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Retrospective evaluation of chemical venous thromboembolism prophylaxis in traumatic brain injury

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ABSTRACT

Background: Traumatic brain injury (TBI) is a risk factor for venous thromboembolism (VTE) but few studies address optimal timing or choice of agent.

Materials and Methods: Retrospective review of moderate to severe TBI patients receiving chemical VTE prophylaxis (early initiation [≤ 72 h from admission], late [> 72 h to 7 days], or delayed [> 7 days]) between 2012 through 2017. Primary outcome was VTE occurrence. Secondary objectives evaluated intracranial hemorrhage (ICH) requiring cessation of prophylaxis and differences between unfractionated (UFH) and low-molecular weight heparin (LMWH).

Results: A total of 198 patients were evaluated; median age was 44 years (IQR 25–60), median Glasgow Coma Scale score 3 (IQR 3–7), and median injury severity score 27 (IQR 22–34). Ten percent of patients ($n = 20$) developed VTE. Median time to VTE prophylaxis was 81 h (IQR 53–152) and there was no difference in VTE incidence across all groups ($p = 0.09$). Intergroup comparison showed patients that received early prophylaxis had lower VTE rates (6% vs. 16%, $p = 0.04$) and mortality (3% vs. 15%, $p = 0.02$) compared to late initiation (but not delayed). There were no instances of new onset or expanded ICH requiring cessation of prophylaxis. VTE rates for patients receiving UFH only or LMWH only, 14/115 (12.2%) vs. 3/46 (6.5%), were not different ($p = 0.4$). Mortality was lower in the LMWH only group (0% vs. 13.0%, $p<0.01$).

Conclusions: Initiating VTE prophylaxis within 72 h of moderate to severe TBI appears to be safe and may be associated with lower rates of VTE and mortality.

1. Introduction

Traumatic brain injury (TBI) has been found to be an independent risk factor for the development of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) [1]. DVT occurs in approximately one third of patients with severe TBI with isolated head injuries and even more frequently in patients with additional extracranial injuries [2]. Risk of VTE further increases with severity of TBI [3]. There are currently no standardized guidelines on providing VTE prophylaxis for patients with TBI. The 2016 Brain Trauma Foundation guidelines on DVT prophylaxis state that there is insufficient evidence to support a recommendation for preferred agent, dose, or timing of chemoprophylaxis in TBI [4]. The 2020 Western Trauma Association (WTA) guidelines to reduce VTE in trauma patients recommend that most TBI patients with a stable follow-up computed tomography (CT) scan may be initiated on enoxaparin prophylaxis within 24 h [5]. Furthermore, they recommend that almost all TBI patients should receive at least some form of pharmacologic prophylaxis within 72 h of injury [5]. The 2021 American Association for the Surgery of Trauma (AAST) Clinical Consensus guidelines echo these recommendations [6]. However, a survey of Eastern Association for the Surgery of Trauma (EAST) members report the practice of chemical VTE prophylaxis use to be highly variable [7]. This inconsistency also appears to be based on the American College of Surgeons (ACS) designation of an institution (level I vs level II trauma center) [8]. Several studies have confirmed that patients with TBI receiving VTE prophylaxis had lower rates of thromboembolism and/or mortality; however, conflicting data exist on whether these regimens increase the risk of

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progression or development of intracranial hemorrhage (ICH) [9–12]. In addition, few studies have examined closely the optimal timing of administration or choice of agent in VTE prophylaxis upon admission for TBI [13–15]. Without a published standard of care, these factors are likely to vary widely across institutions or clinicians. The intent of this study is to retrospectively examine the timing of VTE prophylaxis, the choice of agent, and dosing of these agents in patients presenting with moderate to severe TBI.

