TIMING OF VENOUS THROMBOEMBOLISM PROPHYLAXIS IN SEVERE TRAUMATIC BRAIN INJURY: A PROPENSITY-MATCHED COHORT STUDY

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INTRODUCTION

Trauma is the leading cause of death before the age of 44 in North America [1]. Traumatic brain injury (sTBI) is exceedingly common, affecting 1 in 5 patients with major injury treated at designated trauma centers [2]. Patients with sTBI are at significantly elevated risk for developing venous thromboembolism (VTE) [3], and pulmonary embolism (PE) is a leading cause of death in patients who survive the first 72 hours in hospital [4].

Nonetheless, pharmacologic VTE prophylaxis is often withheld in patients with sTBI out of concern for precipitating extension of intracranial hemorrhage (ICH). Radiologic evidence of ICH is present in more than 45% of patients with TBI [5], and refers to cerebral contusion, subdural hematoma (SDH), subarachnoid hemorrhage (SAH), epidural hematoma (EDH) or intracerebral hemorrhage. These lesions are characterized by a high risk of hemorrhage progression [6, 7]. Therefore, clinicians must simultaneously balance the risks of bleeding and clotting when deciding when to initiate VTE prophylaxis in this most high risk of patient populations.

At present there is no high quality evidence to inform the safe and effective initiation of pharmacologic VTE prophylaxis in patients with sTBI. Guidelines that represent the standard of care vaguely recommend pharmacologic prophylaxis over no prophylaxis, with no mention of safe timing [8]. For this reason, we set out to determine the efficacy of early (<72 hours) versus late (≥72 hours) pharmacologic VTE prophylaxis in patients with sTBI, and to characterize the risk of subsequent intracranial complications or death.

METHODS

Study Design and Definition of Cohort: This was a retrospective cohort study of patients with sTBI who were treated at all level I or II trauma centers participating in the American College of Surgeons Trauma Quality Improvement Program (ACS TQIP) during January 1, 2012 – December 31, 2014.

Data for all patients with sTBI (defined as Head Abberiviated Injury Score [AIS] ≥ 3 and Glasgow Coma Scale [GCS] ≤ 8) who received pharmacologic VTE prophylaxis with either low molecular weight (LMWH) or unfractionated heparin (UH) were derived from ACS TQIP. To mitigate the competing risk of death, patients who died or were discharged before 5 days were excluded from analysis. Patients with penetrating injuries, bleeding disorders, or severe injury to other body regions were also excluded.

Exposure and Outcomes: The exposure of interest was defined as early (<72 hours), versus late (≥72 hours), initiation of pharmacologic VTE prophylaxis. Outcomes were compared between early (EP) and late prophylaxis (LP) groups.

The primary outcome was VTE, defined as PE or deep vein thrombosis (DVT). To capture intracranial complications related to ICH, secondary outcomes were defined as late neurosurgical interventions, and in-hospital death. Late neurosurgical interventions were defined as craniotomy/craniectomy, or intracranial monitor/drain insertion, occurring after 72 hours in hospital. In this patient cohort, more than 90% of neurosurgical interventions were performed within 48 hours of admission – therefore, late interventions likely represent an adverse event or deviation in clinical course.

Covariates: Covariates considered in adjusted analyses reflected patient baseline and injury characteristics. Patient baseline characteristics included, age, gender, race, insurance status and comorbid conditions. Injury characteristics included mechanism of injury, severity of head injury (head AIS), as well as specific traumatic intracranial lesions. The early clinical course was considered as presenting emergency department (ED) characteristics (total and motor GCS, shock and early blood transfusion), as well as early neurosurgical interventions (craniotomy/craniectomy or intracranial monitor/drain insertion before 48 hours). The type of VTE prophylaxis initiation (LMWH or UH) was also considered.

Statistical Analysis: Standardized differences were calculated to compare baseline characteristics between patients who received EP versus LP [9]. Standardized differences of ≥10% represented meaningful differences between groups [10]. Three analytic approaches were then used.

