International Journal of Surgery 51 (2018) 128–132

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Original Research

Trauma patients with lower extremity and pelvic fractures: Should *anti*-factor Xa trough level guide prophylactic enoxaparin dose?☆

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ARTICLE INFO

Keywords:
Deep vein thrombosis
Enoxaparin
Extremity fracture
Pelvic fracture
Trauma
Venous thromboembolism

ABSTRACT

Background: Adequate venous thromboembolism (VTE) prophylaxis is essential after trauma, especially in patients with lower extremity and/or pelvic fractures. We sought to investigate if prophylactic enoxaparin dosed by *anti*-Xa trough levels could reduce clinically evident VTE in trauma patients with lower extremity or pelvic injury.

Methods: Prospective data was collected on trauma patients admitted for at least two days with any lower extremity and/or pelvic fracture and who received enoxaparin for VTE prophylaxis between October 2013 and January 2016. Patients in the control cohort received enoxaparin at 30 mg twice daily. Patients in the adjustment cohort had *anti*-Xa trough levels measured after three or more consecutive doses of enoxaparin. Those with a trough level of 0.1 IU/mL or lower had their dosage increased by 10-mg increments.

Results: Of the 159 patients included, 58 (36.5%) were monitored with *anti*-Xa trough levels. The cohorts were similar in age, sex, regional AIS, ISS score, ICU and hospital length of stay, proportion of patients with diagnostic testing for VTE, and time to first enoxaparin dose. Initial enoxaparin dosing in the majority of patients (84.5%) who had *anti*-Xa trough levels measured was subprophylactic. Patients receiving enoxaparin dosed by *anti*-Xa trough level had a significantly lower VTE rate than those who did not (1.7% v. 13.9%, p = 0.03).

Conclusions: Prophylactic enoxaparin adjusted by *anti*-factor Xa level may lead to a decreased rate of clinically evident VTE among trauma patients with lower extremity and/or pelvic fractures. Our findings indicate that the initial dose of enoxaparin was frequently too low.

1. Background

Venous thromboembolism (VTE) poses a significant challenge after trauma. Patients diagnosed with VTE tend to have worse outcomes with longer hospital stays, disability at discharge, costs, and mortality [1–4]. The rate of VTE varies considerably within the literature, ranging from 11.8% to 63% for deep vein thrombosis (DVT) and 1.5%–22% for pulmonary emboli (PE) [5–7]. Given the clinical and economic implications of VTE, there has been considerable interest in understanding the risk factors for VTE and developing methods to reduce their occurrence [8–10]. One population highly susceptible to developing VTE is trauma patients with lower extremity and pelvic fractures [11] as these patients meet Virchow's triad for VTE development: endothelial injury, venous stasis, and the presence of a hypercoagulable state. In addition, these patients are frequently immobile, which increases the risk for VTE [12,13].

For patients with lower extremity and/or pelvic fractures, mobility protocols and utilization of pneumatic compression devices may reduce the occurrence of VTE, however, more reliable evidence is needed to clearly demonstrate the efficacy of these measures [14,15]. Pharmacologic thromboprophylaxis reduces the risk for DVT, but similar to mobility protocols and mechanical prophylaxis, no reduction in the incidence of PE has been demonstrated [16]. Other studies have suggested that pharmacologic thromboprophylaxis with low molecular weight heparin such as enoxaparin sodium is superior to unfractionated heparin in trauma patients [17,18]. Many centers administer enoxaparin sodium 30 mg twice daily, although there is evidence to suggest that this dose is inadequate [19]. Ko et al. appreciated a reduction in the incidence of VTE among trauma patients after titrating enoxaparin sodium dose specifically to *anti*-factor Xa trough levels. In addition, most patients required enoxaparin sodium 40 mg twice daily to reach the desired *anti*-factor Xa trough level [20]. While the role of

☆ This manuscript was an e-poster presentation at the 88th Scientific Session of the Pacific Coast Surgical Association in Indian Wells, CA, February 17–20, 2017.

