Early venous thromboembolism prophylaxis in patients with trauma intracranial hemorrhage: Analysis of the prospective multicenter Consortium of Leaders in Traumatic Thromboembolism study

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BACKGROUND: The optimal time to initiate venous thromboembolism prophylaxis (VTEp) for patients with intracranial hemorrhage (ICH) is controversial and must balance the risks of VTE with potential progression of ICH. We sought to evaluate the efficacy and safety of early VTEp initiation after traumatic ICH.

METHODS: This is a secondary analysis of the prospective multicenter Consortium of Leaders in the Study of Thromboembolism study. Patients with head Abbreviated Injury Scale score of > 2 and with immediate VTEp held because of ICH were included. Patients were divided into VTEp ≤ or >48 hours and compared. Outcome variables included overall VTE, deep vein thrombosis (DVT), pulmonary embolism, progression of intracranial hemorrhage (pICH), or other bleeding events. Univariate and multivariate logistic regressions were performed.

RESULTS: There were 881 patients in total; 378 (43%) started VTEp ≤48 hours (early). Patients starting VTEp >48 hours (late) had higher VTE (12.4% vs. 7.2%, $p = 0.01$) and DVT (11.0% vs. 6.1%, $p = 0.01$) rates than the early group. The incidence of pulmonary embolism (2.1% vs. 2.2%, $p = 0.94$), pICH (1.9% vs. 1.8%, $p = 0.95$), or any other bleeding event (1.9% vs. 3.0%, $p = 0.28$) was equivalent between early and late VTEp groups. On multivariate logistic regression analysis, VTEp >48 hours (odds ratio [OR], 1.86), ventilator days >3 (OR, 2.00), and risk assessment profile score of ≥5 (OR, 6.70) were independent risk factors for VTE (all $p < 0.05$), while VTEp with enoxaparin was associated with decreased VTE (OR, 0.54, $p < 0.05$). Importantly, VTEp ≤48 hours was not associated with pICH (OR, 0.75) or risk of other bleeding events (OR, 1.28) (both p = NS).

CONCLUSION: Early initiation of VTEp (≤48 hours) for patients with ICH was associated with decreased VTE/DVT rates without increased risk of pICH or other significant bleeding events. Enoxaparin is superior to unfractionated heparin as VTE prophylaxis in patients with severe TBI. (*J Trauma Acute Care Surg.* 2023;95: 649–656. Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level IV.

KEY WORDS: Traumatic brain injury; intracranial hemorrhage; venous thromboembolism; deep vein thrombosis; pulmonary embolus; chemoprophylaxis.

Traumatic brain injury (TBI) is known to be a major and independent risk factor associated with the development of venous thromboembolism (VTE) after trauma.[1–4] The incidence of VTE in TBI patients ranges from 20% to 54% in different studies of TBI or TBI subgroups.[5–7] The underlying pathophysiology of VTE and how it is impacted by TBI are multifactorial and only partly understood at this time. First, immobilization after TBI and associated injuries will cause venous stasis and enhanced clot formation. Second, the postinjury systemic inflammatory response, comprising a series of alteration of coagulation function that frequently culminate in a prothrombotic state, will create an environment for VTE formation.[8,9] In addition, VTE prophylaxis with anticoagulant medications including unfractionated (UF) or low-molecular-weight heparins (LMWH) is frequently delayed or even foregone in patients with intracranial hemorrhage (ICH) because of the fear of bleeding progression and associated neurologic complications or need for surgical intervention.[10,11]

Both deep vein thrombosis (DVT) and pulmonary embolism (PE) can lead to serious consequences. The acute propagation of DVT to PE or the formation of de novo pulmonary thrombosis (PT) can result in significant morbidity or even mortality. Autopsy studies in trauma patients have reported PE as the third leading cause of deaths after 72 hours.[12] The postthrombotic syndrome can affect long-term quality of life as well.[13] Timely administration of venous thromboembolism prophylaxis (VTEp) has been shown to significantly decrease VTE rates, and delayed administration remains a major modifiable risk factor for VTE.[10,14] However, the optimal VTEp timing for severe TBI patients remains an area of significant debate and wide practice variation. Most available published series have been limited to single-center analyses or reviews of large data sets that were not specifically designed for VTE data. The aim of this study was to use a prospective multicenter database specifically designed to examine questions around VTE to evaluate the timing and safety of VTEp in the TBI population. Our hypothesis was that initiating early VTEp for severe TBI patients would reduce the incidence of VTE and would not be associated with progression of intracranial hemorrhage (pICH) or other adverse bleeding events.

