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Thromboembolic Events among Multiple Trauma Victims with Pelvic Fractures with Injury Severity Score Greater Than 16 with and without Deep Vein Thrombosis Prophylactic Doses of Enoxaparin

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ABSTRACT

Introduction: Venous thromboembolism (VTE) is a common life-threatening complication in patients affected by severe trauma. The clinical manifestations of VTE are deep venous thrombosis (DVT) and pulmonary embolism (PE). Various prophylactic pharmacological strategies are used. We studied the efficacy of enoxaparin in preventing VTE in our level 1 trauma center.

Materials and Methods: This cross-sectional study included patients with polytrauma with an Injury Severity Score (ISS) of greater than 16 units and a pelvis fracture diagnosis. Clinical features, laboratory data, and images were reviewed from medical documents. Moreover, the prophylactic medication regimens were recorded. Development of VTE was identified in patients, and a *p*-value <0.05 was considered statistically significant.

Results: A total of 327 patients were examined, of which 18 had developed VTE (5.5%). The frequency was relatively higher in males, cases with fractures, and cases with a history of VTE. Patients with two or more pelvic fracture sites and those with a history of VTE manifested are statistically more likely to develop VTE than those with fewer than two pelvic fracture sites and no history of VTE (*p*-value = 0.02 and 0.006, respectively). Moreover, the administration of prophylactic doses of enoxaparin n had no statistically significant effect on VTE prevention (*p*-value = 0.08).

Conclusion: In conclusion, we found no significant correlation between the prophylactic doses of enoxaparin and VTE probability. Furthermore, a history of VTE and more fracture sites would increase the probability of VTE.

KEYWORDS: Multiple Trauma, Enoxaparin, Venous Thrombosis

INTRODUCTION

In our country, high-energy blunt trauma can occur as a result of various mechanisms: the most common causes are motor vehicle accidents and falls from heights [1, 2]. Road injuries are a leading cause of morbidity and mortality worldwide. However, the burden in developing countries with low and middle income is substantially higher, often regarded as the "neglected epidemic" [3, 4]. As the patients may suffer from various morbidities as a result of the traumatic incidents, further subsequent complications are not uncommon. Venous thromboembolism (VTE) is a major complication of severe trauma. The incidence of DVT in the aforementioned injuries ranges from 10% to 20%, with PE rates between 1% and 2% [5-7]. Injured patients, for various reasons, are predisposed to developing deep vein thrombosis (DVT) or pulmonary embolism (PE). This can occur during the course of hospitalization or even after discharge. DVT often presents clinically with tenderness, warmth, and erythema in the affected limb, and PE is the third most common cause of death in patients surviving the first 24 hours posttrauma [8, 9]. In the absence of treatment, VTE is associated with a 30-day mortality rate of about 3% for DVT and 31% for PE [10]. As patients are already affected by the psychological and physical consequences of trauma, it is important to prevent further complications and suffering. Therefore, VTE might be overlooked if not actively screened. The literature has suggested that only half of the hospital patients receive VTE prophylaxis following accepted evidence-based guidelines [11, 12]. In this regard, numerous pharmacological and nonpharmacological interventions are employed to manage hospitalized patients. Anticoagulation therapy remains the mainstay of prophylaxis. Low-molecular-weight heparins (LMWH) and warfarin are commonly administered. Prophylactic medications include unfractionated heparin, LMWH, oral anticoagulants (like coumarins), thrombin inhibitors (like hirudin), and specific factor Xa inhibitors (like fondaparinux). One of the challenges in using pharmacologic agents is balancing the benefits of anticoagulation with the risk of bleeding. In this study, we aimed to examine the efficacy of enoxaparin in trauma patients with ISS over 16 and pelvic fracture in a referral trauma center in South Iran.

MATERIALS AND METHODS

Patient Selection

This cross-sectional study included patients with polytrauma admitted to Shahid Rajaee Hospital Trauma Center of Shiraz University of Medical Sciences (SUMS), Shiraz, Iran, from 2018 to 2020. We evaluated the risk of developing thromboembolic events, including DVT and PE, during the course of hospitalization. We included all patients admitted over a 2-year period with an ISS greater than 16 units, for whom the diagnosis of pelvic fracture had been confirmed. Every type of fracture was considered, including the sacrum, ilium, ischium, pubis, acetabulum, and femoral head or neck fractures. The head injury also has described as any concussion, contusions, brain hemorrhage, intracranial hematomas, diffuse axonal injury, penetrating brain injury, and second impact syndrome. Exclusion criteria of our study were defined as the absence of pelvis or hip fracture, ISS ≤16, pregnancy, and contraindications for prophylactic enoxaparin, such as intracranial hemorrhage (ICH). The ethics committee approved the study protocol of SUMS, and legal permission was obtained to access patients' medical documents.

