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A Stitch in Time Saves Clots: Venous Thromboembolism Chemoprophylaxis in Traumatic Brain Injury

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Abstract

Background: Venous thromboembolism chemoprophylaxis (VTE-CHEMO) is often delayed in patients with traumatic brain injury because of the concern for intracranial hemorrhage (ICH) progression. We hypothesize that (1) late time to VTE-CHEMO (> 48h) is associated with higher incidence of VTE, and (2) VTE-CHEMO use does not correlate with ICH progression.

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Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article. Dr. Goodman is an Associate Editor for the Journal of Surgical Research; as such, he was excluded from the entire peer-review and editorial process for this manuscript.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jss.2020.08.076>.

Materials and methods: This is a multiinstitutional retrospective study of patients with traumatic brain injury admitted between 2014 and 2016. Inclusion criteria were head Abbreviated Injury Code 2, ICH present on initial head computed tomography, and two or more head computed tomography scans after admission. The primary outcome was VTE, and the secondary outcome was ICH progression. Patients were classified as receiving VTE-CHEMO early (<48 h) or late (≥ 48 h). Multivariable analysis with Cox proportional hazards regression was performed.

Results: Overall, 1803 patients were included. Patients with VTE ($n = 137$) were more likely to have spinal cord injury, blunt cerebrovascular injury, pelvic or femur fractures, and missed VTE-CHEMO doses. After multivariable regression, body mass index >30 (hazard ratio [HR], 1.05; $P = 0.002$), Injury Severity Score (HR, 1.004; $P < 0.001$), pelvic or femur fractures (HR, 1.05; $P < 0.0001$), spinal cord injury (HR, 1.28; $P = 0.02$), and missed VTE-CHEMO doses (HR, 1.08; $P = 0.01$) were significant predictors of VTE. In those who required neurosurgery, late VTE-CHEMO predicted VTE (HR, 1.21; $P = 0.0001$). Overall, 32% patients experienced ICH progression, which did not correlate with VTE-CHEMO use or timing.

Conclusions: This multicenter study highlights benefits from early VTE-CHEMO and identifies high-risk groups who may benefit from more aggressive prophylaxis. These data also emphasize risk to patients by withholding VTE-CHEMO.

Keywords

Traumatic brain injury; Venous thromboembolism; Chemoprophylaxis; Intracranial haemorrhage progression

Introduction

Traumatic brain injury (TBI) is responsible for significant morbidity and mortality in the United States, contributing to 2.9 million emergency department visits annually and nearly a third of all deaths in severely injured trauma patients.^{1,2} Morbidity associated with TBI is significant, including venous thromboembolism (VTEs) consisting of deep venous thromboses (DVTs) and pulmonary emboli (PEs).^{3–6} TBI itself is a risk factor for VTE in severely injured patients, potentially because of composite effects of coagulation alterations as a result of the brain injury to prolonged immobilization and hospital stay.^{4–6} Despite this risk, venous thromboembolism chemoprophylaxis (VTE-CHEMO) strategies are often delayed in patients with TBI, with studies reporting time to chemoprophylaxis of up to 15 d after injury.⁷ This aversion to or delay in VTE-CHEMO is not without a clinical consequence, given reported association of an increased risk of VTE with delayed prophylaxis initiation.⁸

Reluctance to initiate VTE-CHEMO is presumably related to concern for bleeding, specifically worsening of intracranial hemorrhage (ICH). There has been a significant variability in overall reported rates of ICH progression in patients with TBI and association with timing of VTE-CHEMO. Furthermore, in the existing literature, there are inconsistencies in recommended VTE-CHEMO strategies from national groups' guidelines, and discordance between recommended VTE-CHEMO initiation timing and actual practice in the clinical setting.^{9,10} Complicating this, national guidelines and recommendations are

generally based on retrospective data reviews from select patient populations, limiting their generalizability. Ultimately, best practices for VTE-CHEMO in patients with TBI, which do not also result in increased ICH progression, are unclear.

The objective of this multicenter study is to determine whether there is an association with the incidence and timing of VTE-CHEMO and VTE in patients with TBI and to examine whether variability in VTE-CHEMO timing impacts ICH progression on serial head imaging. We hypothesize that (1) late time to VTE-CHEMO (> 48 h) is associated with a higher incidence of VTE, and (2) VTE-CHEMO use and timing do not correlate with worsening of ICH progression.

Materials and methods

This was a multiinstitutional retrospective study of patients with moderate to severe head injury admitted between 2014 and 2016 to five level I and level II trauma centers (Figure). This study was approved by Multiinstitutional Review Board (COMIRB 17–1464) and other sites' respective regulatory boards with approved waiver of consent as a retrospective study.

