The American Journal of Surgery xxx (xxxx) xxx

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.elsevier.com/locate/amjsurg

Original Research Article

Timing of venous thromboembolic pharmacological prophylaxis in traumatic combined subdural and subarachnoid hemorrhage

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ARTICLE INFO

Keywords:
Venous thromboembolism
Subdural hematoma
Subarachnoid hemorrhage
Prophylaxis

ABSTRACT

Background: The combination of subdural and subarachnoid hemorrhage is the most common intracranial bleeding. The present study evaluated the timing and type of venous thromboembolic chemoprophylaxis (VTEp) for efficacy and safety in patients with blunt head trauma with combined acute subdural and subarachnoid hemorrhage.

Methods: Patients with isolated combined acute subdural and subarachnoid hemorrhage were extracted from the ACS-TQIP database (2013–2017). After 1:1 cohort matching of patients receiving early prophylaxis (EP, ≤48 h) versus late prophylaxis (LP, >48 h) outcomes were compared with univariable and multivariable regression analysis.

Results: Multivariable regression analysis identified EP as an independent protective factor for VTE complications (OR 0.468, CI 0.293–0.748) but not mortality (p = 0.485). The adjusted risk for delayed craniectomy was not associated with EP compared to LP (p = 0.283). The type of VTEp was not associated with VTE complications (p = 0.301), mortality (p = 0.391) or delayed craniectomy (p = 0.126).

Conclusions: Early VTEp (≤48 h) was associated with fewer VTE complications in patients and did not increase the risk for craniectomies in patients with combined acute subdural and subarachnoid hemorrhage.

1. Introduction

In 2019, a total of 61,000 traumatic brain injury (TBI)-related deaths were recorded in the United States.[1] Importantly, TBI accounts for approximately one-third of all trauma deaths. Patients with severe TBI are also at risk for significant morbidity, including a high risk for venous thromboembolism (VTE), which may occur soon after the traumatic event.[2] TBI in severely injured patients itself is a risk factor for VTE, due to the systemic release of tissue factors, which may trigger a hypercoagulable state.[3–5] Prolonged immobilization and hospital stay may further contribute to the high risk of VTE in patients with severe TBI.

The early initiation of pharmacological prophylaxis reduces this risk of VTE, but there is concern it may increase the risk for progression of the intracranial hemorrhage.

A systematic review demonstrated that VTEp administration within 24–72 h postinjury in patients with TBI and stable injury is effective and safe.[6] Of the 21 included studies the majority defined early VTEp as initiation within 72 h of admission. However, four studies suggested that administering VTEp within 24 h of injury in patients with stable TBI does not lead to progressive intracranial hemorrhage. As a consequence, for the present study we defined early prophylaxis as initiation of VTEp within 48 h of admission.

In a recent study[7] of isolated blunt traumatic injuries with acute subdural hematoma (SDH), it was reported that early VTE prophylaxis (≤48 h) was associated with fewer thromboembolic events. The early initiation of VTE pharmacological prophylaxis (VTEp) was safe and not associated with an increased risk of bleeding complications. In order to eliminate confounding factors which could complicate the analysis and interpretation of the efficacy and safety of VTEp, the study excluded patients with severe associated extracranial injuries or other types of intracranial hemorrhages. However, simultaneous occurrence of different types of hemorrhage is common, especially in severe traumatic

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https://doi.org/10.1016/j.amjsurg.2021.11.021
Received 22 October 2021; Received in revised form 13 November 2021; Accepted 15 November 2021
Available online 18 November 2021

brain injury. Furthermore, subarachnoid hemorrhage (SAH) in particular is known to cause extracranial manifestations, such as fever, tachycardia, EKG and troponin abnormalities.[8] Different types of intracranial hemorrhage with the subsequent physiological changes may be associated with different risks of VTE complications, and therefore may respond differently to pharmacological prophylaxis.

SDH is the most common intracranial bleeding and often associated with SAH.[9,10] In a multicenter study from Italy, the incidence of traumatic subdural hemorrhage in patients with TBI admitted to the intensive care unit (ICU) was 31.7%. The simultaneous occurrence of a subarachnoid hemorrhage was documented in 61.5%.[11] The aim of the present study was to evaluate the efficacy and safety of early VTEp in isolated TBI patients with the frequent combination of SDH and SAH. We hypothesized that early VTEp in patients with severe TBI and combined SDH and SAH is safe and associated with fewer thromboembolic events.

