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Original Research

Pharmacist recommendations for prophylactic enoxaparin monitoring and dose adjustment in trauma patients admitted to a surgical intensive care unit

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Abstract

Background: There is limited information describing pharmacist participation in prophylactic enoxaparin monitoring in the surgical intensive care unit (SICU).

Objective: Our study sought to: 1) characterize pharmacist recommendations for enoxaparin monitoring in trauma patients admitted to the SICU, 2) describe the frequency that medical providers accept pharmacist recommendations for enoxaparin monitoring in trauma patients admitted to the SICU, and 3) illustrate the frequency that trauma patients admitted to our SICU service achieve anti-factor Xa trough concentrations (AFXa-TRs) of 0.11 - 0.20 IU/mL following pharmacist recommendation to adjust prophylactic enoxaparin dosing.

Methods: Adult patients who had an AFXa-TR drawn after at least three consecutive prophylactic enoxaparin doses between June 1, 2017 and March 1, 2018 were identified through chart review and included in this study. Patients were excluded based on the following criteria: 1) age less than 18 years, 2) anti-factor Xa (AFXa) level not representative of a trough concentration, 3) AFXa-TR not representative of steady state concentration, and 4) non-trauma based prophylactic enoxaparin dosing. This study was exempt from IRB review.

Results: The final analysis consisted of 42 patients. A pharmacist provided at least one recommendation in 97.6% (41/42) of trauma patients with enoxaparin monitoring during their SICU stay. In total, a pharmacist made 170 recommendations, mean of 4.2 (SD 1.8) recommendations per patient. Recommendations were: 1) obtain an AFXa-TR, n=90; 2) adjust enoxaparin dose based on AFXa-TR, n=58; and 3) maintain enoxaparin dose based on AFXa-TR, n=22. Medical providers accepted 89.4% (152/170) of pharmacist recommendations for enoxaparin monitoring. Dose adjustments were made in 33 patients following pharmacist recommendation; of these, 27 had a repeat AFXa-TR following at least one dose adjustment. Target AFXa-TRs were achieved in 19/27 patients, indicating 70.4% had recommended AFXa concentrations.

Conclusions: Pharmacists provided recommendations for prophylactic enoxaparin monitoring and dose adjustment in trauma patients admitted to the SICU. Medical providers regularly accepted pharmacist recommendations and trauma patients commonly achieved target AFXa-TR following pharmacist recommendation for dose adjustment. Further research is required to identify the optimal enoxaparin dose for VTE prophylaxis in trauma patients.

Keywords

Enoxaparin; Factor Xa; Intensive Care Units; Critical Care; Pharmaceutical Services; Pharmacists; Evaluation Studies as Topic; United States

INTRODUCTION

Trauma patients admitted to the surgical intensive care unit (SICU) commonly use subcutaneous enoxaparin 30 mg twice daily (BID) for venous thromboembolism (VTE) prophylaxis.[1] This regimen is based on limited evidence and there are at least three studies suggesting similar VTE rates when compared to once daily enoxaparin or three times daily unfractionated heparin.[2-4] Interestingly, recent evidence has identified rare achievement of target anti-factor Xa trough concentrations (AFXa-TR) and significant VTE reduction when adjusting enoxaparin dose to achieve AFXa-TRs of 0.11 - 0.20 IU/mL.[5-7] Some experts, therefore, recommend adjusting enoxaparin in trauma patients based on AFXa-TR.[6,7]

In June 2017, Upstate University Hospital started adjusting enoxaparin VTE prophylaxis based on AFXa-TR in trauma patients admitted to the SICU based on discussion between pharmacy and attending trauma physicians about the above noted literature.[1-7] Upstate University Hospital has a multidisciplinary SICU team that includes an attending surgical physician who specializes in trauma care, three surgical residents, a pharmacist who specializes in critical care, and nurses certified in the treatment of trauma