Eligible patients were identified using trauma registry data. Inclusion criteria were moderate to severe head injury, defined as head Abbreviated Injury Scale (AIS) ≥ 2, hospital length of stay (LOS) ≥ 72 h, and two or more head computed tomography (CTH) scans after admission. Patients were excluded if any of the following criteria were met: <18 y old, history of preexisting VTE, history of previously placed inferior vena cava filter, or isolated concussion.

The primary outcome explored in this study was VTE—either PE or DVT—during hospital admission or within 3 mo of discharge. A secondary outcome was radiological TBI progression, as defined by progression on CTH imaging. Reports from consecutive CTH images were reviewed and the presence of subarachnoid, subdural, epidural, intracerebral, intraparenchymal, or intraventricular hemorrhage was individually noted. The bleeding was graded as “better,” “worse,” or “stable” per assessment by the radiologist at the time of patient care as derived from the radiologist's report (based on the stability or progression of hemorrhage); a random subset of these was reviewed by a blinded reviewer to assure reliability in reported radiological findings.

Patients were classified as receiving no VTE-CHEMO, early VTE-CHEMO (initiated within 48 h of admission), or late VTE-CHEMO (initiated at or after 48 h); a cutoff of 24 h for early *versus* late VTE-CHEMO was also evaluated. We considered the effects of immediate or delayed neurosurgical (NS) intervention, which was defined as craniotomy or craniectomy on the day of hospital admission (“early,” within 24 h) or after 24 h (“late”), respectively. We also considered likelihood of radiological progression of ICH after VTE-CHEMO initiation.

All statistical calculations were performed using Statistical Analysis Software (SAS) version 9.4 statistical software (SAS Institute, Cary, NC). Patients who developed VTE were compared with those who did not develop VTE, and patients who received early VTE-CHEMO were compared with those who received late VTE-CHEMO and never received

VTE-CHEMO. In addition, we compared the rate of ICH progression with timing of VTE-CHEMO initiation (early *versus* late) for an association with timing of VTE-CHEMO. Two-tailed Fisher exact or chi-square tests were used for the comparison of proportions, and the Mann-Whitney *U*-test was used for comparison of nonnormally distributed continuous variables. We performed a multivariable analysis with Cox proportional hazards regression. Our analysis identified inconsistent practices in VTE-CHEMO across centers (as detailed in Supplemental Digital Content 1 and subsequently), differing VTE rates, and variable adherence to institutional protocols within individual centers, thus for the multivariable analysis, robust sandwich variance estimators were used to account for intrafacility clustering. Risk was defined using hazard ratios (HRs). Statistical significance threshold was declared at $P < 0.05$.

Results

A total of 1803 patients were included in the study (Table 1). Patients were predominantly male (69%), with a median age of 55 y and a median Injury Severity Score (ISS) of 22. The majority presented after blunt trauma ($n = 1628$; 96%), specifically fall ($n = 876$; 49%), or motor vehicle crash ($n = 334$; 19%). On hospital arrival, the median systolic blood pressure was 137 mm Hg; only 59 patients (3%) presented in shock with an initial systolic blood pressure of <90 mm Hg. Most patients sustained a severe head injury, with head AIS of 4 or 5 ($n = 971$; 54%). A total of 334 patients (19%) underwent either craniotomy or craniectomy during hospital admission, with most of them undergoing an immediate NS intervention on the admission hospital day ($n = 228$; 68%).

Although most patients had isolated head injury ($n = 1644$; 91%), defined as no other region AIS >2 , a minority presented with polytrauma, including spinal cord ($n = 37$; 2%), pelvis ($n = 134$; 7%), femur ($n = 81$; 4%), or tibia ($n = 92$; 5%) injuries. Patients with isolated TBI were more likely to never receive VTE-CHEMO (30% *versus* 8% in polytrauma patients; $P < 0.001$), although the proportion started on early VTE-CHEMO was similar (24% *versus* 27% in polytrauma patients). Although a greater proportion of patients with isolated TBI never received VTE-CHEMO, VTE incidence was significantly higher in the polytrauma patients compared with isolated TBI (24% of polytrauma *versus* 6% in isolated TBI; $P < 0.0001$). There was no difference in mortality rates between patients with isolated TBI and polytrauma (8% *versus* 12% in polytrauma; $P = 0.13$).

Overall, 472 patients (29%) had some form of anticoagulant or antiplatelet as a home medication, most commonly 325 mg of aspirin daily (3%), 75 mg of clopidogrel daily (4%), various doses of warfarin (8%), and various doses of rivaroxaban (1%); on univariate analysis, the VTE incidence in these patients was not different compared with patients without these home medications (comparing anticoagulants and antiplatelets both collectively and by an individual agent).