Due to neuroprotective properties, we further hypothesized that low-molecular weight heparin (LMWH) is superior to unfractionated heparin (UH) in patients with severe TBI and combined SDH and SAH.

2. Material and methods

The study was approved by the Institutional Review Board of the University of Southern California.

2.1. Patient selection and data collection

This is a cohort-matched study using the American College of Surgeons Trauma Quality Improvement Program (ACS TQIP) database from January 2013 to December 2017. The database was queried to identify all adult patients (≥16 years old) who sustained a traumatic brain injury (TBI) that resulted in combined acute SDH and SAH. The patients were identified by AIS PreDot codes associated with combined acute SDH and SAH. Patients with isolated acute combined SDH and SAH were then extracted by excluding those with face, neck, chest, abdomen, spine, extremity and external AIS ≥3. Patients with other associated intracranial hemorrhages such as epidural, intra-parenchymal and intraventricular hemorrhages were also excluded.

Additionally, patients were excluded if they died or were discharged within 72 h from admission or were transferred from another facility. Other exclusion criteria were: patients who received any pharmacological venous thromboembolic other than unfractionated heparin (UH) or low molecular weight heparin (LMWH) and patients with a history of bleeding diathesis or with missing data regarding VTEp and its timing. Furthermore, patients who underwent a craniectomy or an ICP monitor placement before the initiation of VTEp were also excluded.

Variables extracted from the TQIP database included patient demographics (age, gender), admission data [systolic blood pressure (SBP), heart rate (HR), Glasgow Coma Score (GCS)], abbreviated injury scores (AIS), injury severity score (ISS), timing and type of VTE prophylaxis. Primary outcomes of interest were pulmonary embolism (PE), deep venous thrombosis (DVT) summarized as VTE (PE + DVT), return to the operating room, delayed craniectomy (defined as performed after the initiation of VTEp) and mortality. Secondary outcomes included need and duration intensive care unit (ICU) stay, need and duration of mechanical ventilation, and hospital length of stay (LOS).

Patients were finally divided in two groups based on timing of VTEp initiation: early prophylaxis, defined as ≤48 h (EP), or late prophylaxis, defined as >48 h (LP) after admission.

2.2. Cohort matching

A 1:1 cohort matching of patients receiving EP vs LP was performed on the basis of the following criteria: age (≥65, <65 years), gender, hypotension (SBP <90 mmHg), tachycardia (HR > 120 bpm), GCS, head AIS and the type of VTEp (LMWH, UH). The matching tolerance was 0 for all matching criteria. Matching was performed without replacement.

2.3. Statistical analysis

Normality of distribution was assessed using histograms, skewness, kurtosis, and the Shapiro-Wilk test. Univariate analysis was performed to identify differences between the EP and LP group. Pearson's chi-squared or Fischer Exact test was used to compare proportions for categorical variables, while the Mann-Whitney *U* test was used to compare continuous variables. Results were reported as numbers and percentages for categorical variables or medians and interquartile ranges (IQR) for continuous variables.

In the matched cohorts the effect of timing and type of VTEp was further analyzed with logistic regression analysis. Outcomes (VTE complications including DVT and PE; mortality and delayed craniectomy) were included as dependent variables in the logistic regression analysis. Clinically important predictor variables (Age >65, gender, hypotension, tachycardia, GCS <9, AIS head, VTE type) were correlated with the dependent variables using Pearson's chi-squared or Fischer Exact as appropriate and entered in the regression models if the p value was <0.2. Correlation between variables were tested with multicollinearity analysis. Results were reported as odds ratio (OR) and 95% confidence interval (CI). Regression model performance was assessed using goodness of fit, Snell's R-square, and adjusted R-square. Variables with p value < 0.05 were considered significant. All statistical analysis was performed using SPSS version 23.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Unmatched cohort characteristics

A total of 7,380 patients with isolated blunt TBI with a combined acute SDH and SAH met the inclusion criteria (Fig. 1). Of these, 4,876 patients (66.1%) received LP and 2,504 (33.9%) received EP.

3.2. Cohort matching

A 1:1 cohort matching resulted in 2,152 matched cases, which formed the basis of the present study. All matching variables [age (≥65, <65 years), gender, hypotension (SBP < 90 mmHg), tachycardia (HR > 120bpm), GCS, head AIS and the type of VTEp (LMWH, UH)] were equally distributed between patients receiving EP and LP. As well, the ISS between the two groups was similar [$16^{10–18}$ vs $16,^{10–20}$ p = 0.206] (Table 1).

