0.447
Pulmonary	36 (6.7)	5 (7.9)	0.607
Gastrointestinal	12 (2.2)	0 (0.0)	0.625
Cardiovascular	240 (44.8)	29 (46.0)	0.850
Malignancy	5 (0.9)	0 (0.0)	1.000
Diabetes	75 (14.0)	7 (11.1)	0.698
Psychiatric	90 (16.8)	12 (19.0)	0.600
Autoimmune	15 (2.8)	1 (1.6)	1.000
Renal	2 (0.4)	0 (0.0)	1.000
Alcohol and substance use	255 (47.6)	21 (33.3)	0.032*

Percentages in each group are calculated using the total number of therapeutic and super-therapeutic assays, respectively.
*Statistically significant.

Xa levels below a therapeutic range of 0.2 IU/mL, can leave patients unprotected from potentially preventable VTE. A recent series from our institution and others provide support that sub-therapeutic levels with standard recommended dosing schedules are common, and adjustment of these levels to within the therapeutic range correlates with a reduction in both DVT and VTE.[4-6] For example, the IMPACT-IT Project, implemented as a quality improvement initiative in 2015 at our institution, found that the incidence of symptomatic VTE decreased significantly post-implementation from 2.0% to 0.9% (p = 0.009) with the institution of anti-Xa–based dosing adjustments after initial dosing based on clinical guidelines.[5] Similar results were reported by Singer and colleagues[6] in which they observed a significant decrease in the incidence of DVT from 20.5% to 7.1% (p = 0.031). Although that study focused on achieving anti-Xa levels of ≥0.2 IU/mL, over aggressive dosing to super-therapeutic levels (>0.5 IU/mL) might place patients at higher risk of bleeding complications. This scenario is especially relevant in the trauma population because outcomes in injuries such as splenic or liver lacerations and traumatic brain injury have the potential to be worsened significantly if pharmacologically induced bleeding complications occur.

The recognition of the failure of the current dosing guidelines to reliably protect all patients via the attainment of therapeutic anti-Xa levels has sparked interest in altered weight-based dosing regimens (specific mg/kg bid dosing schedules) and the clinical factors that can affect the pharmacokinetics of enoxaparin. Bickford and

Table 3. Injuries on Admission

	Therapeutic (n = 536)		Super-therapeutic (n = 63)		
Variable	**n**	**%**	**n**	**%**	**p Value**
Orthopaedic					
Upper extremity fracture	136	25.4	15	23.8	0.787
Lower extremity fracture	220	41.0	21	33.3	0.238
Dislocation	19	3.5	1	1.6	0.711
Pelvic fracture	94	17.5	11	17.5	0.988
Sprain, strain and tear	20	3.7	2	3.2	1.000
CNS					
Traumatic brain injury	165	30.8	22	34.9	0.503
Cord injury	7	1.3	0	0.0	1.000
Spinal fracture	174	32.5	21	33.3	0.889
Skull fracture	31	5.8	5	7.9	0.571
Genitourinary					
Bladder	5	0.9	0	0.0	1.000
Kidney	8	1.5	1	1.6	1.000
Other genitourinary injury	2	0.4	0	0.0	1.000
Thoracic					
Rib fracture	193	36.0	24	38.1	0.744
Hemothorax and pneumothorax	116	21.6	13	20.6	0.854
Diaphragm	2	0.4	0	0.0	1.000
Lung laceration and contusion	60	11.2	5	7.9	0.526
Cardiac	4	0.7	0	0.0	1.000
Vascular	26	4.9	3	4.8	1.000
Eye and adnexa	25	4.7	2	3.2	1.000
Skin and mucosa	380	70.9	44	69.8	0.862
Peripheral nervous system	23	4.3	2	3.2	1.000
Gastrointestinal	69	12.9	1	1.6	0.006*
Oromaxillofacial	74	13.8	9	14.3	0.849

Percentages in each group are calculated using the total number of therapeutic and super-therapeutic assays, respectively.
*Statistically significant.