Evaluation of Clinical Data

Initially, patients with multiple trauma and pelvic fractures referred during the above-mentioned time period were identified using the hospital's database. We examined the plain radiographs of each patient to ensure the presence of a pelvic fracture. Subsequently, ISS was calculated for each patient. The ISS, developed by Baker et al. in 1974 [13], is still considered the gold standard tool for assessing injury severity [14]. This score indicates the severity of injury based on the characteristics of trauma in patients. In fact, ISS has been derived from the Abbreviated Injury Scale (AIS). The body is evaluated in 6 anatomic regions, and a particular score is attributed to each part. The summation of squares of figures from the three most injured regions makes up the total ISS score. ISS has been shown to be highly reliable for predicting trauma mortality. [15]

After identifying the eligible patients, we thoroughly reviewed their medical records and available radiographs on the Picture Archiving and Communication System (PACS) of SUMS. Color Doppler ultrasonography and chest CT scans were analyzed in terms of the diagnosis of DVT and PE. In summary, the following data were collected: demographic characteristics (age and gender)

and laboratory results, including prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), hemoglobin (Hb), fibrin D-dimer, and base excess (BE) [15]

Data were analyzed using IBM SPSS Statistics software Windows version 16.0. Qualitative variables are reported in frequency and percentages, while mean and SD were calculated for quantitative variables. A *p*-value lower than 0.05 was deemed as a significant level.

RESULTS

A total of 327 patients were included for analysis, of which 18 (5.5%) had developed VTE. Among the 327 patients, 176 (54.79%) had received prophylactic enoxaparin, of which 14 (77.78%) had developed DVT or PE. Among the remaining 141 patients, 4 (22.22%) were affected by DVT or PE, which was not statistically significant (*p*-value = 0.08).

Table 1 summarizes the frequency of developing VTE based on the patients' characteristics. It was found that there was no statistically significant difference between variables, including gender and head injury (*p*-value = 0.44 and 0.49, respectively). Moreover, the patients with two or more pelvic fracture sites were more prone to VTE than those with less than two pelvic fracture sites, which was statistically significant (*p*-value = 0.02). However, the presence of VTE was significantly higher in the individuals with a past history of VTE previously vs. patients with no history of VTE (*p*-value = 0.006).

Table 2 demonstrates the mean of laboratory data, including PT, PTT, INR, Hb, BE, and fibrin D-dimer, among patients with VTE in comparison to unaffected patients. There was no statistically significant correlation between the presence of VTE and the aforementioned laboratory data except for fibrin D-dimer, which was statistically higher in those who developed VTE (*p*-value = 0.004).

DISCUSSION

Our study demonstrated although the number of patients with a history of VTE was lower than those with negative history, the patients in that group were almost twice as likely to develop VTE, which was statistically significant (*p*-value = 0.02).

The aforementioned finding is in parallel with a study conducted by Lobo et al., who claimed that the history of VTE is the strongest risk factor for VTE in both univariate and multivariate analyses [16]. Nordstrom et al. [17] and Prandoni et al.[18] have also demonstrated that the history of previous VTE is a substantial risk factor for developing a new VTE after pelvic trauma fracture.

Based on our analysis, the presence of multiple fracture sites would increase the probability of VTE significantly (p value= 0.02). Huerta et al.[19] similarly displayed that a significant risk factor for PTE is multiple fractures. Furthermore, the parallel results were reported by Cafferata et al. [20] and Anderson Jr. et al. [21].

The difference in the mean of laboratory data of patients in the VTE group and their counterparts was not considerable except for fibrin D-dimer. Based on our result, the level of the D-dimer is significantly higher in those who developed VTE (*p*-value = 0.004). There is an overall agreement on D-dimer elevation during VTE in the literature, even though several studies have shown that this assay has a high negative predictive value and is a relatively sensitive but nonspecific marker for DVT [23]. Brotman et al. evaluated the utility and limitations of D-dimer testing for the evaluation of VTE in hospitalized patients [24]. Leclercq et al. reported no long-term thromboembolic complications in 64 patients using a combination of the D-dimer assay and clinical probability strategies to rule out PE in the outpatient setting [25]. A study by Dunn et al. had the largest cohort of patients with suspected PE undergoing D-dimer assay in the emergency department. The high negative predictive value (99.6%) led these authors to conclude that a negative D-dimer ELISA assay can almost always exclude PE in the emergency department setting [26]. From all stated above, we could say that the fibrin D-dimer level would display the probability of VTE significantly.