2. Materials and methods

2.1. Study design and patient population

A single-center, retrospective, observational study was conducted at an 886-bed academic medical center with ACS Level I trauma designation. All adult patients (≥17 years) with moderate to severe TBI (Glasgow Coma Scale [GCS] score ≤ 12 at initial emergency department [ED] evaluation), discharged from the hospital between January 1, 2012 and December 31, 2017 were screened for inclusion. Patients were included if they received at least one dose of prophylactic unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) by day 14 of admission. Patients were identified from an intradepartmental database (i.e., trauma registry) as well as the electronic medical record (EMR). Patients were excluded based on the following criteria: chronic venous insufficiency or peripheral vascular disease, hypercoagulability or inherited thrombophilia, active cancer diagnosis, history of deep vein thrombosis or pulmonary embolism, death within 72 h of admission, penetrating brain injury, or therapeutic anticoagulation or antiplatelet therapy prior to admission. The study was approved by the Institutional Review Board and the requirement for informed consent was waived.

Information obtained from the trauma registry included patient age, sex, race, height and weight, date/time of injury (if known), date/time of admission, GCS at ED admission, injury severity score (ISS), abbreviated injury scale (AIS) and AIS body regions affected, intensive care unit (ICU) and hospital length of stay (LOS), and disposition. A manual chart review was conducted to gather information on cause of injury, type of TBI, timing, dosing and choice of agent used for VTE prophylaxis, presence of intermittent pneumatic compression devices (IPCs), presence of a peripherally inserted central catheter (PICC), and development of a thromboembolism or expansion of ICH.

2.2. Outcomes

The primary objective of the study was to determine if patients who received early initiation of VTE prophylaxis (≤ 72 h from admission) had a decreased risk of thromboembolism within the hospitalization compared to those with late (> 72 h to 7 days) or delayed initiation (> 7 days). Secondary objectives were to determine if early initiation had an increased risk of new onset or expansion of ICH requiring cessation of VTE prophylaxis, to determine if UFH or LMWH was associated with lower risk of VTE, and to compare in-hospital mortality rates between early, late, and delayed prophylaxis. Only patients that received UFH alone or LMWH alone throughout their hospitalization were included in the secondary analysis of these outcomes. If patients received one agent and were changed at any point of the hospitalization they were excluded from this secondary analysis.

2.3. Data analysis

Patient demographics are reported descriptively. Continuous variables were analyzed using a Wilcoxon Rank Sum Test or Kruskal-Wallis Test, as appropriate. Categorical variables were analyzed using Fisher's Exact test.

3. RESULTS

3.1. Baseline characteristics

A total of 2093 patients were screened for inclusion, of which 358 patients met inclusion criteria based on age and severity of TBI. Further screening resulted in an additional 159 patients being excluded (Fig. 1). Therefore, 198 patients were included in the study.

Baseline characteristics were similar across the early, late, and delayed prophylaxis groups (Table 1). The majority of patients were white (80.3%), male (74.2%), with a median age of 44.2 years (IQR 25.3–59.7). Most patients experienced a subarachnoid injury (70.2%), followed by subdural (51.5%). The most common causes of TBI were motor vehicle accident (57.1%) and fall (23.7%). Overall, median time to VTE prophylaxis was 80.6 h (IQR 52.7–151.8). Median time to VTE prophylaxis was 50.8 h (IQR 37.8–61.4), 106.2 h (IQR 87.3–137.2), and 221.6 h (IQR 193.5–287.9) in the early, late, and delayed prophylaxis groups, respectively. Hospital length of stay did not differ significantly between the groups; however, patients in the late and delayed groups had significantly longer ICU LOS.

Most patients (168/198, 84.8%) were classified as severe TBI (GCS 3–8) with a median GCS of 3 (IQR 3–7). The median ISS of all patients was 27 (IQR 22–34); however, there was a significant difference in ISS across the early, late and delayed prophylaxis groups ($p<0.001$), with increasing severity in the late and delayed groups, respectively. Escalating ISS was reflective of increasing rates of extremity and pelvic girdle injury ($p = 0.008$). Median head AIS was also significantly different between groups, with a higher distribution of scores in the delayed group.

There were no significant differences across early, late, and delayed groups in percentage of patients that received UFH for prophylaxis. Similar results were found for enoxaparin and dalteparin (Table 1). Unfractionated heparin was the most commonly used agent for VTE prophylaxis with 76.3% of patients receiving at least one dose. A total of 161 patients received one agent or the other throughout their hospitalization, but 37 (18.7%) were initiated on one agent and then transitioned to another agent during hospitalization based on clinician preference.

