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Characterizing the delays in adequate thromboprophylaxis after TBI

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ABSTRACT

Background We sought to compare enoxaparin dosing for venous thromboembolism (VTE) prophylaxis in trauma patients with and without traumatic brain injury (TBI) to better understand the time and dose required to reach target anti-Xa levels. Our hypothesis was that patients with TBI have significant delays in the initiation of adequate pharmacological prophylaxis and require a higher enoxaparin dose than currently recommended.

Methods The medical records of trauma patients who received enoxaparin dosing based on anti-Xa trough levels between August 2014 and October 2016 were reviewed. Patients were included if their anti-Xa trough level reached the target range (0.1 IU/mL to 0.2 IU/mL).

Results A total of 163 patients had anti-Xa levels within the target range of which 41 (25.2%) had TBI. Patients with TBI had longer delays before initiating enoxaparin (7.5 days vs. 1.5 days after admission, p<0.01) and were more likely to receive unfractionated heparin prior to enoxaparin (46.3% vs. 11.5%, p<0.01). Anti-Xa levels reached the target range later in patients with TBI (11 days vs. 5 days after admission, p<0.01). Enoxaparin 40 mg two times per day was the median dose required to reach the target anti-Xa levels for both cohorts. VTE rates were higher among patients with TBI (22.0% vs. 9.0%, p=0.03). Four patients (9.8%) had progression of their intracranial hemorrhage prior to receiving enoxaparin, although none progressed during enoxaparin administration.

Conclusion Among patients with TBI who reached target anti-Xa levels, 11 days after admission were required to reach a median enoxaparin dose of 40 mg two times per day. Unfractionated heparin was used as pharmacological prophylaxis in about half of these patients. The delay in reaching the target anti-Xa levels and the use of unfractionated heparin likely contribute to the higher VTE rate in patients with TBI.

Level of evidence Level III, therapeutic.

INTRODUCTION

Compared with patients without traumatic brain injury (TBI), those with TBI are at a higher risk of developing venous thromboembolism (VTE).[1 2] This increased risk may be partially attributed to delayed initiation of pharmacological prophylaxis secondary to the concern for progression of intracranial hemorrhage (ICH).[2] In addition, despite broad research that favors enoxaparin for VTE prophylaxis after TBI instead of unfractionated heparin, practice patterns for pharmacological prophylaxis remain widely variable.[3–11] One study suggested unfractionated heparin dosed at 5000 U three times a day was proposed as 'non-inferior' to enoxaparin,[12] although more recently, enoxaparin 30 mg two times per day was considered superior at the prevention of VTE.[8 10 11]

The early initiation of enoxaparin is safe and associated with lower VTE rates.[11 13–25] Given that patients with TBI are at risk of ICH progression, the appropriate dosing of pharmacological prophylaxis remains elusive. The aim of this study was to compare the delay in reaching the target anti-Xa levels in trauma patients with and without TBI, as well as the median dose of enoxaparin required to achieve adequate VTE prophylaxis in patients with TBI. Our hypothesis was patients with TBI have significant delays in the initiation of adequate pharmacological prophylaxis and require higher doses of enoxaparin than currently recommended.

PATIENTS AND METHODS

Study design

We performed a retrospective review on trauma patients who received enoxaparin for pharmacological prophylaxis and reached target anti-Xa trough levels at our institution between August 2014 and October 2016. As this study required confirmation that an adequate enoxaparin dose was received, only trauma patients 18 years and older were included if their anti-Xa trough levels reached the target range (0.1 IU/mL to 0.2 IU/mL). Patients were excluded if no anti-Xa trough level reached the target range, which included patients who were discharged prior to receiving enoxaparin and those patients who had measured anti-Xa trough levels that did not reach the target range. Patients were also excluded if they did not receive enoxaparin due to renal impairment or heparin-induced thrombocytopenia, of if they were admitted with preexisting VTE or were on an anticoagulant or antiplatelet agent prior to admission. Patients were included if they were started on unfractionated heparin and then transitioned to enoxaparin dosing that reached target anti-Xa trough levels. If unfractionated heparin was administered, the dose was 5000 U subcutaneously three times a day.