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PATIENTS AND METHODS

Population Data

The original Consortium of Leaders in Traumatic Thromboembolism (CLOTT) was a multicenter prospective observational study designed to address the issue about posttraumatic PT. It contained 7,880 deidentified patient data collected during

January 2018 to December 2020 from 17 level 1 trauma centers in the United States. The study was funded by Department of Defense, so only patients within the typical military deployable age range (18–40 years) were involved. Trauma patients admitted to one of the participating centers were included if they were anticipated to stay in the hospital for more than 48 hours and had at least one of the following known risk factors for VTE: pelvic fracture, lower extremity fracture above ankle, head/chest/abdominal injury of Abbreviated Injury Scale (AIS) score of 3 or greater, required ventilator support for 3 days, shock on admission, spinal cord injury, major vein injury, or requiring major operations on the day of admission. This study was a secondary analysis from the CLOTT database. To identify patients with severe head injury, we selected patients having head AIS scores of 3 to 5 and length of stay more than 72 hours from the database and having (1) no VTEp within 24 hours due to ICH or (2) receiving any emergent neurosurgical interventions, that is, craniotomy, craniectomy, and intracranial pressure (ICP) monitoring/drain placement. Exclusion criteria included nonsurvivable head injury (AIS=6), no VTEp or without documentation, and VTEp interruption for reasons irrelevant to concern of bleeding or procedures, for example, patient refusal or medication administration error.

Data Collection and Outcome Measures

Demographic data, initial vital signs, AIS from different body regions, Injury Severity Score, preexisting condition, use of tranexamic acid, the timing and methods of VTEp, missing doses, and reasons were collected. We used the risk assessment profile (RAP) score to stratify the risk of VTE.[15] A RAP score greater than 4 was deemed as high risk. The detailed definition of the RAP scoring system is listed in Supplemental Digital Content (Supplementary Data 1, http://links.lww.com/TA/D72).

Emergent neurosurgical procedures were recorded if patients received a craniotomy, craniectomy, ICP monitoring, or external ventricular drain placement. All eligible patients were then separated into early versus late initiation of VTEp using a cutoff point of 48 hours from admission. Patients were followed until the time of death, transfer to another facility, or discharge. The primary outcome was the development of VTE including DVT, PE, or primary PT. Because the focus was on the incidence of new VTE after initiation of VTEp, patients with VTE diagnosed before 48 hours from admission were not included for analysis since they had VTE before prophylaxis. Secondary outcomes included progression of ICH or any bleeding complications that were deemed to be potentially related to VTEp. The surveillance for VTE and medications for VTEp were used at the discretion of treating clinicians from different sites without a universal protocol. Deep vein thrombosis was diagnosed by duplex ultrasound or computed tomography (CT). Pulmonary embolism/thrombosis was diagnosed if identified in a CT angiography of the chest.

Statistical Analysis

Categorical variables from different groups were compared by χ^2 or Fisher's exact test. Mann-Whitney *U* test was used for continuous variables when there was nonnormal distribution. Missing values were all less than 2% and therefore without further imputation. Univariate analysis was conducted to compare the differences between developing VTE or not. Variables with p value of <0.2 then proceeded to multivariate logistic regression to identify the independent factors associated with VTE. Confounders were maintained if they were considered relevant to outcome or produced more than 10% change in the odds of association with the outcome of interest. Since our interest was the timing of VTEp, we kept this factor in the final model. Collinearity was checked to ensure that variance inflation factors were less than 2. The same method was applied to identify factors associated with pICH or any bleeding events. Statistical significance was set as $p < 0.05$. All statistics were performed using SPSS 28.0 (IBM Corp., Armonk, NY). The study was approved by the institutional review board at our institution and followed the STrengthening the Reporting of OBservational studies in Epidemiology guideline (Supplemental Digital Content, Supplementary Data 2, http://links.lww.com/TA/D72).

