Outcomes of Early Initiation of Venous Thromboembolism Prophylaxis in Isolated Traumatic Brain Injuries

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Project Purpose

Trauma patients are at increased risk of venous thromboembolism (VTE) events. Traumatic brain injured (TBI) patients are at especially high risk due to prolonged immobility, associated traumatic injuries, and sedative use (1). TBI is associated with 50,000 deaths and nearly 300,000 hospitalizations annually in the United States. (2) . Incidence of VTE in TBI patients ranges between 18-58% (3). Skrifvars et. al found that despite mechanical and pharmacological prophylaxis, VTE occurs in one out of every five patients with TBI (4). Several limitations are encountered when initiating chemical VTE prophylaxis in TBI patients, including concern for ongoing intracranial hemorrhage (ICH) and ongoing coagulopathy due to endogenous tissue-type plasminogen activator (tPA) causing clot lysis.

Previous VTE prophylaxis protocols have been shown to decrease rate of VTE events (5). Due to the paucity of evidence on VTE prophylaxis guidelines in TBI patients, chemical VTE prophylaxis initiation remains variable. In the CENTER-TBI study, a provider profiling survey indicated that most centers use VTE prophylaxis frequently (27.3%) or always (66.7%). Additionally, 21.2% would wait 72 hours after presentation prior to commencing VTE prophylaxis in the absence of hemorrhagic brain lesions, while 43.9% wait 72 hours after presentation in the presence of hemorrhagic brain lesions. Further, 65% of centers indicated that they would always implement VTE prophylaxis. Given these findings, the authors acknowledged a lack of consensus on management of chemical VTE prophylaxis (6).

A meta-analysis published in 2013 by Jamjoom et al. showed that delayed VTE prophylaxis group (defined as greater than 72 hours, with an average time of 4.85 days) showed a DVT rate from 2.7-12.5% (7). Given the high risk of VTE, the timing of initiation of VTE prophylaxis needs to be weighed against the risk of ICH expansion. Koehler et. al found that there was no difference in the rate of ICH expansion between early (less than 72 hours) and late (greater than 72 hours) initiation of VTE prophylaxis. There were no additional craniotomies performed in the early initiation of VTE prophylaxis treatment group. Therefore, the authors deemed early DVT prophylaxis to be safe in the stable TBI patient (8). A similar review by Kim et. al showed no increase in the bleeding complications in patients who were administered early (less than 72 hours) versus late (greater than 72 hours) VTE prophylaxis (9). The majority of the studies found in the literature defined “early” initiation as less than 72 hours after injury (8, 9).

However, Scudday et. al examined early chemical VTE prophylaxis and concluded that early VTE prophylaxis, defined as after 24 hours of a stable or improved head CT, reduced the incidence of VTE and did not increase the risk of intracranial bleed (10). VTE in setting of TBI carries significant prolongation of length of stay (LOS) and presents a difficult clinical conundrum when initiating full anticoagulation therapy. Therefore, prevention of VTE in this patient population is paramount. Our study aims to achieve the following:

Aim 1: Establish that early initiation (less than 24 hours after the last stable head CT) of VTE chemoprophylaxis would result in a decreased risk of VTE and would not increase risk of ICH expansion in isolated TBI patients. The primary outcome is to identify VTE rates in groups receiving no VTE prophylaxis, early initiation (<24 hours) and late initiation (>24 hours) of VTE prophylaxis from the last stable head CT (defined as "stable", "improved", or "no change" as dictated by a radiologist). Further outcomes are to identify ICH expansion (defined as progression of bleed as dictated by the radiologist with a follow up head CT which may or may not require a neurosurgical intervention) in each of the groups.

Aim 2: Examine outcomes in VTE rates in patients with isolated TBI who have received different agents; low molecular weight heparin (LMWH) 0.5mg/kg every 12 hours, LMWH 30mg subcutaneous injection every 12 hours, LMWH 40mg subcutaneous injection every 12 hours, LMWH 30mg daily and LMWH 40mg daily, and unfractionated heparin (UH) 5,000 units subcutaneous injection every 8 hours, while in hospital. Use of Anti-Xa levels to guide VTE prophylaxis management and its effect on VTE prevention will further be studied.

Aim 3: Evaluate differing VTE screening practices across institutions and inferior vena cava filter (IVCF) usage in patients with isolated TBI.

Research Strategy

a. Significance

The burden of VTE related complications in TBI patients are significant. Developing VTE in TBI patients has shown to worsen morbidity, LOS and presents a clinical conundrum when initiating full anticoagulation in the setting of TBI. Therefore, in conjunction with existing literature and performing a retrospective multicenter cohort study examining risks of VTE in TBI patients is vital. Current literature and guidelines lack consensus in timing of VTE prophylaxis initiation in TBI patients. A multicenter study to examine the relationship of ICH expansion and early VTE chemoprophylaxis initiation will be beneficial to guide practicing trauma surgeons and neurosurgeons. This study will further examine the VTE rates associated with early initiation of different chemoprophylaxis agents. Successful completion of this study would help us elucidate the common question asked while caring for TBI patients: "When can we start VTE chemoprophylaxis?".