Clinical characteristics such as age, sex, race, Body Mass Index (BMI), body surface area (BSA), creatinine clearance (CrCl), mechanism of injury, type of injury sustained, regional Abbreviated Injury Scale (AIS) scores, and Injury Severity Scores (ISS) were collected. Further details regarding pharmacological prophylaxis included the timing of

enoxaparin or unfractionated heparin, the anti-Xa trough levels, and all dose adjustments required were also collected.

Institutional VTE prophylaxis protocol

During the study period, trauma patients were started on subcutaneous enoxaparin 30 mg two times per day with adjustments made to reach a target anti-Xa trough level between 0.1 and 0.2 IU/mL. Trough levels were checked before the fourth consecutive dose as previously described.[13] Briefly, the anti-Xa trough level was obtained within 1 hour prior to the fourth dose of enoxaparin, processed in our laboratory and followed by our pharmacy department. Dose adjustments were made in increments of 10 mg two times per day, and anti-Xa levels were redrawn before the fourth dose of the new adjusted dose until the target range was reached.

The initiation of enoxaparin or unfractionated heparin was determined through a collaboration between the trauma and neurosurgical services with consideration given to the risk of bleeding, ICH, and anticipated surgical interventions. Once initiated, pharmacological prophylaxis could be held for operative procedures or suspected bleeding risk based on clinical judgment. Sequential compression devices were used for all patients unless specifically contraindicated by extremity injury. During the study period, the guidelines at our institution for patients with TBI recommended pharmacological prophylaxis within 24–48 hours of a CT of the brain that demonstrated no progression of ICH. A repeat CT of the brain was obtained 6 hours after the previous study if the previous study demonstrated progression. Further imaging was also obtained if there was a change in mentation or a worsening neurological examination. After achieving an enoxaparin dose that reached the target anti-Xa trough range, all trauma patients underwent continued anti-Xa monitoring and adjustments.

Outcome measures

The primary outcomes were days after admission until enoxaparin initiation, days after admission required to reach the anti-Xa level target range, and median enoxaparin dose required to reach the target range. The secondary outcomes included incidence of VTE, diagnosed by duplex ultrasonography for deep vein thrombosis (DVT) and chest CT angiography (CTA) for pulmonary embolisms (PEs). Upper and lower duplex ultrasonography and chest CTA were ordered in symptomatic patients based on clinical suspicion of VTE. Proximal lower extremity DVTs included those in the popliteal, femoral, or iliac veins, whereas distal lower extremity DVTs were located below the knee. Other outcomes data included the rate of unfractionated heparin dosing, intensive care unit (ICU) and hospital length of stay (LOS), transfusion requirements, the rate of ICH progression, and mortality.

Statistical analysis

Data were analyzed using SPSS V.24 statistical software and are summarized as percentages for categorical variables and as medians with IQR for continuous variables. Comparisons of medians were conducted using t test or Mann-Whitney U test, where appropriate. Categorical variables were compared using Pearson χ^2 test or Fisher exact test. A p value of <0.05 was considered statistically significant.

RESULTS

There were 4014 trauma patients reviewed during the study period from August 2014 to October 2016, of which 705 had TBI and 3309 did not. Of the 163 trauma patients who reached the target anti-Xa trough range, 41 (25.0%) had TBI. The cohorts were comparable with respect to age, sex, race, BMI, BSA, and CrCl (table 1). The median ISS was 18 in the study population, with patients with TBI having a higher ISS than patients without TBI (26 vs. 17, p<0.01).

During the study period, all brain trauma was the result of blunt injury. There was no difference between the specific mechanism resulting in blunt injury between TBI and non-TBI trauma patients (table 1). Likewise, the associated injury profiles were similar with a high rate of lower extremity fractures (29.4%), followed by spine fractures (26.4%). Patients with TBI commonly had a subdural hematoma (48.8%), followed by either a subarachnoid hemorrhage (43.9%) or a contusion (26.8%). The TBI cohort more likely required operative intervention (87.8% vs. 54.9%, p<0.01), most commonly for a percutaneous gastrostomy tube (48.8% vs. 8.2%, p<0.01) and tracheostomy (41.5% vs. 10.7%, p<0.01) (table 2).