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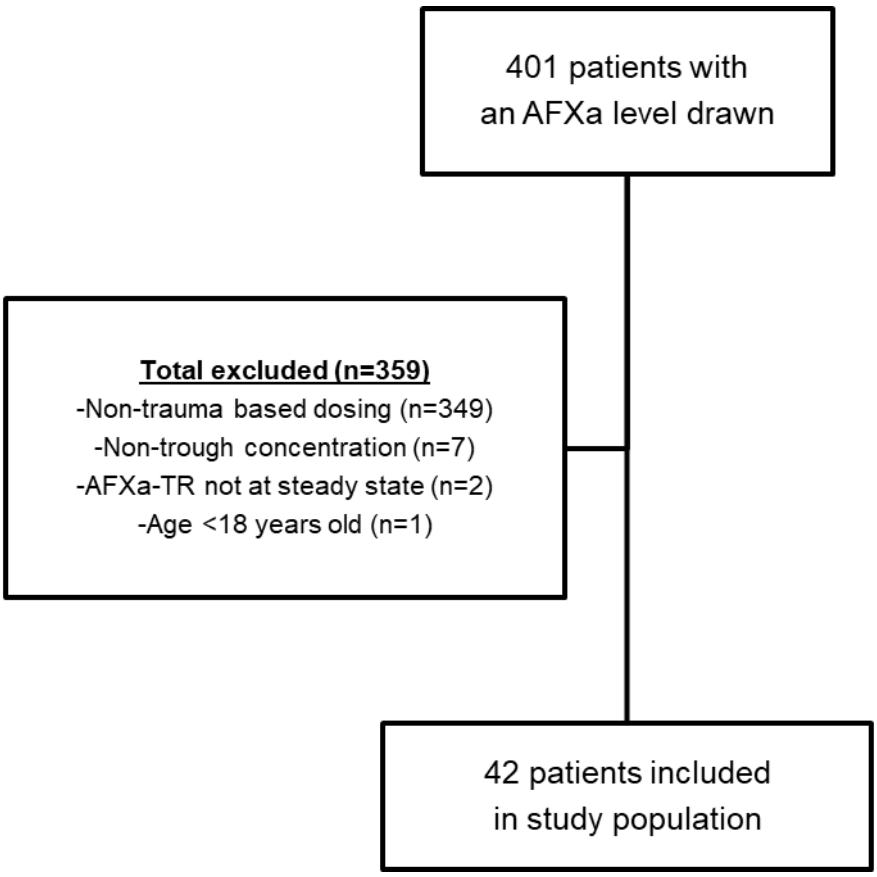

Figure 1. Inclusion and Exclusion Criteria

patients. A critical care pharmacist, who has been an active member of the trauma team for approximately five years, rounds with the team five days a week. Additionally, rotating staff pharmacists with critical care experience provide operational support and clinical advisement 24 hours a day. At any one time the SICU team cares for 5-10 patients with a variety of traumatic injuries including but not limited to motor vehicle accidents (MVA), penetrating traumas, and burns. All treatment decisions are at the discretion of the attending physician including the initiation of enoxaparin VTE prophylaxis, ordering of AFXa-TR, and dose adjustments based on resultant AFXa-TR; as currently there is no official protocol at our institution describing this process. All patients receiving enoxaparin for VTE prophylaxis are initiated on enoxaparin 30 mg BID and after discussion with the treatment team, doses are adjusted up or down in 10 mg/dose increments to achieve an AFXa-TR of 0.11 – 0.20 IU/mL.[5,6] AFXa levels are routinely used at our institution and our laboratory services run AFXa assays 24 hours a day.

All pharmacists, including staff and clinical pharmacists, were provided education and were expected to make recommendations, interpret, and adjust enoxaparin dosing based on AFXA-TRs from trauma patients. There is limited information describing pharmacist participation in prophylactic enoxaparin monitoring in the SICU and our study sought to: 1) characterize pharmacist recommendations for enoxaparin monitoring in trauma patients admitted to the SICU, 2) describe the frequency that medical providers accept pharmacist recommendations for enoxaparin monitoring in trauma patients admitted to the SICU and 3) illustrate the frequency that trauma patients admitted to our SICU service achieve AFXa-TRs of 0.11 - 0.20 IU/mL following pharmacist recommendation to adjust prophylactic enoxaparin dosing.

METHODS

This retrospective, single-center, cohort study was performed at Upstate University Hospital, a 472-bed academic medical center that is also a Level-1 trauma center. This study was exempt from institutional review board review. Consecutive patients with at least one AFXa concentration were identified via a query of laboratory records between June 1, 2017 and March 1, 2018. Patients were excluded based on the following criteria: 1) age less than 18 years, 2) AFXa level not representative of a trough concentration, defined as an AFXa concentration drawn 10 – 13 hours after a dose, 3) AFXa-TR not representative of steady state concentration, defined as an AFXa-TR drawn following at least three consecutive enoxaparin doses, and 4) non-trauma based prophylactic enoxaparin dosing, defined as a total daily enoxaparin dose less than 60 mg/day as Upstate University Hospital routinely uses AFXa monitoring in other populations and indications.