VTE-CHEMO was generally delayed with a median time to initiation of 63 h (interquartile range [IQR], 42–88). Overall, 519 patients (29%) never received VTE-CHEMO during hospital admission, 443 (25%) received early VTE-CHEMO, and 841 (47%) received late VTE-CHEMO. Only 53 patients (3%) had initiation of VTE-CHEMO within 24 h (Table

2). Most centers used enoxaparin twice a day or subcutaneous heparin (SQH) three times a day, with two institutions (Institutions nos. 1 and 5) prescribing these two regimens at slightly higher rates than the others. Very few patients were prescribed the following agents and there was no difference in their infrequent use across centers: enoxaparin every day, dalteparin three times a day, SQH every day, SQH twice a day, unfractionated heparin twice a day, and unfractionated heparin three times a day.

Overall, 29 patients (2%) developed PE and 118 patients (7%) developed DVT, for an overall rate of VTE of 8% ($n = 137$). Among all the PEs, 10 occurred in setting of concomitant DVT, whereas 19 occurred without a documented DVT. Compared with patients without VTE, patients who developed a VTE were younger (51 *versus* 56 y; $P = 0.01$), more likely to have a body mass index (BMI) >30 (27% *versus* 15%; $P < 0.001$), and more severely injured (ISS 27 *versus* 21; $P < 0.001$) (Table 3). Patients with VTE were also more likely to have associated spinal cord injury (7% *versus* 2%; $P < 0.001$), blunt cerebrovascular injury (10% *versus* 5%; $P = 0.03$), pelvic fractures (16% *versus* 7%; $P < 0.001$), and femur fractures (13% *versus* 4%; $P < 0.001$). Because of the established relationship between missed doses and VTE risk,¹¹ we compared patients who missed any VTE-CHEMO doses ($n = 196$) to those who did not ($n = 1092$) (Table 4). Compared with patients with no missed doses, patients who missed doses at any point were more likely to be more severely injured (median ISS 27 *versus* 22; $P < 0.001$), present with polytrauma (22% *versus* 9%; $P < 0.001$), and have a longer LOS (median 17 *versus* 8 d overall and 12 *versus* 4 d in the intensive care unit; $P < 0.001$ for both). Compared with patients with no missed doses, those with missed doses had a shorter time to VTE-CHEMO initiation (median time of 56 *versus* 64 h; $P = 0.01$), but a higher rate of VTE (20% *versus* 8%; $P < 0.001$). Patients with VTE also had longer hospital LOS (18 *versus* 7 d; $P < 0.001$), intensive care unit LOS (12 *versus* 3 d; $P < 0.001$), and more ventilator days (7 *versus* 0 d; $P < 0.001$). Mortality was higher in the VTE group (15% *versus* 8%; $P = 0.01$).

Most patients (79%) did not require an NS intervention, whereas 15% required early NS intervention and 6% required late NS intervention. Patients who required NS interventions had a higher injury severity (median ISS of 26 in early and 25 in late *versus* 19 in non-NS intervention patients; $P < 0.0001$), which was likely driven by differences in head AIS (median head AIS of 5 in the NS group *versus* 3 in the non-NS group; $P < 0.0001$), higher rate of penetrating trauma (5.9% in early and 8.8% in late *versus* 1.0% in non-NS intervention patients; $P < 0.001$), and higher rate of subdural hematoma (76.8% and 78.4% in early and late *versus* 57.7% in non-NS; $P < 0.0001$). Not surprisingly, patients who underwent early NS intervention were more likely to have a lower Glasgow Coma Scale (median 9 *versus* 14 in the non-NS intervention group and 13 in late NS intervention group) and a higher percent of epidural hematoma (25.0% *versus* 12.1% in late NS, 7.9% in non-NS; $P < 0.0001$ for both).

After multivariable regression, BMI >30 (HR, 1.05; $P = 0.002$), ISS (HR, 1.004; $P < 0.001$), pelvic or femur fractures (HR, 1.05; $P < 0.0001$), spinal cord injury (HR, 1.28; $P = 0.02$), and missed VTE-CHEMO doses (HR, 1.08; $P = 0.01$) remained significant predictors of developing VTE (Table 5). In those who required NS intervention, there was a significant interaction between VTE rates and VTE-CHEMO timing, such that delayed VTE-CHEMO

predicted VTE (HR, 1.13 [$P=0.04$] in the early NS group and HR, 1.21 [$P=0.0001$] in the delayed NS group).