First, we used a propensity score (PS)-matched technique to match patients who received EP, to patients who received LP, based on a PS for EP derived from the covariates described. The incidence of outcomes were then compared between matched EP and LP groups. Odds ratios (ORs) and 95% confidence intervals (CIs) for EP vs. LP were esimated using multilevel mixed models [11] which accounted for the paired nature of the data, and clustering of patients within trauma centers.

Second, multilevel logistic regression models were used on the original unmatched patient cohort to determine the adjusted relationships between EP and the outcomes of interest. This analysis allowed for the effect of prophylaxis type (LMWH vs. UH) to be assessed. A subgroup analysis was also performed on patients at "high risk" for ICH progression, as determined by the Berne-Norwood Criteria [12].

Finally, a center-level analysis was performed, considering hospital EP utilization as the exposure of interest. This analysis answered the question of whether center practices with respect to prophylaxis timing in patients with sTBI affects patient outcomes, and avoided confounding by indication at the patient-level.

RESULTS

During the study period we identified 3,634 patients with sTBI admitted to 186 trauma centers. In this patient population, median GCS was 3 (IQR 3 – 6) and 89% had presence of ICH. There was significant variability in timing of prophylaxis initiation, with a median of 84 hours (IQR 48 – 150 hours). LMWH was the most common agent used (55%). Overall rates of PE and DVT were 1.7% and 6.5% respectively. Approximately 3.7% of patients underwent late neurosurgical intervention, and 8.9% died.

Patients with higher head AIS, worse patterns of intracranial injuries (SDH, EDH, SAH or multi-compartment hemorrhage), and need for early neurosurgical intervention were more likely to receive LP (**Table 1**).

Propensity-Matched Cohort: Propensity score matching yielded a cohort of 2,468 patients well-balanced with respect to baseline characteristics (**Table 1**). After PS-matching, patients who received EP had significantly lower odds of developing PE (OR 0.48; 95%CI 0.25 – 0.91) or DVT (OR 0.51; 95%CI 0.36 – 0.72) compared to LP patients (**Table 2**). There was no significant difference with respect to rates of late neurosurgical interventions or death between matched EP and LP groups.

Prophylaxis Type and High Risk Subgroup: Multilevel logistic regression modelling for the original unmatched patient cohort demonstrated similar results. Specifically, EP was associated with lower odds of VTE compared to LP (OR 0.48; 95%CI 0.35 – 0.65), with no association observed with late neurosurgical intervention or death. Of interest, LMWH was associated with a significantly reduced odds of VTE compared to UH (OR 0.59; 95%CI 0.44 – 0.81). Subgroup

analysis of patients meeting “high risk” criteria for ICH extension demonstrated that EP was protective against VTE, with no increased risk of late intervention or death.

Trauma Center-Level Analysis: There was significant variability in trauma center use of EP (median 34%, IQR 18 – 54%). A trend was observed for hospitals with greater utilization of EP to report lower rates of VTE (**Table 3**). Specifically, trauma centers in the quartile with greatest EP use (>54%) had significantly lower rates of VTE than trauma centers with lowest EP utilization (VTE rate 6.0% vs. 8.6%; OR 0.52; 95%CI 0.30 – 0.91). There was no relationship between hospital EP utilization and rates of late neurosurgical intervention, or mortality.

DISCUSSION

In this observational study of patients with sTBI, we found that pharmacologic VTE prophylaxis initiated before 72 hours was associated with lower odds of PE or DVT compared to late prophylaxis. There was no elevated risk of late neurosurgical intervention or death associated with early prophylaxis. Furthermore, trauma centers with greater utilization of early prophylaxis were observed to benefit from a significantly lower rate of VTE than trauma centers where fewer patients received early prophylaxis.

Severe TBI is a common form of major injury, and patients with sTBI are at risk for secondary injury due to extension of ICH and raised intracranial pressure (ICP) [6, 7]. The same patients are at high risk for developing VTE, including potentially fatal PE [3, 13]. Therefore, clinicians are faced with a critical dilemma with respect to safe timing of initiation of pharmacologic VTE prophylaxis. To date, limited evidence exists to guide this decision-making process, and significant variability exists across trauma centers with respect to timing of pharmacologic prophylaxis initiation [14]. Previous studies examining the influence of prophylaxis timing on VTE rates and adverse outcomes have been strongly limited by small sample sizes at single institutions [15-18]. As a result, current standard of care guidelines are inadequate, and do not address the safety of early VTE prophylaxis in patients with sTBI [8].