A single reviewer blinded to the study objective performed manual chart review for included patients and collected

Table 1. Patient Demographics and Mechanism of Injury	
Characteristic	**Value (n=42)**
Mean Age in Years	44 (SD= 20.4)
Male, n (%)	32 (76.2)
Mean Weight (kg)	84.1 (SD= 20.4)
Mean BMI[a] (IQR) kg/m^2	28.0 (23.8 - 33.2)
Mean CrCl[b] (ml/min)	142.9 (SD= 55.3)
Mechanism of Injury, n (%)	
Motor vehicle accident	27 (64.3)
Penetrating trauma	6 (14.3)
Assault	3 (7.1)
Burn	3 (7.1)
Fall	3 (7.1)
[a]BMI=body mass index, [b]CrCl=creatinine clearance	

data using a standardized data collection form. Patient demographics, including age, gender, height, weight, body mass index (BMI) and serum creatinine (SCr) were collected. Creatinine clearance (CrCl) was calculated by the Cockcroft Gault equation, which uses patient age, gender, ideal body weight (IBW)estimated using the Devine equation, and SCr.[8] Collected clinical data included mechanism of injury, AFXa-TR result and collection time, enoxaparin dose and dose adjustments, pharmacist recommendations for prophylactic enoxaparin monitoring and dose adjustment, medical provider acceptance of pharmacist recommendations, and rationale. Our laboratory utilizes Liquid Anti-Factor Xa 8 kit (Diagnostica Stago, Parsippany, NJ) calibrated with low molecular weight heparin (LMWH) for anti-Xa analysis. We also attempted to identify a reason if a medical provider did not accept a pharmacist recommendation. Pharmacist recommendations and rationale data were initially documented and later retrieved through a pharmacy invention documentation system integrated into the electronic medical record.

Target AFXa-TR range was defined as 0.11 – 0.20 IU/mL, based on evidence in hip replacement patients suggesting increased VTE risk with an AFXa-TR < 0.11 IU/mL and increased bleeding risk with an AFXa-TR > 0.20 IU/mL.[9] This range has also been used in recent publications assessing enoxaparin dosing in trauma patients.[6,7] All statistical analyses were performed using Microsoft© Excel 15.33 and presented using descriptive statistics, including number (n) and percentage (%) for categorical data and mean and standard deviation (SD) or median and interquartile range (IQR) for continuous data.

RESULTS

Four hundred and one patients with an AFXa concentration while on enoxaparin were identified. Three hundred and fifty nine were excluded (as shown in Figure 1) for the following: 1) therapeutic enoxaparin dosing or non-trauma based prophylactic enoxaparin dosing, defined as a total daily enoxaparin dose less than 60 mg/day, n=349; 2) AFXa level not representative of a trough concentrations, defined as an AFXa concentration drawn <10 hours or >13 hours following a dose, n=7; 3) AFXa-TR not representative of steady state concentration, defined as an AFXa-TR drawn following at least three consecutive enoxaparin doses, n=2; and 4) age less than 18 years, n=1.

In total, 42 patients were included in this analysis. Table 1 shows patient demographics and mechanism of injury. Our population was mostly male and most suffered injuries due to motor vehicle accidents (n=27). The median BMI (IQR) was 28.0 (23.8 - 33.2) kg/m^2, which is considered overweight according to the obesity classification system.[10] All patients were started on enoxaparin 30 mg