Overall, 580 patients (32%) experienced radiological progression of ICH. Among patients who never received VTE-CHEMO, 25% had ICH progression compared with 13% in the early VTE-CHEMO group and 47% in the late VTE-CHEMO group. Within the late VTE-CHEMO group, of those who progressed, 34% had ICH progression before VTE-CHEMO and 12% had ICH progression after VTE-CHEMO ($P<0.0001$). Among those who had progression after initiation of VTE-CHEMO ($n=164$), there was no significant difference in the proportion of CTH progression by VTE-CHEMO initiation timing, with 36% of those with progression receiving early prophylaxis and 64% of those with progression receiving late prophylaxis ($P=0.59$). In addition, among the patients who had a late NS procedure (craniotomy), none received VTE-CHEMO before their NS procedure. Overall, there was a mortality rate of 8% among patients with ICH progression (9% in whole study population). Among patients with no VTE-CHEMO, the mortality rate among patients with ICH progression was 12%, *versus* 4% in early VTE-CHEMO, *versus* 9% in late VTE-CHEMO ($P<0.01$). However, it is important to mention a cause of death analysis was not performed.

Discussion

In this multicenter study of over 1800 patients with TBI, we examined rates and timing of VTE-CHEMO and its correlation with VTE incidence and ICH progression. Consistent with the previous literature,^{5,12–15} we identified a benefit from early VTE-CHEMO and identified subgroups with unique risk factors for VTE who may benefit from more aggressive VTE-CHEMO, including patients with obesity, severe injury, and concomitant pelvic or femur fractures or spinal cord injury. Our data also highlight heightened VTE risk in patients in whom VTE-CHEMO is withheld. Although an ICH progression rate of 32% was noted among all patients, there was not a temporal association with VTE-CHEMO initiation; interestingly, the highest rate of ICH progression was in patients who never received VTE-CHEMO.

Despite the relationship between early VTE-CHEMO and decreased VTE identified in our data, there remains conflicting evidence on the topic, with some studies failing to identify a benefit from earlier VTE-CHEMO initiation.^{5,12} An explanation for the conflicting data within previous series and our study may be our patient selection criteria and population, which differ from other published series. For example, in one analysis of 2128 patients who sustained isolated neurotrauma, the reported time to VTE-CHEMO was longer in patients who had a VTE, and authors concluded benefit from earlier VTE-CHEMO. However, 703 patients were excluded (including those who did not receive VTE-CHEMO).¹³ Similarly, in another study of a propensity-matched cohort study of patients with isolated TBI, early VTE-CHEMO (<72 h) was associated with decreased risk of PE and DVT; however, in this study of 12,403 patients, 5586 were excluded, including 2774 patients because of never receiving VTE-CHEMO.¹⁴ Importantly, the exclusion of those who did not receive VTE-CHEMO may introduce bias by exclusion of patients who are more injured or critically ill and consequently had a higher VTE rate despite any VTE-CHEMO strategies;

or, conversely, these excluded patients may have a VTE rate so low that they would not benefit from any intervention. Overall, given that most of the literature on the topic of VTE-CHEMO in TBI is based on highly selected patient populations with isolated TBI, we feel that the inclusion of a more heterogeneous trauma population, which includes polytrauma patients, is novel and was an *a priori* decision when the reported study was designed so as to enhance generalizability. Although a separate analysis of our data was performed without polytrauma patients (isolated TBI only) and the overall results and conclusions remained the same, this report includes the results from our analysis of patients with both polytrauma and isolated TBI. Ultimately, identification of factors increasing risk of VTE in patients with TBI, such as the concomitant injuries described, is an important contribution to clinical practice by providing data for discussion in polytrauma patients in which a paucity of literature exists. If, as has been found in numerous publications cited in this report, practitioners are wary to initiate VTE-CHEMO in those with TBI, knowledge of increased VTE risk in those with particular injury patterns may mitigate this reticence and may lead to earlier initiation, more aggressive dosing, and usage of assays for efficacy, if available, in the future.

Our results demonstrate the variability of current chemoprophylaxis practices and a significant delay (or complete withholding) of VTE-CHEMO in patients with TBI, which confers higher VTE rates, highlighting the need to reevaluate VTE risk mitigation in patients with TBI. Although the coagulation profile of TBI is poorly understood, there may be a paradoxical hypercoagulability resistant to current VTE-CHEMO strategies.¹⁶ In a prospective study of over 11,000 patients who underwent NS intervention, most patients who developed a VTE were on VTE-CHEMO at the time of VTE diagnosis, supporting the idea that current VTE-CHEMO strategies may be insufficient to mitigate VTE risk because of hypercoagulable state.¹⁷ Our results also support a growing body of the literature describing higher risk of VTE in patients who miss VTE-CHEMO dosing.^{11,18} Although further research is required to better understand the bleeding risk with VTE-CHEMO in the perioperative period, the existing literature does not link VTE-CHEMO with bleeding complications in the perioperative period.¹⁹ Given the higher VTE risk by withholding VTE-CHEMO, these data highlight the need to reevaluate withholding practices for procedures.

