**Study Title:** Optimizing Venous Thromboembolism Prophylaxis (VTEp) in Patients Who Have Sustained Operative Spinal Trauma

**Use this area to briefly outline the burden of the problem to be examined.**

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant and potentially life-threatening complication in patients who have sustained spinal trauma. The incidence of VTE in this population is notably high due to factors such as immobilization, endothelial injury from trauma, and hypercoagulability associated with acute injury responses.

Spinal trauma patients often require prolonged bed rest and may have additional risk factors like surgical interventions, further increasing their susceptibility to VTE. Balancing the initiation of pharmacologic VTE prophylaxis is challenging because while early administration can reduce the risk of thromboembolic events, it may increase the risk of bleeding complications such as spinal epidural hematomas. These hematomas can lead to neurologic deterioration, further complicating the recovery process for these patients. Current guidelines recommend initiating VTE prophylaxis (VTEp) within 24-72 hours post-injury, but the optimal timing remains unclear.

This uncertainty may pose challenges in clinical decision-making, resulting in variability in practice and potentially suboptimal patient outcomes. A recent review of the literature calls for prospective multicenter evaluation of early VTEp after spine injury.[2]

This study will investigate the effect of prophylaxis timing in patients with operative spinal column injury with or without spinal cord involvement, aiming to determine the best time for intervention to prevent VTE and other complications.

**Briefly review what major published studies exist on the topic of the proposed project.**

Zeeshan et al 2018 examined time to thromboprophylaxis in patients who sustained spinal trauma requiring operative intervention.

Kim et al. 2015 found that early VTE prophylaxis (within 48 hours) in spine trauma surgery reduced VTE incidence without increasing bleeding or neurological complications.

Aito et al. 2002 showed that early use of low molecular weight heparin and mechanical measures reduced DVT incidence from 26% to 2% in spinal cord injury patients admitted within 72 hours.

Yorkgitis et al. 2022 developed a clinical protocol for early VTE prophylaxis (within 48 hours) in trauma patients with spinal fractures or spinal cord injuries. They highlighted the importance of reducing VTE risk while managing bleeding risks, especially in cases of traumatic brain and spinal cord injuries.

Khan et al. 2018 conducted a propensity-matched analysis on nonoperative blunt spinal trauma patients. Early initiation of thromboprophylaxis (within 48 hours) significantly lowered the rates of DVT and PE without increasing bleeding risk or mortality.

**Use this area to briefly outline how this idea is innovative and its anticipated impact.**

There are no prospective studies investigating VTEp in spinal trauma patients. Furthermore, studies have not investigated VTEp in different vertebral regions (cervical, thoracic, lumbar,

sacral). The anticipated impact of this study is to inform trauma providers of optimal VTEp timing and modality in operative spinal trauma patients. There is a critical need for evidence-based guidance to determine the optimal timing of VTE prophylaxis that minimizes both thromboembolic and bleeding risks. Addressing this gap has the potential to improve morbidity and mortality rates among spinal trauma patients and enhance the quality of care delivered.

**Describe what & how the proposed MCT will add to the existing body of knowledge & literature.**

The proposed multicenter trial will provide empirical evidence on the optimal timing of VTEp across different types of spinal injuries requiring operative management, a topic with limited prospective analysis. By stratifying patients based on spinal cord involvement, injury location, and severity, the study will offer nuanced insights that may be lacking in the current literature. This approach will help clarify the risk-benefit profile of early versus delayed VTEp initiation after spinal operation, potentially informing evidence-based guidelines and reducing practice variability.

**Primary aim**

To determine the optimal time to administer VTEp in patients who have sustained operative spinal injury with or without spinal cord involvement. We hypothesize that earlier VTEp will confer superior clinical outcomes.

**Secondary aim**

1. Analyze how injury severity, spinal cord injury, and injury location influence the outcomes related to VTEp timing after operative management. We hypothesize that higher injury severity, presence of spinal cord involvement, and injury involving higher vertebral segment will have higher incidence of thrombotic events.
2. Evaluate for undesired complications such as bleeding and nonbleeding complications associated with VTEp timing.

**Inclusion Criteria**

- Blunt mechanism of injury.
- 16 years or older at the time of injury.
- Hemodynamically stable patients eligible for pharmacologic prophylaxis within 0-72 hours post-injury.
- Isolated spinal trauma (AIS Spine $\geq 3$) with or without spinal cord involvement requiring operative management
- Spinal bony and cord injuries associated with cord hematoma who do not undergo intervention.