RESULTS

There were 881 patients enrolled. The majority were from blunt injury mechanisms (91.8%), with a median Injury Severity Score of 26 (Table 1). Venous thromboembolism prophylaxis ≤48 hours (early group) accounted for 42.9% of the patients. Of the VTEp >48 hours (late) group, the median initiation time was the fourth day (interquartile range, 3–5). Patients with VTEp >48 hours were more severely injured overall than patients with VTEp ≤48 hours and presented with a higher proportion of head AIS of 5 (43.1% vs. 28.8%, $p < 0.001$), as well as required more neurosurgical interventions (33.4% vs. 23.3%, $p < 0.001$) and more prolonged mechanical ventilation (49.1% vs. 36.2%, $p < 0.001$). The incidence of DVT was significantly higher in the VTEp >48 hours group compared with the ≤48 hours group (11.0% vs. 6.1%, $p = 0.012$), as well as the incidence of overall VTE (12.4% vs. 7.2%, $p = 0.012$) (Table 2). There was no significant difference in the rates of pICH or other bleeding complications between the early versus late VTEp groups, including hemorrhage from solid organ injury, gastrointestinal bleeding, or genitourinary bleeding (Fig. 1).

The patient characteristics and factors related to VTE, pICH, and any bleeding complications related to VTEp were evaluated (Supplemental Digital Content, Supplementary Data 3–5, http://links.lww.com/TA/D72) and then entered into a backward stepwise multivariate logistic regression. Venous thromboembolism prophylaxis >48 hours (odds ratio [OR], 1.86; 95% CI, 1.11–3.10), ventilator use >3 days (OR, 2.00; 95% CI, 1.21–3.31), and RAP score >4 (OR, 6.70; 95% CI, 2.05–21.94) were independently associated with an increased VTE rate (Table 3). Use of enoxaparin was associated with lower VTE compared with UF (OR, 0.54; 95% CI, 0.33–0.88). If using VTEp initiating day as a continuous variable and adjusting with the same variables listed previously, the VTEp initiating day had an OR of 1.06 (95% CI, 1.01–1.11), showing that each day of delay VTEp was related to a 6% increase in odds of VTE. As shown in Table 4, VTEp ≤48 hours (early) was not significantly associated with pICH or any bleeding events after initiation of chemoprophylaxis. There was a significant relationship between pICH and the need for craniectomy (OR, 5.41; 95% CI, 1.70–17.26). For all the bleeding events after VTEp, only neurosurgical intervention was a significant risk factor (OR, 8.31; 95% CI, 3.01–22.89). There was no independent

TABLE 1. Patient Characteristics, Risk Factors Related to Venous Thromboembolism, and Prophylaxis Methods