Although we identified a benefit from VTE-CHEMO initiation within 48 h, this benefit may be more robust if VTE-CHEMO is initiated earlier. Our study used the time point of 48 h to define early VTE-CHEMO; however, the recent literature suggests that peak hypercoagulability after trauma occurs at 24 h.²⁰ A subanalysis was attempted using a more stringent cutoff of 24 h for early VTE-CHEMO, but there were very few patients who received VTE-CHEMO in this early window ($n = 53$), making multivariable analysis with multiple risk factors unreliable. Despite our study and others' indication for benefit in earlier VTE-CHEMO with respect to VTE prevention, surveys of trauma providers suggest that there is hesitation to start VTE-CHEMO at such an early time point or at all. In a survey of nearly 400 practicing surgeons assessing VTE-CHEMO strategies in patients with TBI, 50% considered their VTE-CHEMO practices to be conservative, intentionally delaying VTE-CHEMO compared with their non-TBI patients.²¹ Results from our patient population demonstrate a higher AIS in the no VTE-CHEMO group (4 [IQR, 3–5] *versus* 3 [IQR, 3–4] in the early VTE-CHEMO group and 4 [IQR, 3–5] in the late VTE-CHEMO group; $P < 0.01$), highlighting the fact that providers may be particularly reticent to initiate VTE-

CHEMO in patients with a more severe TBI. In addition, as ICH progression occurs early and frequently, early initiation of VTE-CHEMO would likely be blamed until randomized trial data support otherwise.

On the basis of these conflicting data, there is a lack of consensus at all levels regarding best practices for VTE-CHEMO strategies in patients with TBI, as reflected by inconsistent recommendations by national organizations and guidelines. The Neurocritical Care Society recommends VTE-CHEMO in patients with TBI within 24–48h of presentation, although they rank this evidence as “weak” with “low-quality evidence,” citing the “paucity of randomized, controlled, and adequately powered clinical trials.”²² The Brain Trauma Foundation (BTF) reports use of chemoprophylaxis in patients with TBI as level III evidence, also citing a lack of data to support level I or level II evidence, and thus BTF states they cannot offer specific recommendations regarding timing of prophylaxis.²³ In addition, the Western Trauma Association (WTA) performed a multicenter study of VTE-CHEMO in patients with TBI with serial CTH scans and ultimately concluded that the risk of using low molecular weight heparin (LMWH) may exceed its benefit because of evidence of ICH progression, remarking an inability to demonstrate safety for and recommendation of VTE-CHEMO in TBI.⁹ Despite concerns raised by the BTF and the WTA findings, the American College of Surgeons Trauma Quality Improvement Program recommends VTE-CHEMO within the first 72 h in the context of a stable repeat CTH.²⁴ Beyond the lack of consistency and strength of current practice recommendations, studies that have examined the relationship between VTE-CHEMO rates and timing on VTE incidence in TBI mainly include single-center studies or queries of national registry databases with strict patient inclusion criteria that limit generalizability and interpretation to clinical practice of polytrauma patients.^{13,14} These studies have a variable rate of VTE and ICH progression and different definitions of early VTE-CHEMO (by time and by reference point from injury or stable CTH), complicating interpretation of best unanimous chemoprophylaxis strategies.

Our data identify higher risk groups among patients with polytrauma and TBI, who may in a larger-sampled prospective study show benefit from earlier VTE-CHEMO. Specifically, obesity, more severe injury, and concomitant pelvic or femur fracture and spinal cord injury were significant predictors of VTE (despite a higher rate of VTE-CHEMO in these polytrauma cohorts compared with patients with isolated TBI), risk factors that overlap with those for all trauma patients.^{25–29} The orthopedic trauma literature has detailed the relatively higher risk of VTE among orthopedic trauma patients with pelvic fracture or femur fracture.^{30,31} This disproportionately higher thrombotic morbidity is also well described in the trauma literature, specifically with obesity, lower extremity fractures, and TBI itself significantly increasing risk of thrombotic events.^{28,32} Although we failed to detect an interaction of VTE-CHEMO timing and VTE incidence in these high-risk subgroups, this may be because of the small number of patients with these risk factors in our study. A larger-sampled investigation focused on patients with concomitant orthopedic injury with TBI may identify benefit of earlier VTE-CHEMO or demonstrate a natural history of thrombosis that is difficult to impact.