In the matched cohorts overall VTE complications (2.6% vs 1.3%, p = 0.002) including DVT (2.1% vs 1.0%, p = 0.006) were more common in the LP compared to the EP group. The rate of PE was 0.7% in the LP group vs 0.4% in the EP group, p = 0.228. The craniectomy rate after initiation of VTE prophylaxis were not significantly different between the EP and LP group (1.2% vs 0.8%, p = 0.358). ICU admission rate was higher in the LP group (87.1% vs 80.8%, p < 0.001), including longer ICU LOS [$5^{3–10}$ vs $3^{2–5}$ days, p < 0.001] and hospital LOS [$10^{6–17}$ vs $6^{4–11}$ days, p < 0.001] compared to the EP group. The majority of patients were discharged home with a higher percentage when receiving EP compared to LP (56.2% vs 44.2%, p < 0.001). The mortality in patients with isolated combined acute SDH and SAH was 2.4% when receiving EP and 2.7% when receiving LP. (p = 0.564) (Table 2).

3.3. Adjusted effect of timing and type of VTEp

The adjusted effect of EP in patients with isolated combined SDH and SAH is shown in Table 3. EP compared to LP was independently associated with fewer overall VTE complications (OR 0.468, CI 0.293–0.748) including DVT (OR 0.478, CI 0.285–0.802). The timing of the VTEp had no independent effect on mortality (p = 0.485) or delayed craniectomy (p = 0.283).