To overcome the limitations of previous reports, the strengths of this study included a very large sample size derived from a prospectively-collected, multi-institutional database (ACS TQIP). Our analysis utilized multiple techniques to address potential biases that commonly confound patient selection for timing of VTE prophylaxis initiation. Furthermore, the patient cohort derived in this study were high risk, with ICH present in 89%, making the findings of this study generalizable to the most severely injured patients with sTBI. Findings were further confirmed by subgroup analysis of patients meeting “high risk” criteria of the Berne-Norwood Criteria.

There are several important limitations to consider when interpreting the results of this study. First, there is potential for unmeasured confounding that could not be accounted for in propensity-matched or adjusted analyses. One such important confounder could be change in ICH pattern on head computed tomography (CT), which could not be ascertained in this study, and could affect decision-making to initiate pharmacologic prophylaxis. Furthermore, differencs between trauma centers in practices surrounding mechanical VTE prophylaxis, duplex ultrasound screening for DVT, or critical care of the injured patient, could not be determined. Finally, by using late neurosurgical interventions as a surrogate outcome for intracranial complications or extension of ICH, we would be unable to identify adverse events that did not result in such an intervention. Despite these limitations, our results were robust to multiple analytical techniques, and therefore we are confident that the observed effect of EP compared to LP on patient outcomes is genuine.

CONCLUSIONS

EP was associated with significantly lower rates of VTE compared to LP, with no increase in risk of late neurosurgical intervention or death. Trauma centers with greatest utilization of EP appeared to benefit from significantly lower rates of VTE, with no increase in adverse outcomes. Pharmacologic VTE prophylaxis should be initiated before 72 hours in patients with sTBI.

TABLES and FIGURES

TABLE 1. Baseline Characteristics Before and After Propensity Score Matching

Parameter	Before Matching			After Matching		
	EP (N=1,546)	LP (N=2,088)	Standardized Difference (%)[a]	EP (N=1,234)	LP (N=1,234)	Standardized Difference (%)[a]
Patient Demographics						
Median age, years (IQR)	43 (27-57)	44 (28-58)	3.3	43 (27-57)	43 (28-58)	0.7
Male gender (%)	76.3	76.7	1.1	77.0	75.8	2.7
Race (%)			7.2			3.4
White	68.4	67.0		68.2	67.7	
Black	13.6	12.4		13.1	12.5	
Other	18.0	20.6		18.6	19.8	
Insurance status (%)			12.2			3.2
Commercial	26.0	26.4		26.6	26.1	
Non-commercial	66.8	63.1		65.3	66.5	
Other	7.2	10.5		8.1	7.4	
Comorbid illness (%)						
Coronary artery disease	2.2	2.2	<0.1	1.9	2.4	2.8
Hypertension	24.2	22.6	3.8	23.5	23.5	<0.1
Diabetes mellitus	9.9	9.3	2.1	9.6	9.4	0.5
Chronic renal failure	0.8	0.5	4.5	0.9	0.7	1.8
Stroke with deficit	2.2	1.8	2.7	2.1	2.0	0.6
Obesity	8.5	7.8	2.4	8.4	8.0	1.5
Respiratory disease	5.1	5.8	3.2	5.3	5.9	2.8
Functionally dependent	1.7	1.0	5.4	1.5	1.2	2.1
Current smoker	16.8	17.9	2.9	17.1	17.4	0.9
Injury Characteristics						
Mechanism (%)			11.9			3.3
Fall	38.2	38.6		38.7	38.2	
Motor vehicle collision	25.2	21.4		24.8	25.4	
Motorcycle	9.3	9.1		9.6	8.8	
Pedestrian	8.6	11.3		9.2	9.2	
Other	18.6	19.6		17.7	18.4	
Head AIS score (%)			23.5			1.8
3	21.0	12.8		16.5	16.3	
4	43.5	44.0		45.2	44.6	
5	35.5	43.2		38.3	39.1	
Intracranial lesion (%)						
Intracranial hemorrhage	84.3	92.1	24.4	88.0	88.2	0.5
Epidural hematoma	9.1	12.1	9.7	9.9	9.5	1.4
Subdural hematoma	52.1	61.2	18.4	55.4	55.7	0.6
Subarachnoid hemorrhage	48.6	54.7	12.1	51.5	51.5	<0.1
Multicompartment bleed	36.7	44.7	16.3	39.7	39.9	0.3
Cerebral contusion	32.3	39.7	15.3	34.9	34.5	0.9
Intracerebral mass lesion	6.0	7.2	4.9	6.7	6.8	0.3
Compressed basal cisterns	2.4	4.3	10.7	2.8	3.2	2.4
Brainstem lesion	7.4	8.6	4.4	8.0	8.1	0.3
Skull vault fracture	25.2	27.2	4.5	26.3	25.7	1.3
Open scalp laceration	21.5	20.4	2.7	20.2	20.2	<0.1
ED Characteristics						
Shock (SBP < 90mmHg) (%)	2.3	2.4	0.9	2.1	2.0	0.6
Median GCS motor (IQR)	1 (1 – 4)	1 (1 – 4)	1.0	1 (1 – 4)	1 (1 – 4)	0.7
Median total GCS (IQR)	3 (3 – 6)	3 (3 – 6)	1.8	3 (3 – 6)	3 (3 – 6)	0.7
Transfusion of pRBCs in first 12	7.8	10.6	9.7	9.2	8.3	3.2
Early Neurosurg. Intervention (<48h)						
Craniotomy/craniectomy	16.2	21.5	13.6	17.8	18.0	0.4
Intracranial monitor/drain placement	27.3	32.4	11.2	29.6	29.1	1.1