**Exclusion Criteria**

- Less than 16 years old at time of injury
- Non-blunt mechanisms of injury (e.g., penetrating trauma)
- AIS Head, Face, Neck, Thorax, Abdomen, Upper Extremities, Lower Extremities, External $\geq 3$
- Currently Pregnant
- Documented history of recent VTE (within 3 months)

- History of pulmonary embolism
- History of chronic renal failure
- History of liver cirrhosis
- Advanced Directive Limiting Care
- History of Bleeding disorder/Coagulopathy
- Blood transfusion >4 units in first four hours

**Please describe, completely but succinctly, how the project will be conducted.**

This prospective, multicenter observational study will examine isolated spine trauma patients meeting inclusion criteria. Groups will be stratified by presence of spinal cord involvement (Y/N), anatomical location of injury (cervical, thoracic, lumbar), and severity of injury (moderate = AIS ≤ 3, severe = 4-5, will also include ASIA score). The primary analysis will compare VTE incidence in patients with or without spinal cord involvement who underwent operative management receiving VTEp at different time intervals. Secondary analyses will assess the impact of VTEp timing in patients with spinal cord involvement and across other subgroups. Multivariate regression models will adjust for potential confounders. Findings will inform optimal VTEp timing recommendations for each subgroup. Data will be de-identified and collected through trauma registrars without direct patient contact or impact on patient care. Outcomes such as VTE development and other complications will be analyzed. ROC curve analysis will be used to identify the optimal timing for prophylaxis initiation.

**Primary Outcome**

Incidence of VTE in patients with operative spinal involvement relative to prophylaxis timing.

**Secondary Outcome(s)**

1. Occurrence of bleeding complications relative to VTEp timing.

2. Incidence of complications such as acute kidney injury (AKI), stroke (CVA), myocardial infarction (MI), stroke, acute respiratory distress syndrome (ARDS), and in-hospital mortality.

**Variables to be collected and analyzed:**

Demographics, Injury Information, Admitting Vitals, Outcomes, VTE Prophylaxis Type, Time to VTE Prophylaxis

**Outline the data collection plan/tool succinctly**

- Age
- Race
- Ethnicity
- Sex
- ICD-10 Primary External Cause Code
- ICD-10 Additional External Cause Code
- ED Vitals (Temp, BP, HR, RR, SpO2)

- Lowest ED/Hospital Systolic Blood Pressure
- Initial ED/Hospital GCS-Eye
- Initial ED/Hospital GCS-Verbal
- Initial ED/Hospital GCS-Motor
- Initial ED/Hospital GCS-Total
- Initial ED/Hospital Height
- Initial ED/Hospital Weight
- Highest GCS – Total
- Highest GCS – Motor
- Current Smoker
- Preexisting Anticoagulant Use (Y/N)
- Creatinine Clearance
- ICD-10 Injury Diagnoses
- AIS Code
- AIS Version
- ASIA Score
- Received VTEp? (Y/N)
- Time to administer VTEp
- VTEp Drug
- Number of Missed VTEp Doses
- Timing of operative intervention
- Operation(s) in first 72 hours
- PT
- PTT
- INR
- TEG
- Location of bony spine injury
- Spinal cord involvement? (Y/N)
- List of ICD Diagnosis Codes

- Outcomes: Acute Kidney Injury, Acute Respiratory Distress Syndrome, Cardiac Arrest with CPR, Deep Vein Thrombosis, Delirium, Extremity Compartment Syndrome, Myocardial Infarction, Organ/Space Surgical Site Infection, Osteomyelitis, Pulmonary Embolism, Pressure Ulcer, Severe Sepsis, Stroke/CVA, Superficial Incisional Surgical Site Infection, Unplanned Admission to ICU, Unplanned Intubation, Unplanned Visit to Operating Room, Ventilator Associated Pneumonia, Total ICU Length of Stay, Total Ventilator Days, Hospital Discharge Disposition, Epidural Hematoma
- Drain placement? (Y/N)

**Is DUA required for participation in the study?** Not unless a collaborating center requests one.

**Identify the individuals that will primarily be responsible for data collection process:**

Each institution's trauma registry will provide a list of MRNs to the researchers. The MRNs will be used to access electronic medical records to collect deidentified data. The study will have site-specific principal investigators responsible for data integrity and compliance. Each site will be allotted two authorship positions. The organizing center will establish a secure REDCap. Each participating center will be given a unique and password-protected REDCap link to enter their deidentified data. Access will only be granted once proof of IRB approval has been received by the organizing center. Participating centers will only be able to access their own data.

**Is there a primary statistician assigned to assist the PI w/design & data analysis?** Yes

**Include detailed description of the data analysis plan:**

VTE incidence will be compared between patients receiving very early (<8 hours), early (8-24 hours), intermediate (24-48 hours), and late (48-72 hours) prophylaxis using chi-square or Fisher's exact tests.

ROC curve analysis will determine the optimal timing of prophylaxis in both groups (with and without spinal cord involvement).

Regression models will adjust for potential confounders such as injury severity, comorbidities, and treatment type.

The data will be imported and prepared by cleaning missing values and outliers. Key variables will be appropriately coded:

• **Timing of VTE Prophylaxis (VTEp):** Categorized into early (within 24 hours), intermediate (24–48 hours), and late (48–72 hours) initiation.

