THE ROLE OF COMBINED THERAPY WITH ASPIRIN AND ENOXAPARIN IN PREVENTION OF VENOUS THROMBOEMBOLISM IN TRAUMA PATIENTS: A RANDOMIZED-CONTROLLED TRIAL

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STUDY INVOLVES: Testing a drug, device, or biologic, or performing procedures, lab tests (including blood draws) and/or interventions (standard of care and/or experimental)

TYPE OF STUDY: Prospective, Investigator-initiated

DESCRIPTION OF STUDY

STUDY PROTOCOL

Abstract

Venous thromboembolism (VTE) is a significant cause of morbidity and mortality in hospitalized patients, with increased risk demonstrated in the trauma population. VTE is defined as the presence of deep vein thrombosis (DVT) or pulmonary embolus (PE) diagnosed using standard imaging modalities. Greenfield et al. previously developed a Risk Assessment Profile (RAP) for trauma patients to aid in identifying those with the highest risk for VTE. Current accepted prophylaxis modalities used in our trauma center include low molecular weight heparin (LMWH) (enoxaparin 30 mg subcutaneously twice daily) plus/minus mechanical prophylaxis with sequential compression devices. In our prior studies, we have demonstrated a 28% rate of VTE in trauma patients with RAP score > 10, regardless of the use of standard thromboprophylaxis. With the emergence of thromboelastography (TEG) and rotational thromboelastometry (ROTEM), the previously underappreciated contribution of platelets to the formation of VTE is being brought to light.

The use of antiplatelet therapy for thromboprophylaxis has not been conclusively studied in the trauma population. Prior work in orthopedic surgery has demonstrated the benefit of aspirin in prevention of DVT. We hypothesize that the addition of antiplatelet therapy with aspirin to standard of care with enoxaparin will decrease the incidence of VTE in high-risk critically injured patients. We aim to determine the safety and efficacy of dual thromboprophylaxis with aspirin and enoxaparin for decreasing the incidence of VTE in trauma.

Research Background

Venous thromboembolism (VTE), defined by the presence of deep vein thrombosis (DVT) or pulmonary embolism (PE), is a significant healthcare problem with approximately 350,000 to 600,000 new cases of DVT and PE diagnosed in the United States per year and an estimated 100,000 mortalities attributed to these cases.[1,2] This is also associated with an estimated $5.8 to $7.8 billion in healthcare costs.[3] In the trauma population, the rate of VTE is approximately 5% overall, however our previous studies have demonstrated a 25-30% rate of

VTE in high-risk trauma patients.[4,5] Several risk factors for the development of VTE after trauma have been well established by Greenfield et al., among others, which has resulted in the creation of the Greenfield Risk Assessment Profile (RAP) to identify patients at high-risk for VTE.[6,7] Risk factors include underlying conditions (e.g., obesity, malignancy, hypercoagulability), iatrogenic factors (e.g., central venous line use, operation, PRBC transfusion), injury-related factors (e.g., injury severity, Glasgow Coma Scale, pelvic fracture, spinal cord injury), and age.[7] Gearhart et al. have previously validated the use of the RAP score and identified patients at high-risk as a RAP > 5, which was associated with a 10.8% rate of symptomatic DVT and a 64% rate of asymptomatic DVT. No patients with RAP < 5 developed a DVT in this study.[7] Rogers et al. have identified similar predictors of postoperative VTE after general and vascular surgery.[8]

The Eastern Association for the Surgery of Trauma (EAST) put forth a set of practice management guidelines relating to the prevention of VTE in trauma patients in 2002, which also identified various risk factors as well as the role of unfractioned heparin (UFH), low molecular weight heparin (LMWH), and mechanical thromboprophylaxis.[9] They concluded that there was little evidence to support monotherapy with UFH in high-risk trauma patients and that the decision to use UFH in patients with risk for increased bleeding should be physician-dependent.[9] There is little evidence to support the use of pneumatic compression devices (PCDs). Furthermore, the available evidence infers that LMWH is superior to UFH in moderate- to high-risk trauma patients.[9] The American College of Chest Physicians has also supported the use of LMWH or UFH in non-orthopedic surgical patients at high risk for VTE who are not at increased risk for bleeding complications.[10] Therefore, the current standard of care for thromboprophylaxis at our institution is enoxaparin 30 mg subcutaneously twice daily with PCDs if not contraindicated; in patients with severe traumatic brain injury (TBI), enoxaparin is substituted with heparin 5,000 units subcutaneously every 8 hours.