	Total N = 881	VTEp ≤48 h n = 378	VTEp >48 h n = 503	*p*
Age, median (IQR), y	29 (24–35)	29 (24–35)	29 (24–35)	0.91
Male, n (%)	680 (77.2)	293 (77.5)	387 (76.9)	0.84
Blunt/penetrating, n (%)	808/72 (91.8/8.2)	352/26 (93.1/6.9)	456/46 (90.8/9.2)	0.22
Body mass index, median (IQR)	25.4 (22.5–28.9)	25.7 (22.9–29.1)	25.1 (22.3–28.8)	0.23
SBP <90 mm Hg, n (%)	65 (7.4)	22 (5.9)	43 (8.6)	0.12
Pulse >120, n (%)	160 (18.3)	69 (18.4)	91 (18.2)	0.97
Glasgow Coma Scale <9, n (%)	480 (54.9)	197 (52.8)	283 (56.5)	0.28
Head AIS, n (%)				<0.01
3	268 (30.4)	134 (35.4)	134 (26.6)	
4	287 (32.6)	135 (35.7)	152 (30.2)	
5	326 (37.0)	109 (28.8)	217 (43.1)	
Chest AIS ≥3, n (%)	299 (33.9)	132 (34.9)	167 (33.2)	0.59
Abdomen AIS ≥3, n (%)	134 (15.2)	55 (14.6)	79 (15.7)	0.64
Extremity AIS ≥3, n (%)	160 (18.2)	63 (16.7)	97 (19.3)	0.32
ISS, median (IQR)	26 (21–34)	26 (18–34)	27 (21–34)	<0.01
RAP ≥5, n (%)	643 (76.1)	263 (72.9)	380 (78.5)	0.06
Neurosurgical intervention, n (%)	257 (29.2)	88 (23.3)	168 (33.4)	<0.01
Craniectomy	141 (16.0)	51 (13.5)	90 (17.9)	0.08
Craniotomy	135 (15.3)	43 (11.4)	92 (18.3)	0.01
ICP monitor	22 (2.5)	13 (3.4)	9 (1.8)	0.12
External ventricular drain	11 (1.2)	3 (0.8)	8 (1.6)	0.37
Ventilator use ≥4 d, n (%)	384 (43.6)	137 (36.2)	247 (49.1)	<0.01
Tranexamic acid use, n (%)	48 (5.4)	19 (5.0)	29 (5.8)	0.63
VTEp medication, n (%)				<0.01
Heparin	247 (28.0)	132 (34.9)	115 (22.9)	
Enoxaparin	619 (70.3)	239 (63.2)	380 (75.5)	
Others or mixed	15 (1.7)	7 (1.9)	8 (1.6)	
VTEp missing dose, n (%)	271 (30.8)	104 (27.5)	167 (33.2)	0.07
VTE mechanical prophylaxis, n (%)	799 (90.7)	340 (89.9)	459 (91.3)	0.51
IVC filter, n (%)	26 (3.0)	4 (1.1)	22 (4.4)	<0.01

IQR, interquartile range; ISS, Injury Severity Score; IVC, inferior vena cava; SBP, systolic blood pressure.

TABLE 2. Complications and Outcomes

	Total N = 877	VTEp ≤48 h n = 376	VTEp >48 h n = 501	*p*
VTE, n (%)	89 (10.1)	27 (7.2)	62 (12.4)	0.01
DVT, n (%)	82 (9.3)	23 (6.1)	55 (11.0)	0.01
PE/thrombosis, n (%)	19 (2.2)	8 (2.1)	11 (2.2)	0.94
VTE date, median (IQR)	8 (4–15)	11 (4–17)	8 (4–15)	0.75
Complications, n (%)				
Hemorrhage from solid organ injury	1 (0.1)	0 (0.0)	1 (0.2)	1
Intracranial bleeding	16 (1.8)	7 (1.9)	9 (1.8)	0.95
Gastrointestinal bleeding	4 (0.5)	0 (0.0)	4 (0.8)	0.14
Genitourinary bleeding	1 (0.1)	0 (0.0)	1 (0.2)	1
Any bleeding	22 (2.5)	7 (1.9)	15 (3.0)	0.28
Length of stay, median (IQR)	13 (7–24)	10 (5–21)	16 (8–27)	<0.01
ICU length of stay, median (IQR)	8 (3–16)	6 (3–13)	10 (4–18)	<0.01
Mortality, n (%)	44 (5.0)	16 (4.3)	28 (5.6)	0.38

IQR, interquartile range; ICU, intensive care unit.