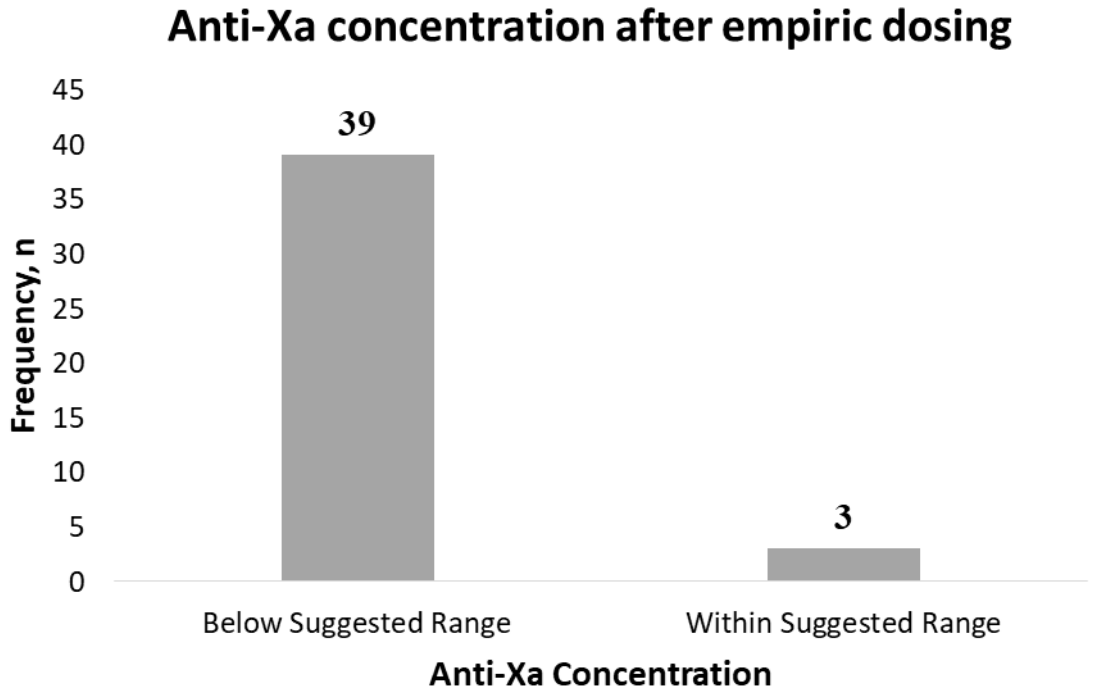

Figure 2. Anti-Xa trough concentrations (AFXa-TRs) after empiric enoxaparin dosing
Target AFXa-TR range = 0.11 - 0.20 IU/mL

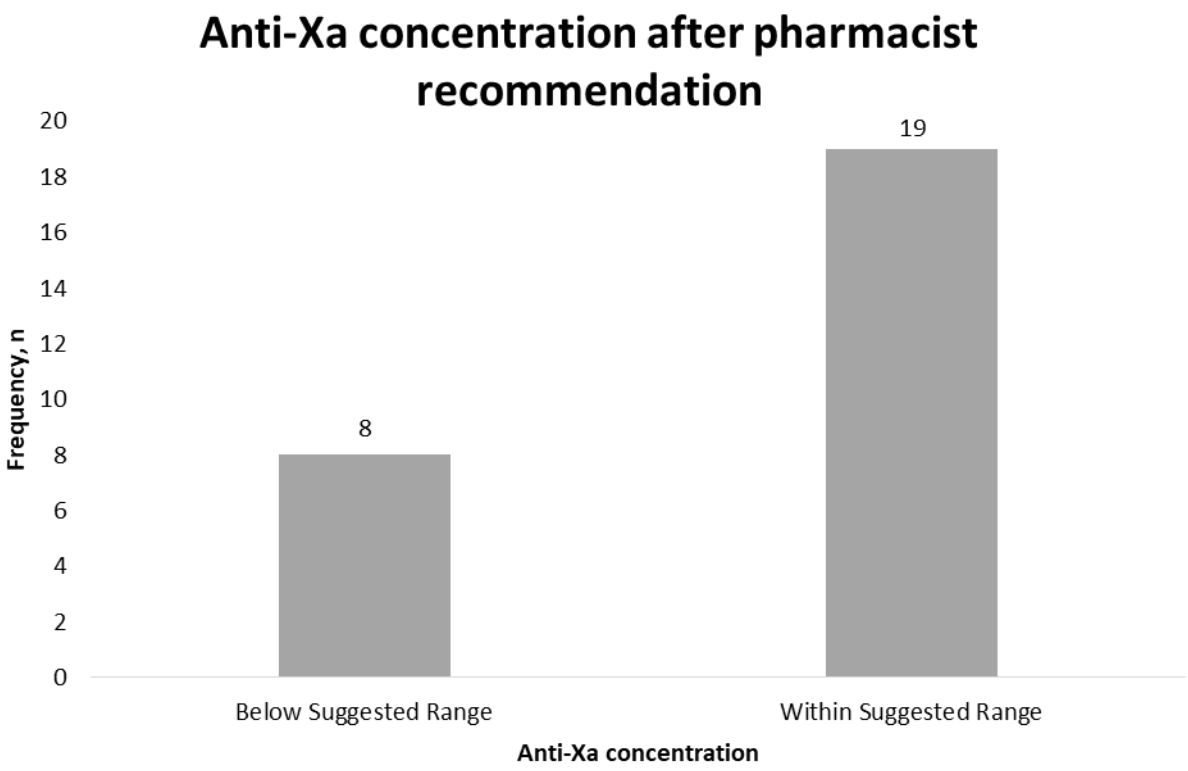

Figure 3. Anti-Xa trough concentrations (AFXa-TR) after pharmacist recommendation
Based on patients with follow-up AFXa-TR after dose adjustment (Target AFXa-TR range = 0.11 - 0.20 IU/mL)