We report a rate of 32% for ICH progression, a rate similar to the previous literature.^{9,10} This rate did not differ between patients who received VTE-CHEMO or received earlier

VTE-CHEMO, and interestingly, the highest rate of ICH progression was observed in patients who never received VTE-CHEMO. A lack of temporal association of ICH progression with initiation of VTE-CHEMO supports the previous literature suggesting its safety.^{12,33,34} However, ICH progression likely prevents providers from initiating VTE-CHEMO or radiological progression may be falsely accredited to VTE-CHEMO. Some have suggested a lack of an association between VTE-CHEMO and ICH progression, including a retrospective cohort study of 669 patients with TBI by Koehler *et al.*¹⁰ in which early (<72 h) VTE-CHEMO did not increase the rate of ICH progression. In contrast, in a WTA multicenter study evaluating VTE-CHEMO in patients with TBI, they reported significantly higher rates of ICH with VTE-CHEMO (42% for those on LWMH *versus* 24% without).⁹ Similarly, in a retrospective study of 340 patients with TBI and an overall progression rate of 32%, VTE-CHEMO was associated with 13-fold increased odds of ICH progression on consequent CTH scans.¹⁵ Ultimately, evidence linking attribution of ICH progression to initiation of VTE-CHEMO remains mixed and highlights need for prospective clinical trials to clarify this relationship.

There are several limitations to this retrospective study. First, possible sampling bias exists, as we were limited to patients who had an admission and serial CTH scans. It is possible that patients who received VTE-CHEMO and never underwent subsequent head imaging had an uncomplicated course; it is also plausible this bias may have led to underestimation of ICH progression. However, we also believe inclusion of patients with a singular CTH would also have biased the results, such that the patients in this group either would have died early from devastating injury, with or without interventions and therapies (survivor bias), or would have been discharged before enough time in hospital to confer VTE risk (and are low-risk patients not relevant to questions of inpatient VTE-CHEMO). We also do not know the reason additional CTH scans were ordered (whether a change in examination warranted radiological investigation or rather a CTH was routinely ordered), and one could argue that when progression may be detected on CTH, it may not be clinically significant. We additionally do not know the ventriculostomy rates or intracranial hypertension data to further contextualize why VTE-CHEMO may have been held; however, we would highlight that our data highlighted a pervasive practice of delaying or holding chemoprophylaxis, so much so that we suspect concerns over intracranial hypertension would not explain most patients' chemoprophylaxis status. Another limitation of this study is the small number of VTE, which may limit power to detect differences by VTE-CHEMO timing; given a low rate of VTE in this population and the seeming lack of large impact of VTE-CHEMO timing, this study highlights the need for prospective multicenter clinical trials to further examine these issues. Our analysis identified inconsistent practices in VTE-CHEMO across centers with the rates and timing differing by institution (one center performed surveillance ultrasounds, as detailed in Supplemental Digital Content 1), differing VTE rates, and variable adherence to institutional protocols within individual centers. However, interestingly, the difference in VTE rates between institutions did not correspond with surveillance practices or chemoprophylaxis strategies, and as such, supports that the heterogeneity in centers' screening and prophylaxis strategies may not bias our analysis on VTE. Despite this, to account for the interfacility heterogeneity, we did perform intrafacility clustering in our statistical analysis to mitigate bias as a result of institutional variability.

Given our data includes level I and level II trauma centers, not surprisingly, several of the patients were transferred from outside hospitals; although it is known that transfer status is associated with higher VTE risk and transfer patients may have longer time to VTE-CHEMO, we compared VTE rates between transfer and nontransfer patients and there was no difference. Finally, we did not have two radiologists for independently reviewing all the CTH scans; given 1803 patients were included who each had up to five head CTs (potentially over 9000 scans to review), we had a random subset selected to ensure an acceptable rate of interrater reliability. Given the interrater reliability was >90%, we feel confident there is minimal bias introduced by different providers reviewing the images.

Conclusions

This study presents multicenter data on VTE incidence and ICH progression in the context of chemoprophylaxis strategies in patients with polytrauma and TBI. We identified benefit from early VTE-CHEMO and identified high-risk groups who may benefit from more aggressive prophylaxis approaches, such as consistent weight-based dosing in all patients (regardless of provider, BMI, and other patient-specific factors) or more frequent or higher dosages of VTE-CHEMO. Future investigation is required to identify if patients with obesity, more severe injury, and concomitant pelvic or femur fracture or spinal cord injury may benefit from more aggressive VTE-CHEMO strategies and whether current recommendations for aggressive VTE-CHEMO strategies should focus on these higher risk groups. These data also highlight undue risk to patients by withholding VTE-CHEMO, and future research is required to investigate the data behind concern for bleeding risk in the perioperative period with VTE-CHEMO. Examination of the safety of VTE-CHEMO in patients with TBI is paramount and further exploration of this data set will more fully characterize risk factors for ICH progression, its clinical significance, and development of VTE despite VTE-CHEMO. Although an important contribution to the literature, these results in the context of previous data suggest true clinical equipoise and the need for a prospective randomized clinical trial with structured strategies and meaningful end points to help refine clinical best practices.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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VTE-CHEMO=VTE chemoprophylaxis, VTE=venous thromboembolism, ICH=intracranial hemorrhage

Fig. 1 –.