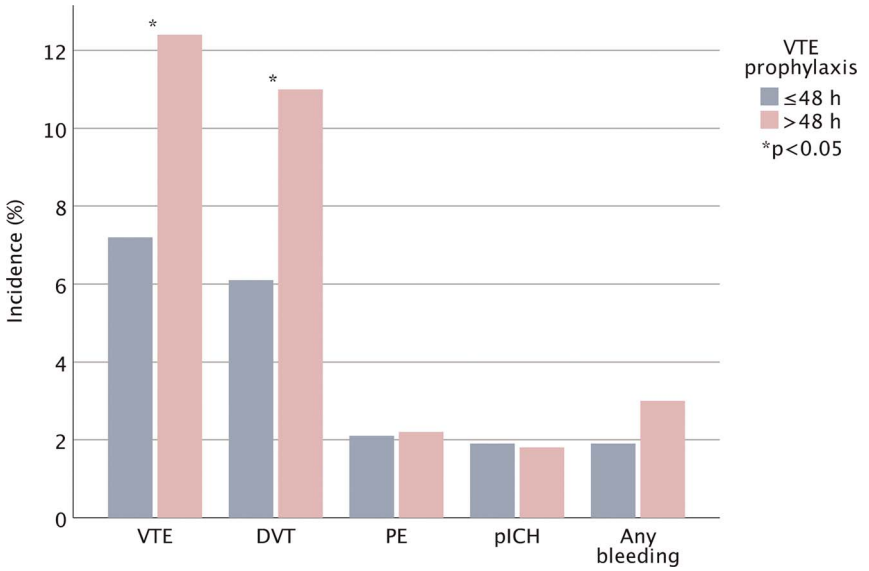

Figure 1. The incidence of VTE and bleeding complications in early (≤48 hours) or late (>48 hours) VTEp patients.

association between the early initiation of VTE prophylaxis and bleeding events in all multivariate models.

DISCUSSION

The prevention, early diagnosis, and treatment of posttraumatic VTE remain a cornerstone of inpatient care of the injured patient and represent a major focus of trauma quality initiatives and trauma center verifications programs. However, there is a consistent common tension in both clinical practice and the VTE literature between prioritizing early VTE chemoprophylaxis administration and the fear of resultant bleeding complications. The present study represents one of the only prospective analyses of the associations between VTEp and outcomes in TBI patients from a database specifically designed to capture data related to thrombotic complications and VTE prophylaxis practices. In this analysis of the CLOTT data set, we found that early (within 48 hours) initiation of VTE prophylaxis is associated with decreased thromboembolic events and no increase in bleeding complications compared with delayed administration.

Previous studies had shown that the later the VTEp starts, the higher the VTE rate will be.[15,16] Byrne et al.[16] analyzed 4,951 blunt TBI patients and found that each additional day of delay was associated with an 8% increase in odds of VTE (adjusted OR, 1.08; 95% CI, 1.04–1.12). Starting VTEp less than 72 hours was proved in several studies to be feasible and effective in decreasing VTE rate.[11,17] Other studies used an earlier initiating timeline, but the study groups and populations have varied significantly. Meyer et al.[18] included 67 penetrating head injuries and found no difference when starting VTEp at 48 hours compared with later initiation. Coleman et al.[19] analyzed those receiving neurosurgical operations and showed a lower VTE rate when VTEp was initiated within 48 hours from admission. In our study, we included the more severe and higher risk head injuries (head AIS, 3–5) with and without neurosurgical interventions and also showed a significant benefit for early prophylaxis. When trying to identify an optimal initiating time, the underlying dynamic coagulation function also needs to be considered. In trauma patients with bleeding, the initial coagulopathy (if present) generally resolves by 24 hours, and the proportion of patients with hypercoagulable state

TABLE 3. Risk Factors for VTE on Multivariate Logistic Regression

	OR (95% CI)	*p*
VTE prophylaxis initiation >48 h	1.86 (1.11–3.10)	0.02
Ventilator use ≥4 d	2.00 (1.21–3.31)	0.01
RAP score ≥5	6.70 (2.05–21.94)	<0.01
VTE prophylaxis with enoxaparin*	0.54 (0.33–0.88)	0.01

*Compared with UF heparin.
χ^2 = 5.192; Hosmer-Lemeshow test, 0.637; Nagelkerke R^2, 0.119.
VTE, venous thromboembolism.