subcutaneously twice daily (approximately 0.36 mg/kg/dose), and 7.1% (3/42) achieved target AFXa-TRs with this regimen; 92.8% (39/42) had initial AFXa-TRs<0.11 IU/mL (Figure 2). Dose adjustments were performed in 84.6% (33/39) with initial AFXa-TRs<0.11 IU/mL.On average (SD), these patients received 1.3 (1.1) dose adjustments with an average terminal dose (SD) of 41.8 mg/dose or 0.51 (0.12) mg/kg/dose. All doses were administered every 12 hours.

A pharmacist provided at least one recommendation in 97.6% (41/42) of trauma patients with enoxaparin monitoring during their SICU stay. The pharmacists providing the recommendations were either pharmacists with special training or board certification in critical care pharmacy or postgraduate year one pharmacy residents making the recommendations under the supervision of the specialized pharmacist. In total, a pharmacist made 170 recommendations, which equates to 4.2 (1.8) recommendations per patient on average (SD). Pharmacists recommendations were: 1) obtain an AFXa-TR, n=90; 2) adjust enoxaparin dose based on AFXa-TR, n=58; and 3) maintain enoxaparin dose based on AFXa-TR, n=22. Medical providers accepted 89.4% (152/170) of pharmacist recommendations for enoxaparin monitoring and acceptance frequencies were as follows: 1) obtain an AFXa-TR, 90.0% (81/90); 2) adjust enoxaparin dose based on AFXa-TR, 84.5% (49/58); and 3) maintain enoxaparin dose based on AFXa-TR, 100% (22/22). In total, 18 pharmacist recommendations were not accepted and reasons for non-acceptance were as follows: 1) hospital discharge, n=7; 2) transfer off of SICU service; n=4; 3) recommendation not accepted and provider rationale unclear, n=4; and 4) concern for increased bleeding risk with dose increase, n=3.

In total, 33 patients (33/39, 84.6%) received a dosage adjustment following pharmacist recommendation to adjust enoxaparin based on AFXa-TR. All dose adjustments were increases of 10 mg/dose and these patients received an average of 1.4 (SD=0.9) dose increases. Repeat AFXa-TRs were available in 27 (27/33, 81.8%) of those patients following at least one dose adjustment and 70.3% (19/27) achieved target AFXa-TRs (Figure 3). Most required a single adjustment (13/19, 68.4%) to achieve target AFXa-TRs; 21.1% (4/19), required two dose adjustments and 10.5% (2/19, 10.5%) required three dose adjustments. Six of the patients who did not achieve target AFXa-TRs, did not have a repeat AFXa-TR assessment following their terminal dose adjustment for unknown reasons. There were no VTE or bleeding events in our study population.

DISCUSSION

This study, to our knowledge, is the first description of pharmacist participation in therapeutic drug monitoring of prophylactic enoxaparin in trauma patients admitted to the SICU and our study had some interesting findings. First, pharmacists actively participated in all facets of enoxaparin monitoring and recommended obtaining AFXa-TRs, helped interpret AFXa-TR, and recommended dose adjustments based on AFXa-TRs. Our pharmacists, in total, made 170 recommendations on prophylactic enoxaparin in 41 trauma patients during their admission to the SICU. Medical providers accepted 89.4% of pharmacist recommendations

signifying that physician acceptance was not a barrier to implementation of this new clinical monitoring service. Anderegg *et al*. and Shanika *et al*. performed cohort studies of hospitalized patients receiving pharmacist recommendations and found medical providers accepted 48 - 73.5% of pharmacist recommendations.[11,12] Additionally, Devlin *et al*. found that 78% of enoxaparin initiation or discontinuation recommendations by pharmacists in trauma patients were accepted by medical providers.[13] Again, it should be noted that our clinical pharmacist actively participates in multiple aspects of patient care, including daily medical rounds and therapeutic drug monitoring. Irrespective of the possible reasons as to why our study had higher acceptance rates, our study showed pharmacists can actively participate in prophylactic enoxaparin monitoring in trauma patients admitted to the SICU and can provide recommendations for enoxaparin monitoring and adjustment, which medical providers may accept.