Enoxaparin initiation was delayed in patients with TBI (7.5 vs. 1.5 days after admission, p<0.01), and a high percentage of these patients received unfractionated heparin prior to enoxaparin initiation (46.3% vs. 11.5%, p<0.01) (table 3). Furthermore, patients with TBI achieved the target anti-Xa range later (11 vs. 5 days after admission, p<0.01). The majority of patients in both cohorts (61.3%) were not within goal range at the first measurement and required at least one dose adjustment before reaching target anti-Xa trough levels. The median enoxaparin dose that reached the target anti-Xa range was 40 mg every 12 hours for both cohorts. Four patients in each cohort had an inferior vena cava (IVC) filter placed (9.8% vs. 3.3%, p=0.11). Three patients received an IVC filter in the TBI cohort due to contraindications for immediate therapeutic anticoagulation in the setting of a diagnosed DVT, whereas one patient received a filter because this patient had a previous hypercoagulable state with concurrent bleeding secondary to polytrauma. Similarly, three patients in the non-TBI cohort were diagnosed with a DVT and were not candidates for immediate therapeutic anticoagulation whereas one patient had a previous history of a PE. Imaging studies were obtained due to a clinical suspicion for VTE at similar rates and there was no difference as to when these studies were obtained.

VTE rates were significantly higher among patients with TBI (22.0% vs. 9.0%, OR 2.8 (1.1 to 7.5), p=0.03), and patients with TBI had more proximal DVTs (17.1% vs. 5.7%, OR 3.4 (1.1 to 10.3), p<0.01) (table 4). No patient was diagnosed with a PE. Patients with TBI were more likely to require admission to an ICU (92.7% vs. 73.0%, p<0.01). Both ICU LOS (14 vs. 3 days, p<0.01) and hospital LOS (21 vs. 12 days admission, p<0.01) were prolonged in patients with TBI; however, mortality rates were similar in both cohorts (4.9% vs. 2.5%, p=0.60). Four patients (9.8%) had progression of ICH prior to receiving enoxaparin. Importantly, no patients developed progression of their ICH or required operative procedures related to pharmacological prophylaxis during the period in which enoxaparin was administered.

DISCUSSION

We analyzed that patients with TBI received enoxaparin approximately 7.5 days after admission due in part to a high percentage of these patients receiving unfractionated heparin, and approximately 11 days after admission were required before patients with TBI reached the target prophylactic enoxaparin dose of 40 mg two times per day. After enoxaparin was started the median

Table 1 Patient characteristics and injury profile

Characteristic	Total (n=163)	TBI (n=41)	Non-TBI (n=122)	P value
Age (years), median	41 (29–60)	47 (32.5–59)	40 (29–60)	0.68
Male, n (%)	110 (67.5)	31 (75.6)	79 (64.8)	0.20
Race, n (%)				
Black	39 (23.9)	8 (19.5)	31 (25.4)	<0.01
White	72 (44.2)	16 (39.0)	56 (45.9)	
Hispanic	15 (9.2)	2 (4.9)	13 (10.7)	
Other/unknown	37 (22.7)	15 (36.6)	22 (18.0)	
BMI, median	24.8 (21.5–27.3)	25 (21.8–25.8)	24.7 (21.1–27.8)	0.57
CrCl (mL/min), median	107.4 (72.9–140.2)	111.5 (101.1.–168.0)	102.5 (46.4–125.4)	0.06
AIS Score, median				
Head/neck	0 (0–0)	4 (3–4)	0 (0–0)	<0.01
Face	0 (0–2)	0 (0–2)	0 (0–2)	0.28
Chest	0 (0–3)	0 (0–3)	0 (0–2)	0.71
Abdomen/pelvis	1 (0–3)	0 (0–2)	1 (0–3)	0.15
Extremity	0 (0–3)	0 (0–3)	0 (0–3)	0.99
External	0 (0–1)	1 (0–1)	0 (0–1)	0.09
ISS, median	18 (11–26)	26 (20.5–32)	17 (10–22)	<0.01
ISS without AIS head/neck, median	17 (10–20)	13 (5–18)	17 (10–22)	0.08
Mechanism of injury, n (%)				
Mechanism of injury, blunt, n (%)	141 (87.1)	41 (100)	101 (82.8)	<0.01
Automobile vs. pedestrian collision	22 (13.5)	4 (9.8)	18 (14.8)	0.07
Motorcycle collision	13 (8.0)	6 (14.6)	7 (5.7)	
Motor vehicle collision	40 (24.5)	6 (14.6)	34 (27.9)	
Fall	49 (30.1)	17 (41.5)	32 (26.2)	
Other	39 (23.9)	8 (19.5)	31 (25.4)	
Injury profile,* n (%)				
Intra-abdominal solid organ injury	19 (11.7)	4 (9.8)	15 (12.3)	0.78
Lower extremity fracture	48 (29.4)	11 (26.8)	37 (30.3)	0.82
Pelvic fracture	36 (22.1)	14 (34.1)	22 (18.0)	0.05
Spine fracture	43 (26.4)	13 (31.7)	30 (24.6)	0.49
Upper extremity fracture	29 (17.8)	12 (29.3)	17 (13.9)	0.09
Type of TBI,* n (%)				
Contusion	–	11 (26.8)	–	–
Epidural hematoma	–	6 (14.6)	–	–
Intraparenchymal hemorrhage	–	4 (9.8)	–	–
Subarachnoid hemorrhage	–	18 (43.9)	–	–
Subdural hematoma	–	20 (48.8)	–	–
Other	–	1 (2.4)	–	–