3.2. Clinical outcomes

A total of 20 patients (10.1%) developed a VTE during hospitalization. There was no significant difference in incidence of VTE across all three groups ($p = 0.09$) (Fig. 2). However, patients who received early prophylaxis had significantly lower rates of VTE than those with late initiation (5.7% vs. 16.2%, $p = 0.04$), but there was no significant difference in VTE between late and delayed ($p = 0.4$) or early versus delayed ($p = 0.47$) (Fig. 2). There were no episodes of new onset or expansion of ICH in any groups requiring cessation of VTE prophylaxis.

There was no significant difference in VTE rates between patients receiving UFH only or LMWH only (14/115 [12.2%] vs. 3/46 [6.5%], $p = 0.4$); however, patients in the LMWH only group had lower rates of mortality (0% vs. 13.0%, $p<0.01$). Patients in the LMWH only group were significantly younger than those in the UFH only group (median age 35 years vs. 50 years, $p = 0.02$) and had lower baseline rates of subarachnoid, subdural, and epidural bleeding with lower median head AIS. Differences in baseline characteristics among these groups are further described in Table 2.

A total of 154 patients (77.8%) had an active order for mechanical VTE prophylaxis during hospitalization. Fourteen patients (9.1%) with an order for IPCs had thromboembolic complications versus 6 (13.6%) in those without an active order ($p = 0.4$).

Sixteen patients died during hospitalization (8.1%). There was a significant difference in-hospital mortality across the three prophylaxis groups ($p = 0.04$), which reflects the higher rate of mortality in the late group versus the early group (14.7% vs. 3.4%, $p = 0.02$). There was no

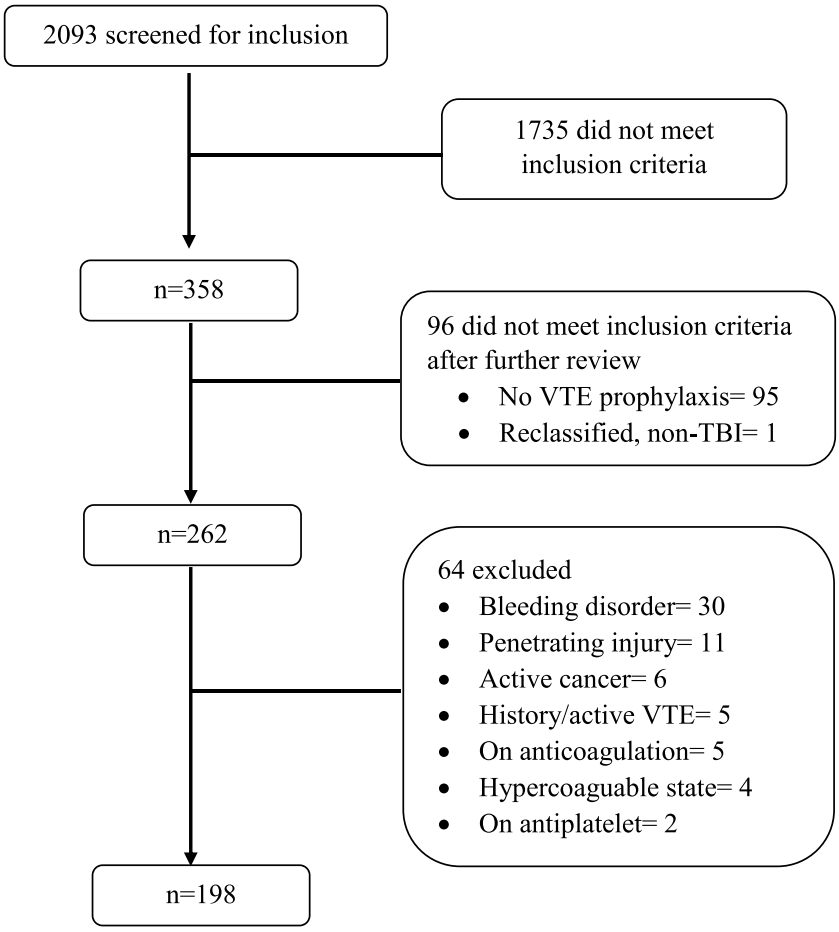

Fig. 1. Flow diagram of subject selection.
Abbreviations: VTE = venous thromboembolism, TBI = traumatic brain injury

significant difference in mortality between late and delayed ($p = 0.36$) or early and delayed ($p = 0.39$) groups (Fig. 2). Twenty percent of patients who developed a VTE died compared to 6.7% without a VTE, however, this difference was not significant ($p = 0.06$).