Aspirin, an irreversible cyclooxygenase (COX) enzyme inhibitor, has also been studied as a potential method for thromboprophylaxis.[11-14] Blocking the function of the COX enzyme results in diminished thromboxane A_2 production, which results in decreased platelet aggregation. Aspirin has been routinely used for several years in the management of myocardial infarction, ischemic stroke, and arterial thrombosis, but its use has never been extended to venous disease. The Antiplatelet Trialists' Collaboration performed a large meta-analysis specifically investigating the utility of antiplatelet agents in the reduction of VTE; their study found significant reductions in both DVT and PE in patients randomized to the aspirin group vs. controls.[11] The PEP trial, a large randomized placebo-controlled trial in orthopedic surgery patients, found absolute reductions of 9 per 1,000 patients VTE events in patients allocated to aspirin vs. placebo therapy.[12] Additionally, there was a 36% proportional reduction in VTE risk in the aspirin group with 4 per 1,000 fatal PEs prevented by aspirin use; an excess 6 per 1,000 bleeding episodes requiring transfusion were evident in the aspirin group.[12] Hovens et al. point out that aspirin monotherapy for VTE prophylaxis is discouraged by current guidelines even though a 25-30% protective effect has been reported; this is largely due to the lack of direct comparisons between LMWH and aspirin for VTE prevention.[13]

It has been previously shown that high-risk trauma patients have an approximate rate of 25-30% for VTE despite standard thromboprophylaxis.[4,5] Furthermore, both the trauma and burn literature have demonstrated that there are significant knowledge gaps regarding the optimal dosing regimen for enoxaparin in trauma; different strategies have been advocated, including standard dosing for all patients, antifactor Xa level based dosing, and thromboelastography (TEG)-based dosing.[15-23] Furthermore, emerging evidence suggests that platelets play a more

prominent role in the hypercoagulability of trauma than was previously appreciated. Harr et al. have shown that platelet count strongly correlates with clot strength.[3] This was further supported by results from Kornblith et al. who also demonstrated that platelets had a greater contribution to clot strength than fibrinogen at all time points during their prospective study in trauma patients.[24]

Collectively, this suggests that further study is warranted to investigate the utility of aspirin for thromboprophylaxis in trauma. No previous studies compare LMWH to aspirin although the success of aspirin in prevention of VTE has been clearly described in the orthopedic surgery literature. Hypercoagulability and VTE are topics of controversy in trauma and we clearly need better answers regarding the optimal method of prophylaxis in our patient population. VTE is a significant patient safety concern and has also been identified by the Centers for Medicare and Medicaid Services (CMS) and others as a potentially "preventable event" with areas for quality improvement; however, the continued occurrence of VTE in patients on "standard" thromboprophylaxis questions whether we are ready to label VTE as a "never event."[4,8]

Research Hypothesis

Combination thromboprophylaxis with LMWH and ASA versus LMWH alone will decrease the incidence of VTE in trauma patients.

Research Outcomes

- Primary Outcome:
    - Incidence of VTE – defined as new cases of:
        - Deep vein thrombosis (DVT), symptomatic or asymptomatic, on venous duplex ultrasonography (VDU)
        - Pulmonary embolism (PE), symptomatic or asymptomatic, on chest computed tomography with angiography (CTA) or ventilation-perfusion (VQ) scan
- Secondary Outcomes:
    - Hypercoagulability – defined using thromboelastography (TEG)
    - Laboratory coagulation studies (PT, PTT, INR, CBC, antifactor Xa)
    - Mortality

Rationale and Methodology

This is a prospective, randomized, controlled, open-label clinical trial evaluating the effect of dual thromboprophylaxis with enoxaparin and aspirin versus enoxaparin alone on the incidence of VTE in trauma patients. Once a trauma patient is admitted to the Intensive Care Unit (ICU), study personnel will pre-screen for entry criteria and, if eligible, will obtain informed consent from the patient or healthcare proxy. After informed consent, a baseline assessment will be performed for screening purposes. Once patients meet all eligibility criteria, they will be randomized into one of 2 groups to receive either standard of care with enoxaparin alone (control group) or dual thromboprophylaxis with enoxaparin plus aspirin (intervention group). Subjects will be randomized using a block randomization scheme. A random number generator will be used to create the random assignments (equally distributed). Alternative thromboprophylaxis will be permitted prior to consent or randomization or at anytime at the discretion of the attending physician for any reason. Standard of care dosing regimens for both enoxaparin and aspirin will be used.

