Specific Aims:

Trauma has been identified as a prothrombotic state that increases the risk of venous thrombosis and pulmonary embolism (VTE), both of which remain a significant source of morbidity and mortality (Shaz 2011, et al). Further work has identified the early post injury phase as a period of thrombus formation (Brackenridge 2011, Geerts 1994, et al); however, the duration of prolonged thrombotic risk is less defined.

Current venous thromboembolism prophylaxis (VTEP) has been codified by multiple studies and organizational guidelines (Rogers 2002, Kearon 2016). Recently, several studies have examined the use of extended VTEP (EVTEP) in the setting of oncologic surgery (Thorson 2013, pariser 2016, Van Haren 2014, Vedovati 2014) and there is a growing body of literature supporting this practice after bariatric surgery (Macgee 2010, Aminian 2017). Since trauma is associated with increased risk of VTE, similar to oncologic and bariatric surgery, the logical next question is: what is the role for extended VTE surveillance and EVTEP in the trauma population?

The role of for VTE surveillance has been well studied. The efforts of Cipolle et al (2001), Piotrowski et al (2001), Azarbal et al (2011), Allen et al (2016) and others have attempted to demonstrate the role, efficacy, risk reduction and changes in incidence, prevalence and outcomes associated with VTE surveillance and predictive models. Yet to date, no clear consensus exists.

Without a clear understanding of the duration of the prothombotic state after injury, determining optimal duration of VTEP is difficult. With this question in mind we propose a prospective multi-institutional cluster randomized clinical trial examining standard duration VTEP (during hospitalization only) compared to EVTEP. We hypothesize that extended venous thromboembolism prophylaxis after major injury would significantly decrease the rate of venous thromboembolism.

Specific Aim1: To determine the difference in incidence of VTE in standard care compared to EVTEP

Primary Outcome: Incidence of VTE

Secondary Outcome: Rates of clinically significant VTE, VTE complications, VTEP-associated complications and readmissions occurring within 90 days.

Specific Aim 2: To determine the incidence of prothrombotic state at 4 weeks post hospital discharge

Primary Outcome: thromboelastogram (TEG) determination of prothrombotic state

Research Strategy:

Significance:

Rates of VTE in trauma patients receiving VTEP range from 6-7% (Knudson 2004, Shackford 1990, Toker 2011), while the reported incidence of VTE after trauma without LMWH prophylaxis was historically reported as 42% (Shackford 1988). Proposed specific aim 1 will demonstrate the incidence of VTE in the patients receiving EVTEP. This study will provide insight into the duration of post trauma prothrombotic state and the need for extended prophylaxis via specific aim 2. Specific aim 1 and 2 if completed will result in a significant change in clinic practice.

Innovation:

It is our assessment that the proposed study is innovative with respect to its conceptual design, disease process and potential significance. While previous studies has examined the role of surveillance for VTE in the post trauma period, little work has been done to demonstrate the duration of risk of VTE or the required duration of prophylaxis. Our proposal while not entirely novel as it utilizes established technologies and relies on established methodologies, it does seek to change current clinical paradigms.

Approach:

We plan to perform a prospective, multi-institutional cluster randomized clinical trial comparing two courses of VTEP. The duration of VTEP will be randomized at the institutional level and will be implemented as a change of standard of care at each center. Where available, each patient will have a TEG collected at follow up for evaluation of coagulopathy or hypercoagulable state. We will follow the CONSORT Statement recommendations for cluster trials. The AAST multi-institutional web portal will be utilized for data collection.

Inclusion Criteria

1: Age > =18

2: Admitted trauma patients with ISS>15

Exclusion Criteria

1: History of prothrombotic or hypercoagulable state

2: History of DVT on admission or clinically significant VTE during index hospitalization

3: History of anticoagulant use on admission

Patients randomized to EVTEP will undergo prophylaxis with low- molecular weight heparin (LMWH) for 30 days post hospital discharge while patients in the standard care arm will have VTEP discontinued at hospital discharge. Patient hematologic specimens will be collected at discharge and at a 4-week follow up. The following data points will be collected by each center.

Patient Demographics: Age, gender, weight, height, race, ISS, injury description, ICD10 codes, admission vitals

Comorbid conditions: history of Cancer, peripheral vascular disease, cerebrovascular disease, inflammatory bowel disease, CHF, COPD, obesity, connective tissue disease, liver disease, AIDS/HIV, diabetes with organ damage, diabetes without organ damage, dementia, Charlson Comorbidity Index

Hospital data: date of admission and discharge, length of stay, ICU length of stay, ventilator days, infectious complications

Procedural data: types of operations/procedures, number of operations/procedures and central venous access device (location, duration)

In order to facilitate each sites reporting of data, the Research Electronic Data Capture (REDCap) web portal will be utilized for data collection. This will allow for ease in reporting and Standardized data collection forms will be made available for each patient and will encompass demographics, injury variables, operative interventions, and associated complications during hospitalization and post discharge. Variables will be analyzed using univariate and multivariate analysis. Student's t-test and Mann-Whitney U test will be utilized for all normally distributed and non-normally distributed continuous variables, as appropriate. Categorical variables will be compared using Fisher's exact test and chi square analysis. All variables with a p value<0.2 will enter multivariable logistic regression analysis to determine independent risk factors for developing VTE post discharge. Odds ratio will be set at 95% confidence interval with statistical significance set at $p<0.05$.

Reported rates of VTE in trauma patients receiving VTEP range from 6-7% (Knudson 2004, Shackford 1990, Toker 2011), while the reported incidence of VTE after trauma without LMWH prophylaxis was historically reported as 42% (Shackford 1988). To detect at least a 20% reduction in the incidence of VTE with EVTEP with 80% power, we will require each arm to enroll at least 191 patients, for a total study population of 382 patients. Accounting for a 33% loss-to-follow-up rate, a total of 508 patients will be enrolled, with approximately 254 randomized to each arm. We propose a minimum of 5 sites with each site enrolling approximately 100 patients.

Communication between sites will be facilitated via electronic form with our institution serving principal institution responsible for the coordination of the study. Each institution address their own issues regarding consent and safety surveillance with issues reported to the principal institution. Inherent to our study design, significant issues with consent, IRB approval and adverse outcome monitoring would be limited.

Our anticipated results demonstrating the need for EVTEP would result in a change of practice regarding the duration of VTEP for all trauma patients. Previously noted in the specific aims section of this proposal, recent works examining the use of EVTEP in the setting of surgical oncology (Thorson 2013, pariser 2016, Van Haren 2014, Vedovati 2014), as well as after bariatric surgery (Macgee 2010, Aminian 2017) have resulted in significant changes in clinical practice. While the risk of VTE after trauma is unclear, this study will hopefully more clearly elucidate this risk and more clearly delineate the need for EVTEP in trauma.

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