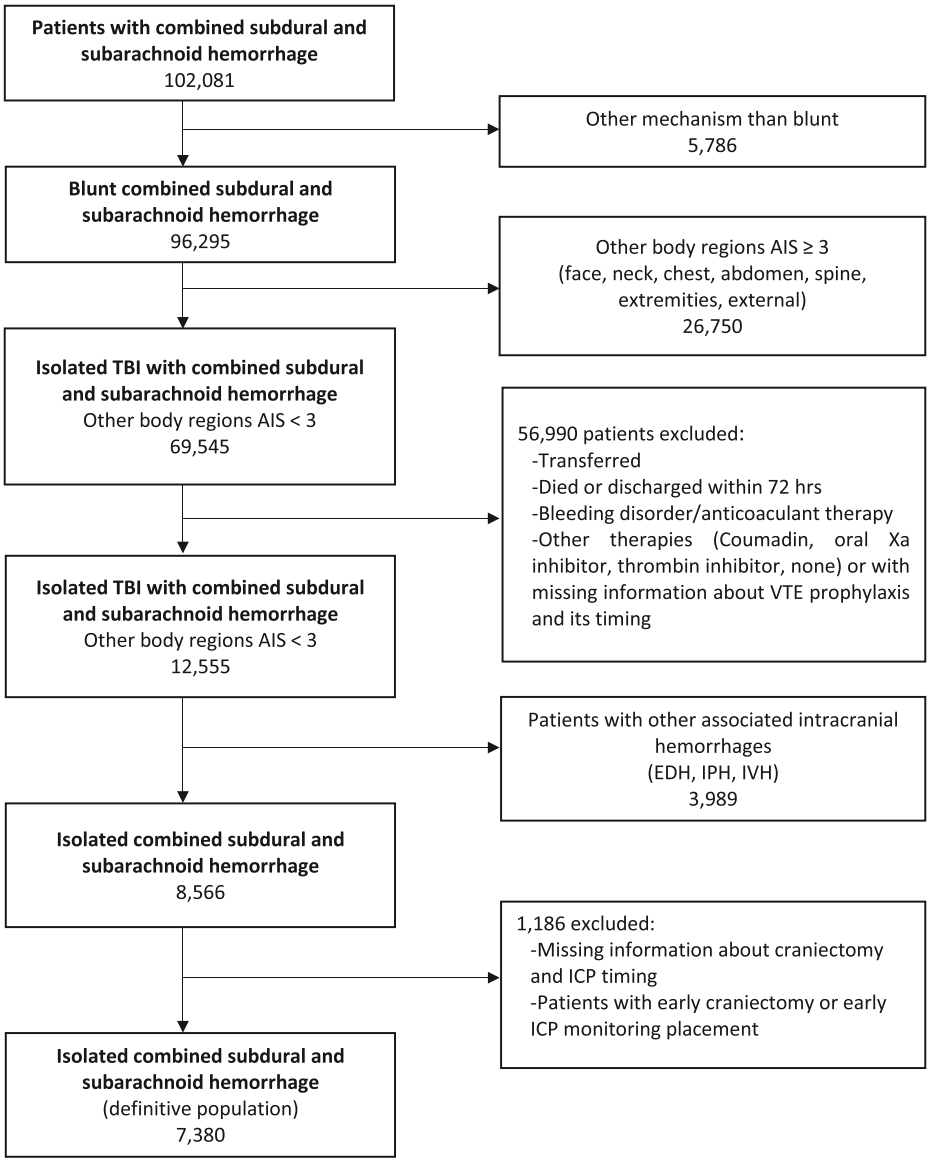

Fig. 1. Patient flowchart.
Abbreviations: AIS, abbreviated injury score; TBI, traumatic brain injury; VTE, venous thromboembolism; EDH, epidural hemorrhage; IPH, intra-parenchymal hemorrhage; IVH, intra-ventricular hemorrhage; ICP, intra cranial pressure.

The type of VTEp was not associated with VTE complications ($p = 0.301$), mortality ($p = 0.391$) or delayed craniectomy ($p = 0.126$). Table 4.

No significant collinearity was detected between the predictor variables of the regression models. The VIF was smaller than 2.0 for all variables included in the regression models. The model performances are outlined in Tables 3 and 4.

4. Discussion

There is evidence that VTEp within 48 h of admission is safe and effective in preventing VTE complications in TBI patients.[7,12–14] However, there remain concerns that initiation of VTEp, especially early initiation, may increase the risk for progression of intracranial bleeding.[15] As a result, the initiation of VTEp after TBI is handled inconsistently and there is wide variability in clinical practice amongst surgeons and institutions across the United States (16–18). This is also reflected by the current guideline-recommendations. The Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition[19] states that there is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for deep vein thrombosis. The American College of Surgeons recommends, in the best practice guidelines for the management of TBI, that VTEp should be considered within the first 72 h following TBI in most cases.[20]

Most studies investigating the optimal timing for VTEp in traumatic brain injury include all different types of intracranial hemorrhage,[3,13,15,21–24] although there is evidence that different types of intracranial hemorrhage may be associated with different risks of VTE complications.[2] The type of intracranial hemorrhage affects the hemodynamic presentation of the patient. This fact may contribute to different risks of VTE complications in different types of intracranial hemorrhages. In particular, SAH is often associated with tachycardia, EKG abnormalities, elevated troponin levels and fever, which could complicate the interpretation of the data.[8] To minimize these problems, the aim of the present study was to evaluate the efficacy and safety of early prophylaxis in patients with isolated severe blunt TBI with the common combination of a combined acute SDH and SAH.

Table 1
Patients Characteristics and Clinical Data after case control matching.

	Total	≤48 h	>48 h	
	4304 (%)	2152 (%)	2152 (%)	***P value***
DEMOGRAPHICS				
Age (years)[a]	56 (40–69)	55 (38–69)	56 (40–69)	0.323
≥65 years	1370 (31.8)	685 (31.8)	685 (31.8)	1.000
Gender				
Male	2970 (69.0)	1485 (69.0)	1485 (69.0)	1.000
PHYSIOLOGIC DATA AND ADMISSION VITALS SIGNS				
Hypotension, SBP <90	8 (0.2)	4 (0.2)	4 (0.2)	1.000
Tachycardia, HR > 120	192 (4.5)	96 (4.5)	96 (4.5)	1.000
GCS[a]	14[12–15]	14[12–15]	14[12–15]	1.000
AIS Head				
3	1480 (34.4)	740 (34.4)	740 (34.4)	1.000
4	2416 (56.1)	1208 (56.1)	1208 (56.1)	
5	408 (9.5)	204 (9.5)	204 (9.5)	
ISS[a]	16[10–20]	16[10–18]	16[10–20]	0.206
TYPE OF VTE PROPHYLAXIS				
UH	2202 (51.2)	1101 (51.2)	1101 (51.2)	1.000
LMWH	2102 (48.8)	1051 (48.8)	1051 (48.8)	

Values are numbers (percentages) unless indicated otherwise.
Abbreviations: SBP, systolic blood pressure; HR, heart rate; GCS, glasgow coma scale; AIS, abbreviated injury score; UH, unfractionated heparin; LMWH, low molecular weight heparin; ICP, intra cranial pressure; PE, pulmonary embolism; DVT, deep vein thrombosis, VTE; venous thromboembolism.
[†]defined as performed after initiation of VTE prophylaxis.
[a] Reported as IQR.