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https://doi.org/10.1016/j.ijsu.2018.01.023
Received 16 October 2017; Received in revised form 30 December 2017; Accepted 4 January 2018
Available online 31 January 2018
1743-9191/

dosing enoxaparin sodium with *anti*-factor Xa trough levels has been shown to be effective in trauma patients overall, its utility in specific trauma populations has not been assessed. We hypothesized that in trauma patients with lower extremity and/or pelvic fractures, a population who is particularly susceptible to VTE, dosing enoxaparin sodium by *anti*-factor Xa trough levels could reduce the clinically evident, or symptomatic, VTE rate.

2. Methods

We retrospectively reviewed prospectively collected data on trauma patients with any lower extremity and/or pelvic fracture admitted for at least two days who received enoxaparin for VTE prophylaxis at an urban level 1 trauma center between October 2013 and January 2016. Patients with a history of renal failure, a creatinine clearance (CrCl) less than 30 mL/min, or a preexisting VTE were excluded. Patients in the control cohort (CONTROL) from October 2013 to July 2014 received enoxaparin at 30 mg twice daily, while patients in the adjustment cohort (ADJUST) from August 2014 to January 2016 were initially given enoxaparin at 30 mg twice daily with dose adjustments according to *anti*-factor Xa trough levels. All patients were initially placed on 30 mg twice daily dosing irrespective of body weight. Enoxaparin initiation was at the discretion of the rounding trauma service. *Anti*-factor Xa trough levels were measured after three or more consecutive doses of enoxaparin. A trough level 0.1 IU/mL or less was deemed to be subprophylactic and the patient's subsequent enoxaparin dose was increased by a 10 mg increment. Per protocol, the dosage was also to be decreased by 10 mg increments if the trough level was above 0.2 IU/mL until the patient was at the appropriate levels, although no patients in ADJUST exceeded 0.2 IU/mL. Per protocol, the trough level was repeated after three or more consecutive administrations at the newer dose with subsequent dose adjustments as needed. Trough levels were monitored and dose adjustments were made until either the patient reached an appropriate trough level between 0.11 and 0.2 IU/mL or the patient was discharged.

The primary outcome was VTE, which was diagnosed with either duplex ultrasonography of the entire extremity, chest computed tomography angiogram (CTA), or lung ventilation-perfusion (VQ) scan to detect deep venous thrombosis (DVT) or a pulmonary embolus (PE). Studies were ordered at the discretion of the rounding trauma service based on clinical suspicion for either a DVT or PE. For the purposes of this study, a proximal DVT was defined as any DVT from the common femoral vein to the popliteal vein, and a distal DVT as any DVT distal to the popliteal vein.

Data including patient demographics, mechanism of injury, injury severity scores, hospital and ICU length of stays (LOS), details regarding enoxaparin administration, *anti*-factor Xa trough levels, and results of imaging studies were collected and compared between the CONTROL and ADJUST cohorts. Data were analyzed using IBM SPSS statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA) and are summarized as percentages for categorical variables and means with standard deviations (SD) and medians with interquartile range (IQR) for continuous variables. Comparisons of continuous variables were conducted using the Mann-Whitney *U* Test. All variables were noted to be nonparametric with the exception of Body Mass Index (BMI) and Body Surface Area (BSA). Categorical variables and proportions were compared using Pearson χ [2] test or Fisher's exact test. A P-value less than 0.05 was considered statistically significant. This study was approved by our Institutional Review Board and registered at ResearchRegistry.com. This work has been reported in line with the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) criteria [21].

3. Results

There were 101 patients in the CONTROL cohort and 58 in the ADJUST cohort. The median age was 37 years and the majority of patients (69.8%) were male. The cohorts were similar with respect to age, sex, race, and injury severity (Table 1). The proportion of patients afflicted with blunt injury and the specific mechanisms were also comparable (Table 2). The resulting orthopedic injuries and operative interventions required to address those specific injuries were also similar among CONTROL and ADJUST. The most common injuries afflicting this population overall included pelvic (34%), femur (30.2%), and tibial (30.2%) fractures. Similar proportions of these fractures were appreciated in both cohorts. Overall, 70.4% of patients required operative treatment. If operative treatment was required, patients most

Table 1
Comparison of baseline characteristics and outcomes between ADJUST and CONTROL.