colleagues[10] prospectively reviewed weight-based dosing of enoxaparin 0.5 mg/kg bid in trauma patients with a BMI of ≥30 kg/m^2 and found that 86% of patients achieved an anti-Xa level ≥0.2 IU/mL. We have adapted these findings in our current protocol, using a dose of 40 mg bid in patients >100 kg (Fig. 2) instead of using calculated BMI. In this study, we used ROC/AUC and subsequent Youden's Index analysis to determine the optimal dose-to-weight (mg/kg) cutoff. Although we were not able to predict a cutoff point for sub-therapeutic vs therapeutic dose range, we were successful in predicting a dose-to-weight cutoff for therapeutic vs super-therapeutic assays. In addition, the dose range of 0.31 to 0.40 mg/kg demonstrated the highest overall sensitivity and accuracy of the various incremental dosing schedules (Table 1). From these data, one can reasonably

Table 4. Logistic Regression Determining Dose-Weight Ratio as an Independent Factor for Achieving Therapeutic Assays

Variable	**p Value**	**Odds ratio**	**95% CI**
Male sex	0.002*	2.98	1.48–5.99
Dose/weight (0.31–0.40 mg/kg/dose)	0.013*	2.56	1.22–5.37
Creatinine clearance			
<30 mL/min	Reference	Reference	Reference
30–90 mL/min	0.083	4.70	0.82–27.19
>90 mL/min	0.010*	10.32	1.75–61.02

*Statistically significant.

Table 5. Likelihood of Achieving Therapeutic Assays with All 3 Independent Factors Present

Variable	p Value	Odds ratio	95% CI
Male; dose/weight ≤0.31−0.40 mg/kg/dose; and CrCl >90 mL/min	<0.001	13.76	3.32−56.96

CrCl, creatinine clearance.

hypothesize that an individualized weight-based dose of 0.4 mg/kg/dose bid would have the highest likelihood of hitting the "sweet spot" by achieving therapeutic anti-Xa levels (0.2−0.5 IU/mL) without crossing into the super-therapeutic (>0.5 IU/mL) range. This, however, remains a subject for additional study and would require prospective validation before routine implementation. This assumption—that individualized weight-based dosing alone is sufficient to reliably achieve therapeutic levels—presumes "all other things equal," however, and fails to consider the potential effect of other clinical factors affecting enoxaparin pharmacokinetics, the results of anti-Xa assays, and the likelihood of achieving a therapeutic anti-Xa level.

Which factors actually affect the reliability of obtaining a therapeutic anti-Xa level remains another area of controversy in the literature and has been studied by several authors and with conflicting results. Malinoski and colleagues[2] found that inadequate anti-Xa levels occurred in 50% of trauma patients in their 2010 study, but failed to demonstrate any significant differences in age, BMI, Injury Severity Score, CrCl, presence of high-risk injuries, and ICU/ventilator days. Similarly, Karcutskie and colleagues[11] also failed to find any variables that significantly predicted a sub-therapeutic anti-Xa level, and almost 50% of patients in their study never reached the therapeutic range, despite titration to up to 60 mg of enoxaparin bid. Similarly, in the series reported by Singer and colleagues,[6] 40.2% of subjects never achieved a therapeutic anti-Xa level, despite progressive titration of their enoxaparin dosage. The authors were unable to identify any clear reason for this observed phenomemon.[6] Imran and colleagues[7] also failed to find any significant differences in sex, weight, BMI, serum Cr, CrCl, Injury Severity Score, and injury type in predicting sub-therapeutic anti-Xa levels.

Other investigators, however, have identified clinical variables that negatively impact the likelihood of achieving a therapeutic anti-Xa level. As suggested by Bickford and colleagues,[10] one such variable is patient weight/BMI. Patient weight/BMI was found in a study by Berndston and colleagues[12] to be the single most important patient factor in achieving a therapeutic level, with an observed correlation between higher BMI and a sub-therapeutic anti-Xa level. Costantini and colleagues[13] found that male sex, greater body weight, and larger body surface area were all more likely to result in failure to achieve a therapeutic anti-Xa level. Consequently, some have suggested that obese patients are a specific subgroup that might be especially appropriate for anti-Xa monitoring.[14] Higher CrCl has also been correlated with lower anti-Xa levels suggesting that the elevated CrCl seen in hyperdynamic trauma patients might result in faster clearance of enoxaparin than that observed in other patients.[4,15]