VTE Prophylaxis Type (%)						
LMWH (vs. UH)	42.0	64.6	46.3	48.2	47.7	1.1

[a] Standardized differences ≥10% indicate a meaningful difference between EP and LP groups

TABLE 2. Outcomes of Interest After Propensity Score Matching

Outcome	Early VTE Prophylaxis (N = 1,234)	Late VTE Prophylaxis (N = 1,234)	Adjusted OR[a] (95% CI)
Venous Thromboembolism			
Pulmonary embolism, n (%)	14 (1.1)	29 (2.4)	0.48 (0.25 – 0.91)
Deep vein thrombosis, n (%)	52 (4.2)	98 (7.9)	0.51 (0.36 – 0.72)
Late Neurosurgical Intervention			
Craniotomy/craniectomy, n (%)	31 (2.5)	36 (2.9)	0.86 (0.53 – 1.4)
Intracranial monitor placement, n (%)	13 (1.1)	17 (1.4)	0.76 (0.37 – 1.6)
Death, n (%)	121 (9.8)	111 (9.0)	1.1 (0.84 – 1.4)

VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval
[a] ORs and 95%CIs estimated using multilevel mixed models accounting for matched pairs and clustering of patients in centers

TABLE 3. Center-level analysis: Early prophylaxis use and trauma center outcomes

			Outcome of Multivariable Model[a]		
Quartile	EP Use (%)	Mean VTE Rate (%)	VTE	Late Neurosurgical Intervention	Death
1	<18	8.6	Reference	Reference	Reference
2	18 - 33	8.5	0.88 (0.52 – 1.5)	0.63 (0.35 – 1.1)	0.79 (0.46 – 1.4)
3	34 - 54	7.5	0.76 (0.44 – 1.3)	0.68 (0.38 – 1.2)	1.2 (0.69 – 2.0)
4	>54	6.0	0.52 (0.30 – 0.91)	0.62 (0.34 – 1.1)	1.1 (0.66 – 1.9)

EP, early prophylaxis (<72 hours); VTE, venous thromboembolism; OR, odds ratio; CI, confidence interval
[a] ORs and 95%CIs estimated using multilevel mixed models accounting for clustering of patients within trauma centers

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