TABLE 4. Risk Factors for Progression of ICH or Any Bleeding Complications After Starting Prophylaxis of VTE

	OR (95% CI)	*p*
Progression of ICH*		
VTE prophylaxis initiation ≤48 h	0.75 (0.24–2.29)	0.61
Craniectomy	5.41 (1.70–17.26)	<0.01
Craniotomy	2.60 (0.85–8.00)	0.10
ICP monitor	3.27 (0.73–14.71)	0.12
Body mass index	1.09 (0.99–1.18)	0.07
AIS head		
3	Reference	0.19
4	1.12 (0.95–13.14)	0.93
5	3.83 (0.43–33.92)	0.23
Any bleeding**		
VTE prophylaxis initiation ≤48 h	1.28 (0.51–3.22)	0.61
Neurosurgical intervention	8.31 (3.01–22.89)	<0.01
Injury Severity Score	1.03 (0.99–1.08)	0.10

*χ^2 = 4.177; Hosmer-Lemeshow test, 0.841; Nagelkerke R^2, 0.209.
**χ^2 = 6.982; Hosmer-Lemeshow test, 0.539; Nagelkerke R^2, 0.137.

increases significantly by 48 hours.[20,21] An analysis of CLOTT-2 database showed that major TBI was independently associated with fibrinolysis shutdown at 24 hours.[22] This evidence theoretically supports the importance of VTEp initiation by the 48-hour time point. However, it is important to recognize that there is no hard science behind using a cutoff point of 48 hours to define early versus late, and there may be an alternative and even earlier time point that would be safe in terms of bleeding and even more effective for prevention of VTE.

In traumatic ICH patients, it is common to see some degree of hemorrhage progression in the first hours after injury (18–65%),[23] with most occurring within the first 24 hours.[24–26] Although some degree of ICH progression is relatively common, particularly in moderate to severe traumatic brain injuries, the majority of these do not require any additional neurosurgical interventions. The reported neurosurgical intervention rates for progression of the initial ICH after repeat CT scan has ranged from 1% to 8% in published studies.[23,27,28] Several previous studies have shown that VTEp does not appear to increase the risk of pICH. Kim et al.[29] analyzed 64 TBI patients using UF and found no increase of pICH if starting VTEp at less than 72 hours. In another study by Koehler et al.[30] specifically examining prophylaxis with LMWH, starting VTEp within 72 hours did not increase the overall pICH rate (1.46% vs. 1.54%, $p = 0.912$). However, they excluded patients receiving ICP monitor or external ventricular drain placement, and thus, the safety remains unproven in that subgroup. Frisoli et al.[31] compared TBI patients starting VTEp <24 hours or >48 hours and did not find a significant difference in pICH rate (18% vs. 17%, $p = 0.83$), but they similarly excluded patients receiving neurosurgical operations. Since the risk of pICH has a close correlation to higher injury severity,[23,26–28] all severe TBI patients need to be included when trying to evaluate the safety of early VTEp. In this study, we used head AIS scores 3 to 5, with or without neurosurgical interventions, and "no VTEp within 24 hours due to concern of ICH" as our primary selection criteria. After adjusting for other relevant factors, starting VTEp within 48 hours did not independently raise the risk of pICH.

It is important to note that there are several prior studies that have not supported the safety of early initiation of VTE chemoprophylaxis. Levy et al.[32] found that, in 92 patients having pICH in initial follow-up CT, patients who received VTEp had a higher ICH progression rate compared with those without initiation of VTEp. Our analysis included a much larger sample size with significantly greater power for both bleeding and VTE outcomes, and the CLOTT data set includes detailed data on VTEp administration continuity and missed dosing. The results show that most of the identified bleeding complications after VTEp were pICH, with a much lower incidence of hemorrhage from solid organ injuries, gastrointestinal bleeding, or genitourinary tract bleeding. Early prophylaxis was found to have no significant association with pICH or any of the other bleeding events. It is also important to note that, although these were all defined as bleeding events after initiation of VTEp, there can be no direct causality assumed.

Enoxaparin showed a protective effect on VTE compared with heparin, which has been shown in previous studies. Specific to TBI, Byrne et al.[16] found lower odds of VTE in LMWH compared with UF (OR, 0.64; 95% CI, 0.49–0.84). While there may be concerns about the risk of bleeding when using LMWH,[33] our data showed no significant difference for either pICH or other bleeding events when comparing LMWH to UF.