BMI calculated as weight in kilogram divided by height in meters squared.
*More than one injury type, type of TBI and operative intervention were possible for each patient.
AIS, Abbreviated Injury Scale; BMI, Body Mass Index; CrCl, creatinine clearance; ISS, Injury Severity Score; TBI, traumatic brain injury.

time required to reach a dose within the target anti-Xa range was 3.5 days for both patients with and without TBI. This delay was in part due to the need to increase the enoxaparin dose multiple times, as well as the time required between troughs. These findings provide guidance that a substantial delay exists between when pharmacological prophylaxis is initiated and when adequate prophylaxis is received.

Our result highlight two challenges in pharmacologic prophylaxis after TBI: (1) timely and (2) effective dosing. A subanalysis in a related study[23] that we performed demonstrated that 48.9% did not receive enoxaparin, of which 26.4% received unfractionated heparin, whereas the remainder did not receive any thromboprophylactic agent. Approximately 1.1% were not started on an agent due to bleeding, whereas 61.8% were either discharged or had an in-hospital mortality before one could be initiated. In this same study, we found that of the patients that were placed on enoxaparin; 75.0% did not achieve adequate anti-Xa levels; 6.4% died, whereas the remainder were discharged before attaining an adequate level. These data provide more insight into the delays that result in adequate dosing.

Although there was no statistical difference as to when a VTE was first diagnosed in this study, diagnosis in the TBI cohort appeared to occur later. This trend may be due to altered mental status secondary to TBI or ventilator dependence, which may impact a clinician's ability to detect a symptomatic VTE, thus leading to later diagnosis. VTE may occur even earlier in patients

Table 2 Comparison of operative interventions

	No. (%)			
	Total (N=163)	TBI (n=41)	Non-TBI (n=122)	P value
Operative interventions,* n (%)				
Patients requiring operative intervention	103 (61.7)	36 (87.8)	67 (54.9)	<0.01
Cardiothoracic operation	1 (0.6)	1 (2.4)	0	0.25
Craniectomy/craniotomy	–	7 (17.1)	–	–
Exploratory laparotomy	22 (13.5)	3 (7.3)	19 (15.6)	0.28
Oral and maxillofacial operation	18 (11.0)	8 (19.5)	10 (8.2)	0.08
Other othopedic operation	58 (35.6)	19 (46.3)	39 (32.0)	0.14
Percutaneous gastrostomy tube placement	30 (18.4)	20 (48.8)	10 (8.2)	<0.01
Spinal operation	12 (7.4)	2 (4.9)	10 (8.2)	0.72
Tracheostomy	30 (18.4)	17 (41.5)	13 (10.7)	<0.01
Vascular repair	4 (2.5)	0	4 (3.3)	0.57

*More than one injury type, TBI, and operative intervention were possible for each patient.
TBI, traumatic brain injury.

with TBI. Given that the inclusion criteria for this study required patients who remained hospitalized until they reached target anti-Xa trough levels, this cohort represents a subset of patients that were inherently more complex than typical trauma patients. Our data demonstrate that many of these patients had additional injuries and required interventions which may have precluded early pharmacological thromboprophylaxis.