A logistic regression was planned to model clinically relevant parameters influencing the development of VTE, however, due to low enrollment and overall low event rates, we were unable to appropriately perform this analysis.

4. Discussion

Patients with TBI are at increased risk of thromboembolic events compared with the general trauma population. Previous studies have shown that chemical VTE prophylaxis significantly reduces the risk of VTE in patients with TBI [9-11,15]. In addition, recent data have supported earlier initiation of prophylaxis with low risk of bleeding [10,12, 14,15]. Despite this, there is significant variability among clinical practice as to ideal timing of prophylaxis, choice of agent, and dosing.

Results from this retrospective analysis demonstrate early initiation of VTE prophylaxis appears to be safe as no patients required cessation of VTE prophylaxis due to concerns for ICH during hospitalization. Result may also suggest that early initiation of VTE prophylaxis ($\leq$ 72 h) in moderate to severe traumatic brain injury is associated with lower rates of both VTE and mortality compared to late initiation ($>$ 72 h to 7 days). However, it should be noted that the early prophylaxis group had significantly lower ISS and ICU LOS, which likely contributed to these findings as less severely injured patients were started on prophylaxis earlier. Overall, these findings were similar to those of previous literature [14]. A large retrospective cohort study of 20,417 patients with isolated severe blunt head injury (AIS $\geq$ 3) showed that initiation of prophylaxis after 72 h was an independent risk factor for both mortality and VTE complications in multivariate analysis [14].

Previous literature has suggested the superiority of LMWH over UFH for VTE prophylaxis in TBI [14–16]. In our analysis, there were no deaths in the LMWH only group versus 15 (13%) in the UFH only group. LMWH was associated with a significantly lower rate of mortality ($p<0.01$); however, there was no significant difference in rate of VTE between the agents (6.5% vs. 12.2%, $p = 0.4$). While these results are supported by previous literature, they should be interpreted cautiously. When examining baseline characteristics of patients that received UFH compared to LMWH regimens, patients that received LMWH only were significantly younger and had lower baseline rates of subarachnoid, subdural, and epidural bleeding. In-hospital mortality rates may have been decreased by improved outcomes overall in younger TBI patients [17].

In addition to chemical VTE prophylaxis, mechanical prophylaxis has been suggested to reduce the risk of thromboembolic complications. The 2016 Brain Trauma Foundation guidelines recommend the addition of compression stockings to all patients for VTE prophylaxis as part of the standard of care; however, the guideline authors suggest that there is an insufficient body of evidence for this recommendation that is specific to TBI [4]. Our study found no difference in rate of VTE between those that had an active order for IPCs versus those that did not. One limitation of our data is the inability to determine how consistently patients were receiving mechanical prophylaxis, rather this data merely reflects if there was an active order in the EMR.

One unique advantage of our study was the inclusion of polytrauma patients with extracranial injuries, with a median ISS of 27 (IQR 22–34).

Table 1
Patient characteristics by time to prophylaxis.