All consented subjects will be followed from admission until 30 days or hospital discharge, whichever occurs first. Data collection will include demographic information, injury pattern, mechanism of injury, need for surgical intervention, admission and daily laboratory values (e.g. basic metabolic profile, complete blood count, coagulation studies, TEG), weekly venous duplex ultrasonography (VDU), admission and subsequent radiologic examinations, medication administration records (including missed doses of thromboprophylaxis), and outcomes measures (complications, VTE, mortality). Blood samples for CBC and coagulation studies will be ordered as medically necessary per the primary team; TEG samples will be taken pre-prophylaxis and post-prophylaxis and will be run in the Trauma Research Office. The amount drawn will not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection will not occur more frequently than 2 times per week.

All clinical care will be at the discretion of the attending physician. Should the attending physician choose to change thromboprophylaxis medication, this will be permitted for the study and included in the data collection. The research team will not dictate the stopping guidelines. Clinical evidence of bleeding or significant changes in hemoglobin and hematocrit are variables that the treating physician may use to determine whether the aspirin must be discontinued. Discontinuation of thromboprophylaxis generally occurs in a standardized fashion once the patient is fully ambulatory; however, should the attending physician stray from this regimen, it is permitted for the study and will be part of the data collection.

For each patient admitted to the ICU and eligible for study participation, routine measures already obtained by clinical staff will be collected/calculated.

Risk/Benefit Assessment

Study participants may be at increased risk of bleeding due to combined use of LMWH and aspirin as well as upset stomach or stomach ulcer. All clinical care will be at the discretion of the attending physician. Cessation of thromboprophylaxis may occur with bleeding complications per the attending physician.

We anticipate that the risk of VTE will be reduced by approximately 5% with the test substance. Therefore, this research will provide potential direct benefits to the test group as well as to the general trauma population. The risk/benefit ratio supports conducting this research as the benefits of decreased pain/discomfort from DVT and mortality from PE are expected to be reduced.

Data

A unique study number and initials will be utilized to identify study subjects. All case report forms will utilize the unique study number and initials of the subjects only. The researchers will know actual names of the subjects. Research documents and database storage systems pertaining to this project will be kept in the locked office of Trauma Research. Data will also be stored on REDCap.

Statistical Design

Our current VTE rate is approximately 25% in the high-risk trauma population. With a 5% expected decrease in VTE with aspirin use, we will require 377 patients per cohort (754 patients total) for 80% power with alpha set at 0.05.

STUDY PARTICIPANTS

Participant age: ≥ 18 years

Maximum # of subjects to be screened in all sites: 3500

Maximum # of subjects to be studied in all sites: 2000

Inclusion criteria:
All patients admitted meeting the following criteria:

- Age 18 years or older
- Blunt or penetrating trauma
- Requirement of VTE thromboprophylaxis
- High-risk for VTE

Exclusion criteria:

- Presence of VTE on baseline VDU screening
- Pregnancy or nursing
- Inability to give informed consent by patient or healthcare proxy
- Contraindication to LMWH therapy
- Contraindication to ASA therapy
- Any intracranial or intraspinal hemorrhage
- Presence, or removal within the last 12 hours, of an epidural or spinal catheter, or recent (within the last 12 hours) epidural or spinal anesthesia/procedures
- Known medical need for antiplatelet therapy for other reasons (e.g. presence of intravascular stents)
- Known aspirin use up to 7 days prior to admission
- Known current use of anticoagulation for other reasons (e.g. warfarin, apixaban)
- Postponement of thromboprophylaxis therapy greater than 72 hours from admission

Recruitment: Intensive Care Unit, Trauma Resuscitation Unit

Recruitment Procedure:

Upon identification of a potential research subject, study personnel will provide a detailed description of the study to the patient or healthcare proxy. Written informed consent must be obtained from either the subject or their legally authorized representative after the study protocol has been discussed. Documentation of the subject's consent for participation in the study will be placed in the subject's record; a copy of the signed consent will be given to the subject and/or healthcare proxy after a determination of incapacity is made by a medical doctor and noted in the patient's medical record. The original signed document will be held in the Principal Investigator's research files. If it is not possible to obtain prior consent from the subject and informed consent is given by the healthcare proxy, the patient will be informed about the trial whenever he/she becomes competent to give an opinion on continuation in the trial and be given the opportunity to withdraw from the trial. If the patient consents to continue in the trial, the patient must be requested to record consent by signing the Informed Consent form. If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the Investigator will inform the subject and/or proxy in a timely manner,

and a written informed consent on a revised form will be obtained. The volunteer nature and dissociation of their decision with resulting clinical care will be emphasized.