The study further delves into various chemoprophylaxis regimens used. The Brain Trauma Foundation Guidelines and the American College of Chest Physicians recommend the use of mechanical compression devices in conjunction with LMWH or UH. However, there are no consensus-based guidelines on timing of VTE chemoprophylaxis initiation. There are

institutional practice pattern variations in dosage, timing and agents used for VTE prophylaxis in TBI patients. We aim to delineate differences in outcomes of TBI patients with different chemoprophylaxis agents as it relates to VTE, ICH expansion, hospital LOS and mortality. Although literature with various chemoprophylaxis agents exist, a multicenter study analyzing outcomes of each chemoprophylactic agent may pave the path towards establishing comprehensive guidelines in type of chemoprophylaxis agent used in TBI. Efficacious timing and agent of chemoprophylaxis use will lead to a significant reduction in morbidity of VTE events without an increase in ICH expansion rate, leading to momentous improvement in the care of the brain injured patient.

Although, the use of screening ultrasounds for VTE and IVC filter placement is not supported by majority of the literature, we aim to delineate the practicality of screening ultrasounds use and IVC filter placement practices across institutions are validated in TBI patients.

b. Innovation

To our knowledge there is currently one retrospective multicenter study examining timing of VTE prophylaxis and ideal chemoprophylaxis agent use in TBI patients (13). This study included patients with injuries to other body regions. With a multicenter retrospective cohort study, efficacy of early administration (<24 hours of stable head CT) of VTE prophylaxis in preventing VTE without a risk of ICH expansion can be studied. Most studies discuss early administration as less than 48 or 72 hours. (12) This study will challenge the definition of "early" administration of VTE prophylaxis as it relates to TBI. While early administration of VTE prophylaxis is not a novel concept in the management of TBI patients, many patient factors as mentioned earlier deter from initiating early VTE prophylaxis. The study will elucidate and refine our care towards TBI patients with regards to VTE prevention.

c. Approach

The primary outcome is to identify VTE rates in groups receiving no VTE prophylaxis versus early initiation (<24 hours) versus late initiation (>24 hours) from the last stable head CT. The late initiation group will further be studied at 48 hour and 72-hour time frames. Further outcomes are aimed at identifying ICH expansion in the early, late and no chemoprophylaxis initiation groups. The secondary outcomes are to examine neurosurgical operative intervention for worsening ICH between all three groups. The average ICU LOS, hospital LOS, ventilator days and mortality between all three groups will also be studied.

Inclusion Criteria

1. All patients greater than 18 years of age with an isolated TBI admitted to a trauma accredited center.
    - Isolated TBI is defined as any patient with only an Abbreviated Injury Scale (AIS) Head injury classified as intracranial hemorrhage (subdural hematoma, subarachnoid hematoma, epidural hematoma, intraparenchymal hemorrhage, diffuse axonal injury) and no other AIS reported.
    - Patients with scalp lacerations or facial lacerations without evidence of facial fractures with ICH

Exclusion Criteria

1. Patients with other concomitant injuries
2. Patients who are less than 18 years of age
3. Pregnant patients
4. Prisoners
5. Patients who are on anticoagulation therapy in the pre-injury period
6. All transfers in

Primary Institutional Review Board (IRB) approval is obtained from the Crozer Keystone Health System. IRB approval from each institution must be obtained prior to collaboration. Records of all patients admitted to a trauma center with an isolated TBI, as defined in the inclusion criteria, will be reviewed in a retrospective fashion from January 2014 to December 2020. The VTE prophylaxis initiation timing is to be determined by calculating the time of the last stable head CT to the administration of the first dose of chemical VTE prophylaxis in hours. VTE is defined as "the formation, development, or existence of a blood clot or thrombus within the vascular system, which may be coupled with inflammation." The diagnosis of VTE is confirmed with a venogram, duplex venous ultrasound or computed tomography (CT) angiogram of the chest as defined by the National Trauma Data Bank. ICH expansion is defined as increase in size or complexity of ICH as dictated by a radiologist, which may or may not have resulted in a neurosurgical intervention. Data collection will be carried out through a secure, de-identified data entry system with password protection (RedCap).

Distributions for demographics (age, sex, race, AIS head, ISS), comorbidities (diabetes, hypertension, CAD, renal disease, underlying coagulation disorder) and clinical outcomes such as evidence of ICH expansion, DVT/PE, hospital LOS, ICU LOS, ventilator days, and mortality will be compared between patient groups receiving no, early and late chemical VTE chemoprophylaxis. Statistical comparisons will be accomplished using chi-square tests and non-parametric Kruskal-Wallis tests for categorical and continuous variables, respectively. Statistical significance will be recognized at the $p < 0.05$ level, while acknowledging that there may be clinically significant differences that do not demonstrate statistical significance.

A retrospective review of our own institutional data, found ICH expansion rates between the 3 groups (<24 h, >24 h, no treatment) 6.6% 4.4%, and 3.7% respectively (p=0.5698). VTE rates in the 3 groups were (<24 h, >24 h, no treatment) 1.6%, 8.0% and 1.2% respectively (p<0.0001). Approximately 5,000 and 6,000 total patients will be required to demonstrate statistical significance with 80% power. Although, the number of patients required to attain this power is not possible, it is the goal of the authors for enrollment of approximately 10 centers.

The authors acknowledge the wide heterogeneity of practice in institutions on VTE chemoprophylaxis timing and agent. However, the study aims to delineate whether these practices affect outcomes of TBI patients.

This is an observational study that will not alter institutional management protocols or patient care, thus enrollment in this study will pose no additional medical risk to participants. Waiver of

informed consent is requested. Data will be recorded on a secured database (RedCap) that is devoid of patient identifiers thus posing minimal risk of breach of confidentiality. Communication with each institution will occur via email or via teleconference held each month or as needed to address issues and concerns.

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