Although we excluded patients with VTEp interruption due to noncompliance, there were still 30.8% patients who had at least one missing dose. The majority of these patients had only one missing dose (73.8%). Previous literature has identified missing VTEp as a potential risk factor for increased VTE rates, but these analyses are significantly confounded by factors including the number and timing of missed doses, the exact medication used, and the reason for the held or missed dose.[19,34] From the CLOTT data set with robust information on the reasons and number/timing of missed doses in detail, we found that there was little effect of missed VTEp doses on overall VTE rates or on bleeding risks.

While the overall VTE and DVT incidence was significantly lower in the early VTEp group, the PE rate was not significantly different. This might be partially explained by other interventions to reduce the risk of symptomatic embolic events, such as the use of mechanical prophylactic measures. In the present study, 4.4% of patients in the VTEp >48 hours group had a prophylactic inferior vena cava filter placement compared with only 1.1% in VTEp ≤48 hours group. However, even with the existing effect of inferior vena cava filter factored into the regression analyses, early prophylaxis still showed an overall lower incidence of VTE. A more likely explanation for the difference between DVT and PE/PT rates is that the two entities originate from different etiology and are not always related in trauma patients.[35]

We identified that those who required emergent craniectomy had a significantly increased rate of pICH even after adjustment for confounding factors. Although patients receiving craniotomy and ICP monitor had a trend of increased incidence of pICH, only craniectomy remained a significant independent associated factor on multivariate analysis. It may be appropriate to interpret this result as those injury patterns that dictate the need for craniectomy were prone to progress rather than the effect of the craniectomy procedure itself, but this remains speculative. Theoretically, patients with more severe head injuries have higher risk of pICH; however, we failed to demonstrate a significant association between head AIS and pICH. A possible explanation is that AIS score does not correlate with the indications for operations very well. It is also important to mention that pICH rate was relatively low in the CLOTT database because only pICH "after initiating VTEp" was documented, and thus, it was not equal to the true overall pICH rate.

One of the major limitations of this study was the lack of details about specific head injury types, detailed CT scans and/or operative findings, and the timing of progression of ICH. The relationship between head injury types and pICH has been elucidated in many studies.[36] Although we focused on severe TBI patients for analysis, variations still existed among the study groups. We did not see a significant difference of PE rate. It is possible that the low incidence of this particular outcome measure results in underpowering of even a large data set such as CLOTT to detect what could be a potentially significant decrease in incidence with early prophylaxis. Another limitation is that CLOTT was an observational study, and thus, imaging procedures for VTE and ICH as well as prophylactic measures and their timing were left to the discretion of the treating surgeons leading to interfacility variations. The database did not include the outcome of pICH, so it was unknown whether those findings needed

intervention or remained subclinical. Another significant limitation is that this database was designed for inclusion only of relatively younger age patients (age 18–40 years) per the specifications of the funding agency, and thus, extrapolation to more elderly populations and those with existing coagulopathies or on anticoagulant medications cannot be made. Finally, although the CLOTT data set is a large and multicenter collection, there remain limitations of the sample size and adequate power for analyses of uncommon events and smaller subpopulations.

CONCLUSION

For severe TBI patients, early initiation of VTE chemoprophylaxis (within 48 hours) after injury was associated with a significant decrease in VTE rates compared with delayed initiation without increasing the incidence of ICH progression or other extracranial bleeding complication. While DVT rates were lower in the early prophylactic group, pulmonary clots were not, suggesting that risk factors for DVT may be different than those of PE/PT in this population. Further prospective studies in specific high-risk subgroups of pICH are warranted to clarify the ideal timing, medication, and dosing for VTE prophylaxis.

AUTHORSHIP

Y.-T.W., M.M.K., and M.J.M. contributed in the study design. E.E.M., A.S., M.M.K., and M.J.M. contributed in the data acquisition. Y.-T.W., C.-Y.C., and M.J.M. contributed in the data analysis. K.M., M.S., K.I., and A.S. contributed in the critical revision. Y.-T.W., M.J.M., E.E.M., M.M.K., M.S., K.M., and K.I. contributed to manuscript preparation.

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DISCLOSURE

The authors declare no conflicts of interest.

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