Patient inclusion with site-specific practices with intracranial progression and venous thromboembolism incidence. ICH, intracranial hemorrhage; VTE = venous thromboembolism; VTE-CHEMO = venous thromboembolism chemoprophylaxis.

Table 1 –

Patient characteristics and outcomes (n = 1803).

Demographics, injury characteristics, and clinical outcomes	N (%) or median (IQR)
Demographics	
Male sex (%)	1247 (69)
Age (y)	55 [35,72]
BMI	25 [22,29]
Institution (%)	
1	705 (39)
2	328 (19)
3	291 (16)
4	262 (14)
5	217 (12)
Injury characteristics	
GCS on arrival	14 [8,15]
ISS	22 [16,27]
Head AIS	4 [3,5]
SBP on arrival (mm Hg)	137 [120, 157]
Mechanisms of injury (%), top 5	
Fall	876 (49)
MVC	334 (19)
MCC	156 (9)
Assault	117 (6)
Pedestrian versus automobile	111 (6)
Isolated TBI (%)	1644 (91)
Spinal cord injury (%)	37(2)
Blunt cerebrovascular injury (%)	99(5)
Pelvis injury (%)	134 (7)
Femur injury (%)	81 (4)
Tibia injury (%)	92(5)
Outcomes	
Neurosurgical intervention, craniotomy or craniectomy (%)	344 (19)
Immediate intervention	288 (16)
Delayed intervention	56 (3)
Length of stay (d)	7 [5,13]
ICU length of stay (d)	3 [2,8]
Ventilator days	0 [0,4]
Disposition (%), top 3	
Home	548 (30)
Acute rehabilitation, SNF, or LTAC	933 (51)
Death	157 (9)

Values are presented as the median with interquartile ranges [IQR] or number (N) with percent as appropriate.

AIS = Abbreviated Injury Scale; BMI = body mass index; GCS = Glasgow Coma Scale; ICU = intensive care unit; ISS = Injury Severity Score; LTAC = long-term care facility; MCC = motorcycle collision; MVC = motor vehicle collision; SBP = systolic blood pressure; SNF = skilled nursing facility; TBI = traumatic brain injury.

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Table 2 –

Timing of prophylaxis and VTE outcomes (n = 1803).

VTE and VTE-CHEMO details	Number (%)
VTE-CHEMO timing	
Early <48 h	443 (25)
Early <24h	53 (3)
Late 48 h	841 (47)
Never	519 (29)
VTE, any	137 (8%)
PE	29 (2%)
DVT	118 (7%)
Median time in hours to VTE prophylaxis initiation (IQR)	63 [42, 88]

Values are presented as the median with interquartile ranges or number with percent as appropriate.

DVT = deep venous thrombosis; IQR = interquartile range; PE = pulmonary embolism; VTE = venous thromboembolism; VTE-CHEMO = venous thromboembolism chemoprophylaxis.

Table 3 –

Comparison of patients who developed VTE to those who did not.

Demographics, injury characteristics, and clinical outcomes	No VTE (n = 1666)	VTE (n = 137)	P value
Male sex (%)	1142 (69)	105 (77)	0.05
Age (y)	56 [35, 72]	51 [33, 64]	0.01
BMI > 30 (%)	250 (15)	37 (27)	<0.001
GCS on arrival	14 [9, 15]	10 [3, 14]	<0.001
ISS	21 [14, 26]	27 [18, 35]	<0.001
Head AIS	4 [3, 5]	4 [3, 5]	0.02
SBP on arrival (mm Hg)	138 [121, 157]	133 [111, 159]	0.22
Isolated TBI (%)	1544 (93)	100 (73)	<0.001
Spinal cord injury (%)	27 (2)	10 (7)	<0.001
Blunt cerebrovascular injury (%)	85 (5)	14 (10)	0.03
Pelvis injury (%)	112 (7)	22 (16)	<0.001
Femur injury (%)	63 (4)	18 (13)	<0.001
Tibia injury (%)	84 (5)	8 (6)	0.69
Neurosurgical intervention (%)			<0.001
Immediate	199 (12)	29 (21)	
Delayed	101 (6)	15 (11)	
None	1366 (82)	93 (68)	
Time to initiation (h)	62 [41, 86]	68 [48, 101]	0.01
VTE prophylaxis timing (%)			<0.001
Early <48 h	413 (25)	30 (22)	
Late 48 h	753 (45)	88 (64)	
Never	500 (30)	19 (14)	
VTE prophylaxis timing (%)			<0.001
Early <24 h	48 (3)	5 (4)	
Late 24 h	1118 (67)	113 (82)	
Never	500 (30)	19 (14)	
Length of stay (d)	7 [4, 12]	18 [10, 28]	<0.001
ICU length of stay (d)	3 [2, 7]	12 [5, 19]	<0.001