Participants will have no costs associated with this study.

INFORMED CONSENT

- Prospective patients will be identified by the clinical and/or research team
- If agreeable, study personnel will follow up with the process for informed consent
- Capacity to consent in the ICU is primarily determined by the treating team, generally using a combination of Glasgow Coma Score (GCS) of 15 and patient interviews to ensure that patients understand their treatment plan. In such instances when the clinical team or GCS assessment determines that the patient is incapacitated, the need for a healthcare proxy for clinical decisions is routinely ordered by attending physician when needed after a neurological assessment. That order is followed by the hospital social worker for establishment of an appropriate surrogate. Once established and after referred to study personnel, they will be approached for informed consent.
- A translated written informed consent document in a language understandable to the participant will be provided for non-English speaking participants to be consented.

VULNERABLE POPULATIONS

Initially, some of the trauma population is comatose due to their injuries and care. Therefore, we will consult with the patient's proxy in order to obtain informed consent in these patients. Should they regain consciousness during the study observation window, we will attempt to re-consent the patient directly.

PROTECTED HEALTH INFORMATION

- Protected health information (PHI) will be accessed prior to contact with subjects in this research and during the course of the proposed research
- We request partial waiver of authorization and HIPAA authorization from subjects
- Patient identifiers will include names and medical record or prescription numbers
- At the earliest possible time, all identifiers and links to research records will be destroyed if not at five years after publication or final IRB report

STUDY DRUGS

- Enoxaparin
- Aspirin

STUDY PHASE

Phase 4 – studies of FDA-approved drugs to delineate additional information including the drug's risks, benefits, and optimal use

CONFLICTS OF INTEREST

None

MONITORING PLANS

- A formally constituted Data and Safety Monitoring Board (DSMB) will monitor the study.
- An internal DSMB has been established to provide additional oversight and monitoring of this study for safety and adherence to the study protocol. The following is a description of the composition of the committee and the methods for communicating findings to the IRB:
    - DSMB will be composed of three (3) trauma/critical care specialists + one (1) anesthesiology/critical care specialist + one (1) clinical pharmacist
    - The DSMB will send findings and recommendations in writing to the principal investigator. These findings and recommendations can result from both the open and closed sessions of the DSMB. If these findings include serious and potentially consequential recommendations that require immediate action, the PI will also promptly notify the IRB.
- There is no external DSMB established for additional oversight/monitoring of this study
- The role of the DSMB will be to monitor regularly the data from the clinical trial, review and assess the performance of its operations, and make recommendations, as appropriate, to the PI with respect to the desirability of proceeding to the completion of the study, interim results of the study for evidence of inadequate efficacy or adverse events, possible early termination of the trial because of safety concerns or inadequate performance, and possible modifications to the clinical trial protocol.
- Meeting frequency and attendance:
    - DSMB meetings will be scheduled upon initiation of the study and with completion of 50 study subjects and at the completion of subject accruals. When appropriate, conference calls may be held in place of face-to-face meetings and email communication will be accepted. Other meetings may be held at the timing and discretion of the DSMB and/or principal investigator.
- Meeting content and confidentiality:
    - The DSMB will review the final protocol during its first meeting. Any protocol changes during the performance of the study may also be reviewed by the DSMB. The DSMB will primarily address issues of patient protection and quality assurance of the research. Its members must be satisfied that the timeliness and accuracy of the data submitted o them for review are sufficient to protect the safety and health of study participants. To ensure confidentiality, the data reviewed by the board will be stored on their password-protected computer accessed only by the board members. Any paper copies of data used by the board will be shredded upon conclusion of the data review.
- Statistical procedures
    - The outcome measures will be assessed by Student's t-test and analysis of variance for quantitative measures. Chi-squared tests will be used for comparison of proportions and for contingency tables. Fisher's exact test will be applied for correction to normality, as necessary, for outcomes that generate a small number (<5). These tests will be used to detect a rejection of the null hypothesis that there is no difference in the outcomes between the two treatment groups.
- A physician can withdraw a patient from this protocol at any time.

- There are no pre-specified criteria, per se, for stopping or changing the study protocol. Outcome will be optimized in each individual patient at the discretion of the attending physician.
- An interim efficacy analysis will be performed after 50 subjects have completed participation.

STUDY FUNDING
None

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