The concern for ICH progression is one reason for delay in timely dosing, although 46.3% of the patients were started on unfractionated heparin prior to receiving enoxaparin, suggesting that many patients were able to receive pharmacological prophylaxis. Fear of ICH progression often delays the initiation of enoxaparin, although increasingly it is administered early after brain trauma.[23–32] Prospective data established that enoxaparin 24 hours after admission was safe for some patients with TBI.[24 25] Subsequently, the decision to initiate pharmacological prophylaxis was based on whether or not ICH progression was observed on the follow-up CT.[26 31 32] If ICH progression was noted, exposure to pharmacological prophylaxis predicted further progression. If no ICH progression was observed, then pharmacological prophylaxis was encouraged.[26 31 32] The rate of ICH progression was about 10% whether or not pharmacological prophylaxis was initiated.[26] When early pharmacological prophylaxis is initiated after TBI, there is a lower VTE rate with no difference in rate of late neurosurgical intervention.[27 31 32]

Since approximately half of the patients with TBI studied were initiated first on unfractionated heparin prophylaxis, the belief that unfractionated heparin is somehow safer than enoxaparin persists despite evidence that the opposite may be true as unfractionated heparin is associated with a higher rate of ICH progression.[3] As enoxaparin has increased bioavailability, longer plasma half life, more predictable pharmacokinetics and pharmacodynamics,[8] interacts less with platelets, and has a lower incidence of heparin-induced thrombocytopenia compared with unfractionated heparin[33] the belief that unfractionated heparin is safer is unfounded.

Unfractionated heparin at 5000 U three times a day continues to be proposed as 'non-inferior' to enoxaparin in part due to a trial that concluded the two medication may have similar VTE rates.[12] This trial was underpowered to demonstrate the actual difference in the VTE rate as it predicted a VTE rate of 44% for unfractionated heparin and 31% for enoxaparin instead of the observed rate of 8.2% for unfractionated heparin and 5.1% for enoxaparin (p=0.2).[8 12] In addition, the trial was not powered to detect a difference in the rate of PE or HIT, both of which impact the complication rate and healthcare costs.[8 10] More recently, enoxaparin 30 mg two times per day was established as superior to unfractionated heparin 5000 U three times a day at reducing VTE.[8 10 11]

The optimal dose for many patients in this study was 40 mg two times per day. At our institution, all trauma patients are started on enoxaparin 40 mg two times per day unless one or more of the following exclusions apply: TBI, spinal cord injury, suspicion for ongoing bleeding, evidence of acute or chronic kidney disease, or 65 years of age or older. Our data demonstrate that the majority of patients with TBI require enoxaparin 40 mg two times per day or higher. The decision to initiate patients with TBI with enoxaparin 40 mg two times per day, in an effort to minimize the time to achieve adequate thromboprophylaxis, will require further investigation. Customized dosing using the

