Timing of Pharmacologic Venous Thromboembolism Prophylaxis in Severe Traumatic Brain Injury: A Propensity-Matched Cohort Study

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BACKGROUND: Patients with severe traumatic brain injury (sTBI) are at high risk for developing venous thromboembolism (VTE). Nonetheless, pharmacologic VTE prophylaxis is often delayed out of concern for precipitating extension of intracranial hemorrhage (ICH). The purpose of this study was to compare the effectiveness of early vs late VTE prophylaxis in patients with sTBI, and to characterize the risk of subsequent ICH-related complication.

STUDY DESIGN: Adults with isolated sTBI (head Abbreviated Injury Scale score $\geq$3 and total Glasgow Coma Scale score $\leq$8) who received VTE prophylaxis with low-molecular-weight or unfractionated heparin were derived from the American College of Surgeons Trauma Quality Improvement Program (2012 to 2014). Patients were divided into EP (<72 hours) or LP ($\geq$72 hours) groups. Propensity score matching was used to minimize selection bias. The primary end point was VTE (pulmonary embolism or deep vein thrombosis). Secondary outcomes were defined as late neurosurgical intervention ($\geq$72 hours) or death.

RESULTS: We identified 3,634 patients with sTBI. Early prophylaxis was given in 43% of patients. Higher head injury severity, presence of ICH, and early neurosurgery were associated with late prophylaxis. Propensity score matching yielded a well-balanced cohort of 2,468 patients. Early prophylaxis was associated with lower rates of both pulmonary embolism (odds ratio = 0.48; 95% CI, 0.25−0.91) and deep vein thrombosis (odds ratio = 0.51; 95% CI, 0.36−0.72), but no increase in risk of late neurosurgical intervention or death.

CONCLUSIONS: In this observational study of patients with sTBI, early initiation of VTE prophylaxis was associated with decreased risk of pulmonary embolism and deep vein thrombosis, but no increase in risk of late neurosurgical intervention or death. Early prophylaxis may be safe and should be the goal for each patient in the context of appropriate risk stratification. (J Am Coll Surg 2016;223:621−631. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Abbreviations and Acronyms

AIS = Abbreviated Injury Scale
DVT = deep vein thrombosis
EP = early prophylaxis
ICH = intracranial hemorrhage
IQR = interquartile range
LMWH = low-molecular-weight heparin
LP = late prophylaxis
OR = odds ratio
PE = pulmonary embolism
sTBI = severe traumatic brain injury
TBI = traumatic brain injury
TQIP = Trauma Quality Improvement Program
UH = unfractionated heparin
VTE = venous thromboembolism

Traumatic brain injury (TBI) is common, affecting 1 in 5 patients treated for major injury at designated trauma centers.[1] Patients with TBI are at elevated risk for developing venous thromboembolism (VTE) due to prolonged immobilization and systemic hypercoagulability.[2-4] Deep vein thrombosis (DVT) frequently complicates the clinical course, and pulmonary embolism (PE) is a leading cause of delayed mortality.[5]

Patients with TBI are at risk for progression of intracranial hemorrhage (ICH), particularly within the early time period after injury. Therefore, pharmacologic VTE prophylaxis is often withheld in patients with TBI out of concern for precipitating extension of ICH. Radiologic evidence of ICH is present in >45% of all patients with TBI[6] and refers to cerebral contusion, subdural hematoma, subarachnoid hemorrhage, epidural hematoma, or intracerebral hemorrhage. These lesions are characterized by a high risk for hemorrhage progression.[7,8] Therefore, clinicians must balance the risk of ICH progression with that of thromboembolism when deciding to initiate pharmacologic VTE prophylaxis.

There is limited high-quality evidence to inform the safe and effective initiation of VTE prophylaxis in patients with TBI,[9,10] and the timing of prophylaxis initiation in this patient population is not addressed in current guidelines.[11-13] It is not clear whether earlier initiation of prophylaxis results in meaningful reductions in VTE rates, and whether this potential benefit outweighs the risk of precipitating extension of ICH. Therefore, we compared the effectiveness of early (<72 hours) vs late (≥72 hours) pharmacologic VTE prophylaxis in patients with severe TBI (sTBI) and characterized the risk of subsequent ICH-related intracranial complications.

METHODS

Study design

This was a retrospective cohort study of patients with sTBI who were treated at Level I or II trauma centers participating in the American College of Surgeons Trauma Quality Improvement Program (TQIP) from January 1, 2012 to December 31, 2014. This project was approved by the Sunnybrook Health Sciences Center Research Ethics Board.

Study subjects

Data for all adult patients (16 years or older) with isolated sTBI (defined as head Abbreviated Injury Scale [AIS] ≥3 and Glasgow Coma Scale ≤8) who received VTE prophylaxis with either low-molecular-weight heparin (LMWH) or unfractionated heparin (UH) were derived from American College of Surgeons TQIP. Derivation of the patient cohort is outlined in Figure 1. The TQIP began collecting VTE prophylaxis data (type and time of initiation) in 2012. Because collection of these data was implemented in a graduated fashion across participating trauma centers, patients were only included in this study if they were admitted to a given center where collection of these data had begun. Trauma centers missing >10% of VTE prophylaxis data were excluded. To mitigate the competing risk of death, the patient cohort was further limited to patients who survived at least 5 days. Patients with penetrating injuries, bleeding disorders, or severe injury (AIS ≥3) to other body regions were excluded.

Data source

The American College of Surgeons TQIP was established to provide an opportunity for trauma centers to compare outcomes and processes of care with peer centers.[14,15] More than 100 patient and hospital variables are collected, including patient baseline characteristics, injury mechanism and severity, emergency department vital signs, in-hospital procedures, as well as in-hospital outcomes information, including morbidity and mortality. Reliability of data is ensured through abstractor training and inter-rater reliability audits at participating sites. At the time of this study, there were >200 participating ACS or state-verified Level I and II trauma centers across North America.

Exposure

The exposure of interest was defined as early (<72 hours) compared with late (≥72 hours), initiation of pharmacologic VTE prophylaxis in keeping with previous literature.[16-18] Outcomes were compared between early (EP) and late prophylaxis (LP) groups.