	Early (n = 88)	Late (n = 68)	Delayed (n = 42)	p-value
Sex, n (%)				
Male	66 (75.0)	49 (72.1)	32 (76.2)	0.89
Female	22 (25.0)	19 (49.0)	10 (23.8)	
Race, n (%)				
White	75 (85.2)	53 (77.9)	31 (73.8)	0.25
Age, median (IQR)	47.3 (28.8–61.4)	42.4 (25.6–59.7)	35.1 (22.3–52.8)	0.11
Weight, mean kg (IQR)	78.0 (68.0–89.5)	82.0 (70.3–90.0)	81.0 (72.3–90.5)	0.19
GCS, median score (IQR)	4 (3–8)	3 (3–7)	3 (3–5)	0.09
ISS, median score (IQR)	24 (17–29)	29 (25–38)	33 (27–38)	<0.01
Extremities/pelvic girdle	38 (43.2)	33 (48.5)	30 (71.4)	<0.01
AIS-head, median score (IQR)	4 (3–5)	4 (3–5)	4 (4–5)	0.04
Location of brain injury, n (%)				
Subarachnoid	59 (67)	48 (70.6)	32 (76.2)	0.58
Subdural	38 (43.2)	37 (54.4)	27 (64.3)	0.07
Epidural	5 (5.7)	7 (10.3)	4 (9.5)	0.49
VTE prophylaxis agent, n (%)				
Unfractionated heparin	65 (73.9)	54 (79.4)	33 (78.6)	0.6
Enoxaparin	33 (37.5)	23 (33.8)	12 (28.6)	0.72
Dalteparin	6 (6.8)	5 (7.3)	5 (11.9)	0.59
Time to VTE prophylaxis, median hours (IQR)	50.8 (37.8–61.4)	106.2 (87.3–137.2)	221.6 (193.5–287.9)	<0.01
Central venous catheter, n (%)	27 (31.8)	28 (41.2)	17 (40.5)	0.42
Length of stay, median days (IQR)				
Hospital	16 (10–27.3)	20 (15–31.3)	20.5 (13–30)	0.06
ICU	9.6 (3.6–18.2)	14 (8.5–22.5)	16 (6.8–22.2)	0.01
Rate of VTE, n (%)	5 (5.7)	11 (16.2)	4 (9.5)	0.09

Abbreviations: IQR = interquartile range, GCS = Glasgow Coma Scale, ISS = Injury Severity Score, AIS = Abbreviated Injury Scale, VTE = venous thromboembolism, ICU = intensive care unit.

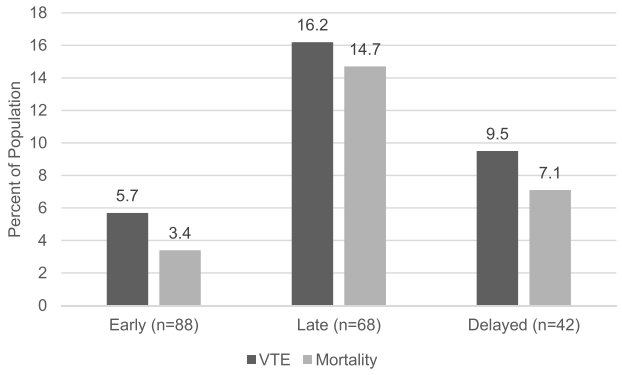

Fig. 2. VTE incidence and mortality by time to prophylaxis groups.
Abbreviations: VTE = venous thromboembolism

Extracranial injuries, particularly lower extremity injury, are known to be independent predictors for DVT [2]. We therefore predicted that inclusion of polytrauma patients would result in a higher overall rate of VTE, which was not demonstrated. There was no significant difference in rate of VTE in those with lower extremity/pelvic girdle injury versus those without (65.0% vs. 35.0%, $p = 0.24$). By including this population,

Table 2
Patient characteristics by VTE prophylaxis agent.

	UFH only (n = 115)	LMWH only (n = 46)	p-value
Sex, n (%)			
Male	87 (75.7)	35 (76.1)	>0.999
Female	28 (24.3)	11 (23.9)	
Race, n (%)			
White	92 (80.0)	38 (82.6)	0.83
Age, median years (IQR)	50.3 (26.4–61.0)	35.4 (23.5–49.5)	0.02
Weight, median kg (IQR)	78.0 (68.0–89.5)	82.0 (70.3–90.0)	0.48
GCS, median score (IQR)	3 (3–8)	3 (3–7)	0.27
ISS, median score (IQR)	27 (22–34)	29 (21–38)	0.69
Extremities/pelvic girdle	55 (47.8)	25 (54.3)	0.49
AIS-head, median score (IQR)	4 (3–5)	3 (3–5)	0.04
Location of brain injury, n (%)			
Subarachnoid	92 (80.0)	23 (50.0)	<0.01
Subdural	74 (64.3)	12 (26.1)	<0.01
Epidural	14 (12.2)	0 (0.0)	0.01
Time to VTE prophylaxis, median hours (IQR)	84.4 (60.3–163.3)	74.5 (40.0–137.8)	0.06
Time to VTE prophylaxis groups, n (%)			0.77
Early	25 (21.7)	9 (19.6)	
Late	50 (43.5)	23 (50)	
Delayed	40 (34.8)	14 (30.4)	
Rate of VTE, n (%)	14 (12.2)	3 (6.5)	0.4