Secondly, approximately 70% of our trauma patients achieved target AFXa-TRs following pharmacist recommendation for enoxaparin dose adjustment. Only three of our 42 trauma patients achieved target AFXa-TRs without dose adjustment. Dose adjustments were made in 33 patients following pharmacist recommendation and of these, 27 had a repeat AFXa-TR following at least one dose adjustment. Target AFXa-TRs were achieved in 19 of the patients with repeat AFXa-TR, indicating 70.4% had achieved recommended AFXa concentrations. Some additional patients may have achieved recommended AFXa concentrations, however, repeat AFXa-TR were not obtained in six patients following their terminal dose adjustment for unknown reasons. These findings are interesting as all patients achieving target AFXa-TRs reached these concentrations following pharmacist recommendation. AFXa-TRs<0.11 IU/mL have been associated with increased VTE following trauma and two recent studies suggest decreased VTE when adjusting prophylactic enoxaparin based on AFXa-TR.[6,7] Ko *et al*. and Dhillon *et al*. performed prospective cohort studies comparing VTE frequency in critically ill trauma patients receiving fixed dose enoxaparin 30 mg BID or twice daily enoxaparin adjusted to achieve an AFXa-TR of 0.11 - 0.20 IU/mL and both authors found lower VTE rates with adjusted dosing.[6,7] There were no VTE or bleeding events in our study. Given this evidence, our study suggests trauma patients can achieve recommended AFXa-TR following pharmacist recommendation, which could possibly prevent VTE in trauma patients admitted to the SICU.

Finally, our data suggests most trauma patients will require enoxaparin doses higher than the current standard of 30 mg BID for VTE prophylaxis. This is consistent with recent literature and some have suggested increased empiric dosing or an initial weight-based enoxaparin dose.[1,14] Unfortunately, this evidence base is still limited and there are no consensus recommendations concerning enoxaparin dosing for VTE prophylaxis in trauma patients. Ko *et al*. and Dhillon *et al*. reported VTE rates less than 2% when adjusting enoxaparin dose based on AFXa-TR.[6,7] This rate is lower than VTE rates reported in hospitalized general medicine patients, who are thought to be at lower VTE risk than trauma patients, therefore this therapeutic drug monitoring approach may have benefits of preserving low VTE rates.[15] We will, therefore, continue our current approach, where trauma patients are initiated on enoxaparin 30 mg BID and their dose is adjusted targeting an AFXa-TR of 0.11 - 0.20 IU/mL. We will, however, continue to monitor the available literature and will adjust our strategy if a consensus is reached concerning the optimal initial enoxaparin dosing strategy for VTE prophylaxis in trauma patients.

Our study has several limitations to consider, apart from its retrospective nature. First, all recommendations were made by pharmacists with specialized training or certifications in critical care that rounded daily with the medical team or a pharmacy resident under the supervision of these pharmacists. Though we feel all hospital pharmacists would likely be able to perform similar interventions, it is unclear how our results apply to pharmacists without specialized training or institutions without pharmacists with similar training or clinical activities. Secondly, our study did not statistically evaluate patient oriented outcomes, such as VTE rates or bleeding. The intent of our study was to describe pharmacist recommendations and medical provider acceptance. It was, therefore, in its simplest essence, not patient oriented. We did, however, try to assess the frequency achieving target AFXa-TR following pharmacist recommendation. This target, as noted previously, has been associated with decreased VTE following trauma. We plan to continue to study this topic and investigate the impact pharmacist recommendations have on the incidence of VTE and bleeding in critically ill trauma patients treated with prophylactic enoxaparin. Thirdly, other institutions may not utilize routine AFXa-TR levels in their clinical practice and our study, therefore, may not apply. Finally, we cannot definitively say medical providers would not have performed actions, including ordering AFXa-TRs or adjusting enoxaparin dose, without pharmacist recommendation and we, therefore, cannot say patients would not have achieved recommended AFXa-TRs without pharmacist recommendation. We do, however, feel the frequency of these actions would have been lower, as only one patient during the study period had enoxaparin monitoring without pharmacy recommendation.

CONCLUSIONS

Pharmacists provided recommendations for prophylactic enoxaparin monitoring and dose adjustment in trauma patients admitted to the SICU. Medical providers regularly accepted pharmacist recommendations and trauma patients commonly achieved target AFXa-TR following pharmacist recommendation for dose adjustment. Further research is required to identify the optimal enoxaparin dose for VTE prophylaxis in trauma patients.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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