In a prospective single-cohort observational study by Norwood et al., the effectiveness of enoxaparin in preventing VTE was investigated in 118 seriously injured blunt trauma patients (ISS >16). Enoxaparin was initiated within 24 hours after admission. The authors concluded that

enoxaparin is a practical and effective agent for decreasing the incidence of VTE in high-risk, seriously injured patients [27]. On the contrary, the incidence of symptomatic VTE was 4.8% (12/250) in antithrombotic users and 4.3% (26/608) in nonusers, which was not statistically significant ($p = 0.718$), which was in parallel with our results.

Another review study by Walker et al., which included a database from 1946 to October 2016, showed that most VTE events occurred in the standard dosing regimen. It was pointed out that standard-dose enoxaparin prophylaxis may not be adequate for general trauma patients, and the application of weight-based enoxaparin dosing was recommended [28]. We also prescribed our patients the standard dose (5000 units Q12h) of enoxaparin.

The aforementioned statement was also supported by findings of another study by Rostas et al., which declared that subcutaneous enoxaparin dosing 30 mg twice a day (bid) is inadequate for most adult trauma patients, particularly obese patients. Thus higher doses are required to obtain desirable anticoagulation [29]. Both aforementioned studies have suggested that using the weight-based enoxaparin dosing (0.5 mg/kg/dose bid) is an option in trauma patients. Considering the decreased bioavailability of enoxaparin in critically ill patients, Nunez et al. conducted a prospective study and exhibited that a weight-based enoxaparin dosing regimen improves and increases anti-Xa levels [30]. This was in line with other studies [31, 32].

According to all the information stated above, the weight-based enoxaparin dosing would be more effective in preventing VTE; however, the risk of bleeding should also be considered.

The current study has the limitation that the medical records only included events that occurred during the hospital stay, so VTEs after discharge could not be recorded.

In conclusion, we found no significant correlation between the prophylactic doses of enoxaparin and VTE probability. For example, those with higher levels of fibrin D-dimer are at a higher risk of VTE. Furthermore, a history of VTE and more fracture sites would increase the likelihood of VTE.

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Table 1. The frequency of developing VTE in relation to the characteristics of patients.

Variable		**No VTE (n = 309)**	**VTE (n = 18)**	***p*-value**
Gender	Male	204 (45.58%)	14 (77.78%)	0.44
	Female	105 (54.42%)	4 (22.22%)	
Past history of VTE[a]	Yes	134 (43.37%)	14 (77.78%)	0.006
	No	175 (56.63%)	4 (22.22%)	
Pelvic fracture	Sites <2	117 (37.86%)	2 (11.1%)	0.02
	Sites ≥2	192 (62.14%)	16 (88.9%)	
Head injury	No	265 (85.8%)	17 (94.4%)	0.49
	Yes	44 (14.2%)	1 (5.6%)	
Outcome	Discharged	295 (95.5%)	15 (83.3%)	0.05
	Dead	14 (4.5%)	3 (16.7%)	
Prophylactic Enoxaparin	Yes	166 (54.79%)	14 (77.78%)	0.08
	No	137 (45.21%)	4 (22.22%)	

[a]VTE: venous thromboembolism.

Table 2. Mean values of laboratory data and their correlation with the occurrence of VTE.

	No VTE [a] **(n = 309)**	VTE **(n = 18)**	*p*-value
Laboratory data (mean ± SD)			
PT[b]	13.84 ± 2.66	13.06 ± 1.48	0.21
PTT[c]	36.22 ± 11.69	36.44 ± 7.97	0.94
INR[d]	1.29 ± 1.27	1.06 ± 0.25	0.44
Hb[e]	12.98 ± 4.36	12.65 ± 2.66	0.75
BE[f]	-2.99 ± 4.06	-2.87 ± 2.97	0.90
Fibrin D-dimer	13.81 ± 12.16	22.25 ± 5.31	**0.004**

[a]VTE: venous thromboembolism; [d]PT: prothrombin time; [e]PTT: partial thromboplastin time; [f]INR: international normalized ratio; [g]Hb: hemoglobin; [h]BE: base excess.