Table 3 Details regarding enoxaparin administration

	Total (N=163)	TBI (n=41)	Non-TBI (n=122)	P value
Time to initiate enoxaparin, median d	2 (1–6)	7.5 (3–10)	1.5 (1–4)	<0.01
Days to first anti-Xa level drawn, median d	4 (2–7)	9 (5–11.5)	3 (2–6)	<0.01
Within goal at first measure, n (%)	63 (38.7)	15 (36.6)	48 (39.3)	0.75
Days to reach goal (from admission), median d	6 (6–13)	11 (7–16)	5 (2–10)	<0.01
Dose adjustments to reach goal, median n	1 (0–1)	1 (0–2)	1 (0–1)	0.61
Optimal dose based on anti-Xa levels (mg), median	40 (30–40)	40 (30–50)	40 (30–40)	0.73
Patients given prophylactic unfractionated heparin prior to enoxaparin, n (%)	33 (20.2)	19 (46.3)	14 (11.5)	<0.01
Days to initiate prophylactic unfractionated heparin, median d	3 (1–3)	3 (2–4)	1 (0–3)	0.01
Patients who underwent IVC filter placement, n (%)	8 (4.9)	4 (9.8)	4 (3.3)	0.11
Duplex ultrasonography ordered based on clinical suspicion, n (%)	50 (30.7)	13 (31.7)	37 (30.3)	0.87
Days to first duplex ultrasonography performed, median d	7.5 (5–12)	10 (6.5–13)	6 (4–11)	0.07
Chest CT angiography ordered, n (%)	22 (13.5)	6 (14.6)	16 (13.1)	0.81
Days to first chest CT angiography based on clinical suspicion, median d	8 (5–18)	16.5 (8–22)	7 (5–12)	0.25

IVC, inferior vena cava; TBI, traumatic brain injury.

Table 4 Outcomes in patients with TBI and patients without TBI

	Total (N=163)	TBI (n=41)	Non-TBI (n=122)	OR or mean difference (95% CI)	P value
VTE outcomes					
VTE, n (%)	20 (12.3)	9 (22.0)	11 (9.0)	2.8 (1.1 to 7.5)	0.03
Proximal DVT	14 (8.6)	7 (17.1)	7 (5.7)	3.4 (1.1 to 10.3)	<0.05
Distal DVT	16 (9.8)	7 (17.1)	9 (7.4)	2.6 (0.9 to 7.5)	0.12
PE	0	0	0	0	>0.99
Days to first VTE diagnosis (from admission), median d	15 (8.5–18)	16 (13.5–20)	7 (4–17)	5.2 (–0.4 to 10.9)	0.09
Blood transfusions					
Required blood while on enoxaparin, n (%)	20 (12.3)	4 (9.8)	16 (13.1)	0.7 (0.2 to 2.3)	0.57
Overall outcomes					
ICU LOS, median d	4 (1–12)	14 (4–20.5)	3 (1–7)	8.8 (5.2 to 12.5)	<0.01
Hospital LOS, median d	14 (7–23)	21 (14–34)	12 (6–20)	12.3 (4.0 to 20.5)	<0.01
Mortality, n (%)	5 (3.1)	2 (4.9)	3 (2.5)	2.0 (0.3 to 12.6)	0.60

DVT, deep vein thrombosis; ICU, intensive care unit; LOS, length of stay; PE, pulmonary embolism; TBI, traumatic brain injury; VTE, venous thromboembolism.

patient's creatinine dosing may result in better optimized initial enoxaparin dosing.[34 35]

This study was limited by its small size and lack of randomization. At times, disagreement occurred between the trauma and neurosurgical services regarding appropriate pharmacological prophylaxis for patients with TBI. This study could not capture the reasons for missed enoxaparin doses. As noted, the two cohorts were not similar with regard to injury severity so the higher VTE rate in patients with TBI could be attributable to reasons other than delayed or inadequate pharmacological prophylaxis. Importantly, the objective of this article was to characterize the delay until an adequate dose of enoxaparin was received in patients with and without brain trauma and not to compare the VTE rates between these cohorts. Despite these limitations, we demonstrated that unfractionated heparin and low enoxaparin doses could be reasons for higher VTE rates in patients with TBI. Although the Brain Trauma Foundation established that there is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacological prophylaxis, these recommendations may be outdated.[36] Partly due to the findings of this study, we have collaborated with our neurointensivist and neurosurgical colleagues at our institution to implement earlier initiation of enoxaparin.

In conclusion, based on anti-Xa levels 11 days after admission were required before patients with TBI received an adequate enoxaparin dose for pharmacological prophylaxis due to delays in its initiation and because unfractionated heparin was frequently used as an intermediate agent. The median enoxaparin dose required to reach target anti-Xa levels for both patients with TBI and patients without TBI was 40 mg two times per day. The early administration of enoxaparin titrated by anti-Xa trough levels should be strongly considered for patients with TBI. A prospective randomized clinical trial with a larger TBI cohort is recommended to improve VTE prophylaxis for this population.

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