Abbreviations: UFH = unfractionated heparin, LMWH = low molecular weight heparin IQR = interquartile range, GCS = Glasgow Coma Scale, ISS = Injury Severity Score.

results of this analysis are pragmatic and thus more applicable to the population seen at most ACS Level I trauma centers. However, due to the overall low rate of VTE, we cannot exclude the possibility that lack of power may have resulted in statistical non-significance.

There were several limitations to our study. An unanticipated but significant limitation was low enrollment. While over 2000 patients were initially identified for screening, only 198 patients were included in the final analysis. The majority of patients did not meet inclusion criteria based on severity of TBI or missing data for initial GCS. While these criteria led to significant reductions in our population, we felt this was an important distinction to only include moderate to severe traumatic brain injury due to the clinical significance as well as increased risk of VTE associated with this level of injury. In addition, our strict exclusion criteria may have contributed to the removal of a high-risk group on prior-to-admission anticoagulation and may have limited the external validity of these results. Another limitation of our study was that we were unable to quantify the number of VTE prophylaxis doses administered or missed and did not routinely monitor anti-Xa levels to assess serum medication concentrations.

One unexpected finding in our data were lower rates of VTE and mortality in the delayed prophylaxis group versus the late prophylaxis group. The delayed prophylaxis group generally had more severe polytrauma and higher rates of lower extremity injury. We predict that VTE prophylaxis may have been intentionally delayed in these patients due to concern for higher risk of bleeding with complicated extracranial injuries, but are unable to assess this with the retrospective nature of our study. It is unclear why these patients with more severe injury had lower rates thromboembolic events and mortality. These results are possibly a result of survivorship bias, as those that were more critically injured most likely died within 7 days and were therefore not included in the delayed group. In addition, we were limited by the inability to follow patients after discharge. We cannot exclude the possibility that patients in the delayed prophylaxis group developed complications after discharge that were not accounted for.

This is a single-center study completed between 2012 and 2017 which may impact the external validity. During this time frame, there

were significant changes to our internal clinical practice which may have influenced time to prophylaxis and choice of agent. For example, dalteparin was removed from hospital formulary and replaced with enoxaparin as the LMWH agent of choice, possibly influencing the low overall use of this agent. Also, due to limited enrollment and low event rate, logistic regression to evaluate mortality between these two regimens, UFH and LMWH, was not possible. Lastly, we sought to analyze not only timing of VTE prophylaxis, but also drug and dosing. However, given the high degree of heterogeneity of drug regimens, dosing was unable to be analyzed to produce any meaningful data. Future prospective studies should aim to assess doses of UFH and LMWH, considering patient specific factors such as weight and renal function.

5. Conclusions

Findings from this retrospective analysis suggest that early initiation of VTE prophylaxis ($\leq$ 72 h after admission) appears to be safe and may be associated with lower rates of VTE and mortality compared to late initiation ($>$ 72 h). Large, prospective, randomized controlled trials are needed to further evaluate optimal timing, agent and regimen for VTE prophylaxis in moderate and severe TBI.

Author contribution statement

The authors confirm contribution to the manuscript as follows: EH, SR, JC, JP contributed to the study conception and design, EH completed data collection, EH and SR completed data analysis and EH, SR, JC, JP helped to interpret the data. EH drafted the manuscript and SR, JC, JP contributed substantially to revisions. EH takes responsibility for the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Disclosure

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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