• **Spinal Cord Involvement:** Classified as present or absent based on AIS codes.

• **Anatomical Location:** Grouped into cervical, thoracic, lumbar, or sacral regions.

• **Injury Severity:** Categorized as moderate (AIS 3) or severe (AIS 4–5).

• **Surgical Intervention:** Noted as yes or no, serving as a surrogate for injury stability.

Descriptive statistics will summarize patient demographics, injury characteristics, and outcomes. Comparisons between groups will be made using chi-square tests for categorical variables and t-tests or non-parametric equivalents for continuous variables.

The primary analysis will use multivariate logistic regression to assess the association between VTEp timing and the incidence of VTE in patients with and without spinal cord involvement. The model will adjust for potential confounders such as age, Injury Severity Score (ISS), ASIA score, comorbidities, injury severity, and surgical intervention status.

Secondary analyses will explore this association in patients with spinal cord involvement and across different anatomical locations and injury severities. The impact of VTEp timing on bleeding complications and other secondary outcomes will also be examined using similar statistical methods.

To determine the optimal timing for initiating VTE prophylaxis, Receiver Operating Characteristic (ROC) curve analysis will be used to help identify the timing that maximizes sensitivity and specificity for preventing VTE and other adverse outcomes without increasing bleeding risks.

Statistical significance will be set at a p-value of less than 0.05, and 95% confidence intervals will be reported for all estimates. Goodness-of-fit tests and checks for multicollinearity will also be performed, ensuring validity of the regression models.

**Include Power Analysis:**

An a priori power analysis was conducted using G*Power version 3.1.9.7 (Faul et al., 2007) to determine the required sample size to test the study hypothesis. To compare VTE rates between early and late thromboprophylaxis cohorts, results indicated the required sample size to achieve 80% power for detecting an effect size of 0.1, at a significance criterion of $\alpha = .05$, was $N = 785$ for Chi Square analysis. To achieve 90% power with this same set of criteria, an $N = 1051$ would be required.

**Please note what your enrollment procedure for this study entails:**

Patients will be enrolled based on injury patterns and inclusion criteria. No patient identifiers will be collected, and there will be no direct patient contact or impact on care.

**Please indicate what resources are available at the primary study institution:**

Presence of a dedicated statistician:

Research personnel:

Availability of data collectors:

**Include a brief listing of key references:**

1. Yorkgitis BK, Berndtson AE, Cross A, et al. American Association for the Surgery of Trauma/American College of Surgeons-Committee on Trauma Clinical Protocol for inpatient venous thromboembolism prophylaxis after trauma. *J Trauma Acute Care Surg*. 2022;92(3):597-604. doi:10.1097/TA.0000000000003475

2. Schellenberg M, Costantini T, Joseph B, Price M, Bernard A, Haut E. Timing of venous thromboembolism prophylaxis initiation after injury: Findings from the consensus conference to implement optimal VTE prophylaxis in trauma. Journal of Trauma and Acute Care Surgery. 2023; 94 (3): 484-489. doi: 10.1097/TA.0000000000003847.

3. Zeeshan, Muhammad MD; Khan, Muhammad MD; O'Keeffe, Terence MD; Pollack, Nina MS; Hamidi, Mohammad MD; Kulvatunyou, Narong MD; Sakran, Joseph V. MD; Gries, Lynn MD; Joseph, Bellal MD. Optimal timing of initiation of thromboprophylaxis in spine trauma managed operatively: A nationwide propensity-matched analysis of trauma quality improvement program. Journal of Trauma and Acute Care Surgery 85(2):p 387-392, August 2018. | DOI: 10.1097/TA.0000000000001916

4. Aito S, Pieri A, D'Andrea M, Marcelli F, Cominelli E. Primary prevention of deep venous thrombosis and pulmonary embolism in acute spinal cord injured patients. Spinal Cord. 2002;40(6):300-303. doi:10.1038/sj.sc.3101298

5. Chang R, Scerbo MH, Schmitt KM, et al. Early chemoprophylaxis is associated with decreased venous thromboembolism risk without concomitant increase in intraspinal hematoma expansion after traumatic spinal cord injury. *J Trauma Acute Care Surg*. 2017;83(6):1088-1094. doi:10.1097/TA.0000000000001675

6. Hamidi M, Asmar S, Bible L, et al. Early Thromboprophylaxis in Operative Spinal Trauma Does Not Increase Risk of Bleeding Complications. *J Surg Res*. 2021;258:119-124. doi:10.1016/j.jss.2020.08.029

7. Khan M, Jehan F, O'Keeffe T, Hamidi M, Truitt M, Zeeshan M, et al. Optimal timing of initiation of thromboprophylaxis after nonoperative blunt spinal trauma: a propensity-matched analysis. J Am Coll Surg. 2018;226:760–768.