Table 2
Interventions and outcomes of patients after case control matching.

	Total	≤48 h	>48 h	
	4304 (%)	2152 (%)	2152 (%)	***P value***
INTERVENTIONS				
Unplanned return to OR	22 (0.5)	8 (0.4)	14 (0.7)	0.200
Delayed Craniectomy[b]	43 (1.0)	25 (1.2)	18 (0.8)	0.358
OUTCOMES				
PE	25 (0.6)	9 (0.4)	16 (0.7)	0.228
DVT	67 (1.6)	22 (1.0)	45 (2.1)	**0.006**
VTE	83 (1.9)	27 (1.3)	56 (2.6)	**0.002**
ICU admission rate	3612 (83.9)	1738 (80.8)	1874 (87.1)	**< 0.001**
ICU LOS[a c] (days)	4[2–7]	3[2–5]	5[3–10]	**< 0.001**
Hospital LOS[a](days)	8[5–14]	6[4–11]	10[6–17]	**< 0.001**
Hospital disposition				
Home	2160 (50.2)	1209 (56.2)	951 (44.2)	**< 0.001**
Rehabilitation center	1062 (24.7)	434 (20.2)	628 (29.2)	
Nursing home	548 (12.7)	262 (12.2)	286 (13.3)	
Hospital	176 (4.1)	64 (3.0)	112 (5.2)	
other	358 (8.3)	183 (8.5)	175 (8.1)	
Mortality	111 (2.6)	52 (2.4)	59 (2.7)	0.564

Values are numbers (percentages) unless indicated otherwise.
Abbreviations: ICP, intra cranial pressure; PE, pulmonary embolism; DVT, deep vein thrombosis; VT, venous thromboembolism; ICU, intensive care unit; LOS, length of stay.
[a] Reported as IQR.
[b] Defined as performed after initiation of VTE prophylaxis.
[c] Reported only for patients who were admitted to ICU.

The present study found that the initiation of early VTEp (≤48 h) was independently associated with fewer VTE complications without an increased risk for bleeding complications after the initiation of VTEp. The timing of VTEp had no independent effect on mortality. Furthermore, the type of VTEp (LMWH or UH) had no effect on mortality, VTE complications or delayed craniectomy.

In a recently published retrospective study performed at our department,[7] similar findings were reported in patients with isolated TBI and acute SDH. Early initiation of VTEp (≤48 h) reduced the risk of VTE, including DVT and PE. In the present study, EP was also associated with fewer overall VTE complications, including DVT. However, we did not observe a significant reduction of PE associated with EP compared to LP. This may be explained by the small overall number of only 25 patients with PE. In line with our findings, initiation of VTEp within 48 h was not associated with an increased risk for craniectomy. It is important to note that there is evidence that an even earlier VTEp (<24 h) may be safe and more effective.[25–27] In the present study, 626 patients (8.5%) received VTEp before 24 h. This small proportion precludes any meaningful further analysis. Future studies should investigate if an even earlier VTEp may be safe and more effective, especially in patients with TBI.

Previous studies reported a protective effect of LMWH over UH in trauma patients.[7,13,28] In particular, in traumatic brain injury, neuroprotective properties, including a reduction of posttraumatic brain edema, may be associated with LMWH and could explain improved outcomes.[29–31] Other studies in TBI patients comparing LMWH with UH found a more efficient prevention of VTE complications when LMWH is used.[13] In particular, a lower rate of PE contributes to better outcomes, including improved mortality. However, in the present study, we did not demonstrate an independent effect of LMWH over UH on mortality, VTE or delayed craniectomy. Especially SAH, with all possible associated physiological changes,[8] may interact differently to pharmacological prophylaxis compared to other types of brain injury. To date, no study has examined the type of VTEp (LMWH vs UH) in isolated subarachnoid hemorrhage in terms of outcomes. Future research should focus on better understanding the different interactions of VTEp in different injury patterns.