Demographics, injury characteristics, and clinical outcomes	No VTE (n = 1666)	VTE (n = 137)	P value
ICU free days	5 [4, 9]	8 [3, 17]	0.26
Ventilator days	0 [0, 3]	7 [0, 14]	<0.001
Ventilator free days	3 [2, 6]	5 [0, 11]	<0.001
Death (%)	136 (8)	21 (15)	0.01

Values are presented as the median with interquartile ranges or number with percent as appropriate.

AIS = Abbreviated Injury Scale; BMI = body mass index; GCS = Glasgow Coma Scale; ICU = intensive care unit; ISS = Injury Severity Score; SBP = systolic blood pressure; TBI = traumatic brain injury; VTE = venous thromboembolism.

Table 4 –

Comparison of patients who missed VTE-CHEMO doses to those who did not (among patients who ever received VTE-CHEMO, $n = 1288$).

Demographics, injury characteristics, and clinical outcomes	Missed doses ($n = 196$)	No missed doses ($n = 1092$)	P value
Male sex (%)	128 (65)	780 (71)	0.09
Age (y)	54 [33, 69]	46 [28, 60]	<0.001
BMI	26.0 [22.4, 29.7]	25.7 [22.4, 29.4]	0.70
GCS on arrival	12 [5, 15]	14 [8, 15]	0.001
ISS	27 [19, 34]	22 [17, 27]	<0.001
SBP on arrival (mm Hg)	127 [110, 147]	138 [120, 156]	<0.001
Spinal cord injury (%)	6(3)	26 (2)	0.62
Blunt cerebrovascular injury (%)	25 (13)	64(6)	0.001
Pelvis injury (%)	42 (21)	77 (7)	<0.001
Femur injury (%)	26 (13)	48 (4)	<0.001
Tibia injury (%)	32 (16)	52 (5)	<0.001
Anticoagulation before injury (%)	31 (16)	266 (24)	0.01
Time to initiation (h)	57 [38, 82]	64 [42, 89]	0.02
VTE prophylaxis timing (%)			0.26
Early <48 h	75 (38)	372 (34)	
Late >48 h	121 (62)	720 (66)	
Length of stay (d)	17 [12, 26]	8 [5, 14]	<0.001
ICU length of stay (d)	12 [5, 18]	4 [2, 8]	<0.001
Ventilator days	5 [0, 14]	0 [0, 5]	<0.001
VTE (%)	39 (20)	82 (8)	<0.001
Death (%)	12(6)	69 (6)	0.99

Values are presented as the median with interquartile ranges or number with percent as appropriate.

BMI = body mass index; GCS = Glasgow Coma Scale; ICU = intensive care unit; ISS = Injury Severity Score; SBP = systolic blood pressure; TBI = traumatic brain injury; VTE = venous thromboembolism; VTE-CHEMO = venous thromboembolism chemoprophylaxis.

Table 5 –

Multivariable analysis using Cox proportional hazards regression for venous thromboembolism risk, accounting for intrafacility clustering and adjusted for age, male sex, BMI >30, ISS, pelvic/femoral fracture, and spinal cord injury ($n = 1579$).

Variable	Hazard ratio	95% Confidence interval	P value
Age	1.00	0.96–1.01	0.29
Male sex	1.03	0.99–1.06	0.07
BMI > 30	1.05	1.02–1.09	0.002
ISS	1.00	1.00–1.00	<0.001
Pelvic or femoral fracture	1.05	1.04–1.07	<0.001
Spinal cord injury	1.28	1.04–1.57	0.02
Immediate NS intervention			
Immediate versus delayed prophylaxis	1.13	1.00–1.27	0.04
Delayed versus no prophylaxis	0.99	0.91–1.08	0.89
Delayed NS intervention			
Immediate versus delayed prophylaxis	1.21	1.10–1.35	0.0001
Delayed versus no prophylaxis	1.03	0.92–1.16	0.55
Missed VTE-CHEMO doses	1.08	1.02–1.14	0.008

BMI = body mass index; ISS = Injury Severity Score; NS = neurosurgical; VTE-CHEMO = venous thromboembolism chemoprophylaxis.