Characteristic	Total (n = 159)	ADJUST (n = 58)	CONTROL (n = 101)	*P* value
Age, y				
Mean ± SD	40.8 ± 17.9	40.1 ± 17.6	41.2 ± 18.2	
Median (IQR)	37 (27–50)	34 (26–52)	38 (27.5–48.5)	0.69
Male, No. (%)	111 (69.8)	37 (63.8)	74 (73.3)	0.28
Race, No. (%)				
Asian	11 (6.9)	5 (8.6)	6 (5.9)	0.36
Black	27 (17.0)	14 (24.1)	13 (12.9)	
White	84 (52.8)	30 (51.7)	54 (53.5)	
Hispanic	24 (15.1)	6 (10.3)	18 (17.8)	
Other	7 (4.4)	2 (3.4)	5 (5.0)	
Unknown	6 (3.8)	1 (1.7)	5 (5.0)	
BMI				
Mean ± SD	24.8 ± 5.0	24.6 ± 5.4	24.9 ± 4.7	0.74
Median (IQR)	24.1 (21.3–27.6)	24.1 (21.6–28.3)	24.3 (21.3–27.4)	
BSA, m^2				
Mean ± SD	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.91
Median (IQR)	1.9 (1.7–2.0)	1.9 (1.7–2.0)	1.9 (1.7–2.0)	
CrCl, mL/min				
Mean ± SD	130.4 ± 58.7	139.1 ± 66.0	125.4 ± 53.8	0.28
Median (IQR)	121.3 (93.8–155.8)	132.9 (93.8–171.6)	118.9 (94.9–149.1)	
AIS Score				
Head/Neck				
Mean ± SD	0.9 ± 1.5	1.1 ± 1.6	0.9 ± 1.5	0.34
Median (IQR)	0 (0–2)	0 (0–3)	0 (0–1)	
Face				
Mean ± SD	0.4 ± 0.8	0.5 ± 1.0	0.3 ± 0.8	0.32
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	
Chest				
Mean ± SD	1.4 ± 1.7	1.6 ± 1.6	1.3 ± 1.7	0.27
Median (IQR)	0 (0–3)	1 (0–3)	0 (0–3)	
Abdomen/Pelvis				
Mean ± SD	1 ± 1.5	0.9 ± 1.4	1.1 ± 1.6	0.62
Median (IQR)	0 (0–2)	0 (0–2)	0 (0–3)	
Extremity				
Mean ± SD	2.6 ± 0.7	2.6 ± 0.8	2.7 ± 0.6	0.52
Median (IQR)	3 (2–3)	3 (2–3)	3 (2–3)	
External				
Mean ± SD	0.9 ± 0.6	0.8 ± 0.6	0.9 ± 0.6	0.94
Median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	
ISS				
Mean ± SD	19.6 ± 13.6	19.1 ± 11.0	19.9 ± 14.9	0.64
Median (IQR)	17 (10–27)	18 (10–24)	14 (9–29)	
Outcomes				
Hospital LOS, d				
Mean ± SD	15.7 ± 14.4	16.5 ± 16.9	15.3 ± 12.8	0.98
Median (IQR)	11 (6–20)	12 (6–22)	10 (7–19.5)	
ICU LOS, d				
Mean ± SD	6.9 ± 7.3	7.5 ± 7.3	6.6 ± 7.4	0.37
Median (IQR)	4 (2–9)	4 (3–12)	3.5 (2–7)	
Required ICU care, n (%)	112 (70.4)	42 (72.4)	70 (69.3)	0.82
Mortality, No. (%)	1 (0.6)	0	1 (1.0)	> 0.99

Abbreviations: AIS Abbreviated Injury Scale; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA, body surface area; CrCl, creatinine clearance; IQR, interquartile range; ISS, Injury Severity Score; LOS, length of stay; SD, standard deviation.