This is the first study evaluating the timing and type of VTEp in patients with isolated severe TBI and a combined SDH and SAH. The frequent combination of SDH and SAH in TBI warrants an analysis of the optimal timing and type of VTEp, particularly because physiologic changes associated with SAH may interact differently with VTE complications and thromboembolic prophylaxis. A strength of the present study is the design, evaluating isolated severe TBI patients only. This helps to minimize confounding factors of heterogenous injury patterns regarding to venous thromboembolic prophylaxis. However, several limitations must be acknowledged: the study is subject to all limitations associated with the retrospective design based on a large database. First, the medical course, including repeated CT scans, is not recorded in the TQIP database and could not be considered for the decision-making process of the initiation of the VTEp. Furthermore, progression of subclinical hemorrhage is not recorded in the TQIP database and could not be considered as a safety parameter. In addition, the administration of UH and LMWH was not randomized. Finally, duration and held doses after initiation of the VTEp, as well as Anti-Xa levels for VTEp monitoring are not recorded by the TQIP database. In conclusion, the initiation and choice of VTEp may have depended on factors that could not be corrected for and therefore may have contributed to bias in our results.

5. Conclusion

Early VTEp (≤48 h) in patients with isolated severe blunt TBI with a combined acute subdural and subarachnoid hemorrhage is associated with fewer venous thromboembolic events without increasing the risk for craniectomies. The type of VTEp (UH vs LMWH) was not independently associated with thromboembolic events, mortality or craniectomies after the initiation of the VTEp. In the appropriate clinical setting, the present study suggests early initiation of VTEp in patients with isolated severe blunt TBI and a combined acute subdural and subarachnoid hemorrhage.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Table 3
Adjusted effect of early VTEp in patients with isolated combined subdural and subarachnoid hemorrhage compared to late VTEp.

	OR	95% CI (upper/lower)		*p* value	Goodness of fit *p*	Cox & Snell R^2	Nagelkerke R^2
VTE complications[a]	**0.468**	0.293	0.748	**<0.001**	0.393	0.017	0.099
PE[b]	0.557	0.245	1.269	0.164	0.949	0.007	0.106
DVT[a]	**0.478**	0.285	0.802	**0.005**	0.322	0.014	0.092
Mortality[c]	0.869	0.587	1.287	0.485	0.349	0.037	0.174
Delayed craniectomy[d]	1.398	0.758	2.577	0.283	0.630	0.007	0.070

Logistic regression analysis.
Abbreviations: VTEp, venous thromboembolism prophylaxis; OR, odds ratio; CI, confidence interval; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; GCS, glasgow coma score; AIS, abbreviated injury score.
[a] Adjusted for gender, tachycardia, GCS, head AIS, VTE type.
[b] Adjusted for gender, GCS, head AIS, VTE type.
[c] Adjusted for age, hypotension, GCS, head AIS, VTE type.
[d] Adjusted for age, gender, GCS, head AIS, VTE type.

Table 4
Adjusted effect of LMWH as VTEp in patients with isolated combined subdural and subarachnoid hemorrhage compared to UH.

	OR	95% CI (upper/lower)		*p* value	Goodness of fit *p*	Cox & Snell R^2	Nagelkerke R^2
VTE complications[a]	0.786	0.498	1.240	0.301	0.393	0.017	0.099
PE[b]	0.710	0.308	1.637	0.421	0.928	0.007	0.104
DVT[a]	0.753	0.453	1.252	0.275	0.322	0.014	0.092
Mortality[c]	0.836	0.556	1.258	0.391	0.474	0.037	0.174
Delayed craniectomy[d]	0.606	0.319	1.151	0.126	0.210	0.007	0.068

Logistic regression analysis.
Abbreviations: LMWH, low-molecular weight heparin; VTEp, venous thromboembolism prophylaxis; UH, unfractionated heparin; OR, odds ratio; CI, confidence interval; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; GCS, glasgow coma score; AIS, abbreviated injury score.
[a] Adjusted for gender, tachycardia, GCS, head AIS, VTE timing.
[b] Adjusted for gender, GCS, head AIS, VTE timing.
[c] Adjusted for age, hypotension, GCS, head AIS.
[d] Adjusted for age, gender, GCS, head AIS.

Grant support

None.

Statement of human rights

The study was approved by the Institutional Review Board of the University of Southern California.

Declaration of competing interest

All authors declare no potential conflict of interest.

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