Other factors not well studied can also affect the effectiveness of enoxaparin in the trauma setting. Severely injured trauma patients have been demonstrated to have an underlying hypercoagulable state.[16] In addition, trauma patients have been demonstrated to be deficient in antithrombin III in a significant proportion of patients—up to 67%, which is relevant because enoxaparin relies on the potentiation of antithrombin III to achieve therapeutic effect.[17] Other studies have identified platelet aggregation can be enhanced after trauma, further potentiating the hypercoagulable state.[18,19]

Based on the data presented in the discussion of the published studies to date, it is clear that the pharmacokinetics of enoxaparin are complex and can be affected by a number of clinical factors. Accordingly, it was our goal to better delineate which factors were significant and worthy of consideration. Of note, the focus in all of the studies mentioned was slightly different than ours, in that they attempted to identify factors predicting non-therapeutic anti-Xa levels, and we, conversely, are attempting to identify predictors of a therapeutic level.

Table 6. Significant Differences Between Male and Female Patients

	Male (n = 352)		Female (n = 247)		
Variable	n	%	n	%	p Value
Creatinine clearance					<0.001*
<30 mL/min	2	0.6	5	2.0	
30−90 mL/min	84	23.3	139	54.5	
>90 mL/min	274	76.1	111	43.5	
Dose/weight (0.31−0.40 mg/kg/dose)	238	67.6	107	43.3	<0.001*

*Statistically significant.

Although it is suggested by most (but not all) authors that the pharmacokinetics of enoxaparin are affected by weight and that calculation of an optimal dose/weight cutoff is therefore useful, it is equally important and necessary to understand the impact of any other factors that might affect the reliability of attaining a therapeutic anti-Xa assay result at a given dose. We chose to examine this broadly, by collecting data, including patient characteristics (enoxaparin dosing, age, sex, Injury Severity Score, CrCl, BMI, comorbidities, vasopressors, diuretics, type of injuries, among others) (Tables 2 and 3). Although 0.31 to 0.4 mg/kg/dose, younger age, male sex, increasing CrCl, higher BMI, history of a substance abuse disorder, and an associated gastrointestinal injury were significantly associated with therapeutic assays; only dosing of 0.31 to 0.4 mg/kg/dose, male sex, and CrCl of >90 mL/min remained significant in the logistic regression (Table 4). More impressively, when this dosing schedule was combined with use in a male patient with a CrCl of >90 mL/min, the likelihood of a therapeutic assay was nearly 14 times greater (Table 5). This is especially interesting, because, if validated prospectively, it might allow identification of a sub-population that can be so reliably predicted to be therapeutic that monitoring would be unnecessary. The differences between male and female sex were further explored via regression analysis (Table 6). When considering the results of the first regression analysis (Table 4) and correlating it with the subsequent male/female comparison (Table 5), males in the series were more likely to have received optimal dosing (0.31 to 0.4 mg/kg/dose), and to have a CrCl >90 mL/min, suggesting that male sex might simply be a surrogate for these 2 variables rather than an independent predictor. Once again, this question is best answered via prospective studies.

This study has several limitations. Although the data were collected prospectively and according to a strict protocol, supplemental data were collected in a retrospective manner. Consequently, although associations might be identified, it is not possible to draw precise conclusions about cause and effect. In addition, data detailing patients' fluid balance was found to be incomplete at times in the electronic medical record. Accordingly, this end point was not evaluated in order to maintain the integrity of the study's overall data analysis. The strengths of the study included identifying predictors of therapeutic anti-Xa levels, its protocolized design and a relatively large sample size compared with other similar studies in the literature.

CONCLUSIONS

These data provide an important and robust addition to the literature that adds to the understanding of the complexities surrounding VTE prophylaxis in this most challenging patient population. Additional prospective studies are necessary to validate the use of optimal weight-based dosing and to better understand the complex relationships between all of the clinical variables affecting the pharmacokinetics and efficacy of enoxaparin use in the trauma setting.

Author Contributions

Study conception and design: Bethea, Samanta
Acquisition of data: Bethea, Samanta, Deshaies
Analysis and interpretation of data: Bethea, Samanta, Richmond
Drafting of manuscript: Richmond, Samanta
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