Clinical Implications of the Impact of Serum Tissue Factor Levels after Trauma

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In the setting of trauma, patients are at significant risk for thromboembolic complications. Platelets release granules containing tissue factor, a pro-coagulant protein that binds to factor VII to initiate the extrinsic pathway of the coagulation cascade. Additionally, traumatic injury activates monocytes which in turn up-regulate expression of membrane-bound tissue factor within hours of the initial insult. Without effective prophylaxis, the risk of developing deep vein thrombosis after trauma may be greater than 50%, and the risk of fatal posttraumatic pulmonary embolism may range from 5% to 50%

The presence of traumatic brain injury however, may alter the physiology of coagulation. Specifically, traumatic brain injury attenuates the expression of tissue factor by circulating activated monocytes. The consequences of this attenuation are not fully understood. Additionally, injury of brain tissue is associated with increased anti-thrombin activity, decreased platelet function, and possible consumptive coagulopathy.

While previous studies have examined the relationship between tissue factor levels and thromboembolic complications, the clinical implications of elevated levels of serum tissue factor in acute trauma are incompletely understood. Furthermore, the consequences of attenuation of these levels in the setting of traumatic brain injury have not been successfully demonstrated due to lack of specificity or insufficient power. Our study would measure serum tissue factor levels in patients with isolated traumatic brain injury, in patients with concomitant traumatic brain injury and other injuries, and in trauma patients without traumatic brain injury. By correlating these levels with incidence of venous thromboembolic events, this study will provide further insight into the need for thromboprophylaxis in patients with traumatic brain injury.

Specific Aims

This study will determine if traumatic brain injury in the setting of severe trauma alters the relationship between serum tissue factor levels.

This study will define the relationship between serum tissue factor levels and thromboembolic events in the setting of severe trauma.

This study will further determine the implications of traumatic brain injury with respect to the setting of severe trauma alters the relationship between serum tissue factor levels and thromboembolic events.
**Inclusion criteria**

We will evaluate for inclusion all trauma patients aged 18-65 requiring critical care admission.

**Exclusion Criteria**

Criteria for exclusion will include pregnancy, state custody of the patient, age less than 18 years or over 65 years, lack of an initial blood draw, and death within 24 hours of arrival.

**Therapeutic Interventions**

The study will be a prospective observational study and will not involve specific therapeutic interventions. Patients will be managed according to the discretion of the responsible surgeon.

**Primary Outcome**

The primary outcome will be 30-day mortality tissue factor expression.

**Secondary outcomes**

Secondary outcomes will include incidence of venous thromboembolic events including pulmonary embolism and deep venous thrombosis, or cerebrovascular accident, and incidence of sepsis.

**Variables**

Measured variables will include demographic data (age, sex), injury data (injury severity scoring, presence of head injury, nature of head injury, mechanism of injury), admission physiology (initial GCS, base deficit, transfusion requirements for packed red blood cells, platelets, or fresh frozen plasma over the initial 72 hours), and management variables (pre-trauma anti-coagulation or anti-platelet medications, medications given to correct coagulopathy, anti-coagulation medications, mechanical DVT prophylaxis, length of stay, ICU length of stay, and performance of an operation within 72 hours of admission).

**Data Collection and Statistical Analysis**

Patients will be assessed for inclusion in the study on arrival. Consent will be obtained as described below.
Blood draws will be performed at the time of admission, and subsequently at 24, 72, 120, and 168 hours. Briefly, blood will be drawn into a green top vacutainer tube with heparin. Samples will be de-identified and given an assigned code. Samples will have serum separated by microcentrifuge and the serum will then transfer to 12.5x40 mm cryovial, frozen, and shipped on dry ice for subsequent evaluation of tissue factor level by ELISA.

Data regarding the previously described variables and outcomes will be abstracted from the chart of the patient, de-identified, and coded to correspond with the blood samples. Secondary outcomes will be assessed based on clinical suspicion.

We will employ Fisher’s exact test for nominal variables and Student’s t test for continuous variables in statistical analysis of patient characteristics. We will perform repeated-measures analysis of variance in comparisons of serum tissue factor levels among the four time points.
Consent Procedures:
This is a prospective observational study, designed to prospectively record data on patients who are managed according to institutional patient management protocols. This study will require collection of blood for analysis by flow cytometry. Consent will be obtained either at the time of admission or retrospectively from the patient or a consenting family member or designated power of attorney. Data will be recorded on a data sheet and transferred to a secured database that is devoid of patient identifiers.

Risk/benefit analysis:
A better understanding of the factors contributing to post-injury thrombotic events may lead to improved prevention of thromboembolic complications, improving outcomes in the entire patient population. The study is primarily observational and management is at the discretion of the treating physicians. Patient identity will be protected through de-identification of data. Risks are minimal and primarily due to the five necessary blood draws. The potential benefit of new knowledge justifies the risks inherent to this study.

References
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Data Collection Tool

Demographic Information

Age __________
Sex __________

Injury

Mechanism (blunt versus penetrating)

Injury Severity Score [ISS] __________________________________________________________
AIS Head/Neck _________________________________________________________________
AIS Face _________________________________________________________________
AIS Thorax _________________________________________________________________
AIS Abdomen _________________________________________________________________
AIS Extremity _________________________________________________________________
AIS External _________________________________________________________________

Initial Glasgow Coma Scale score
Total Motor Eye Verbal ________________

Is the patient known to have been using anti-coagulant or anti-platelet medications prior to admission? _________________________________________________________________

If so, which medication? _________________________________________________________________
Indication? _________________________________________________________________

Initial Management

Transfusion within 72 hours of admission?
PRBCs _________________________________________________________________
FFP _________________________________________________________________
Platelets _________________________________________________________________
Cryo _________________________________________________________________
Patient identity code

Use of tranexamic acid within 4 hours of admission?

Use of prothrombin complex concentrate within 72 hours of admission?

Use of activated Factor VII within 72 hours of admission?

Operative intervention within 72 hours of admission?

Dates of operative intervention?

Anti-coagulation?

Date of initiation?

Anti-coagulant agent?

Prophylactic or therapeutic?

Mechanical prophylaxis?

Outcome

Vascular Thromboembolic Complications

DVT identification?

Location?

Date?

Management?

Pulmonary embolism identification?

Classification?

Date?

Management?

Renal Injury

Renal trauma present?

Nature of renal trauma, if present?

Oliguria or anuria (< 400 ml urine output over 24 hours)

New requirement for hemodialysis modalities?

Modality?

Respiratory Failure

Thoracic trauma present?

Intubation within 48 hours of admission?
Patient identity code

Lung Injury? (P:F ratio <300)

Hepatic Injury
Liver trauma present?
Nature of liver trauma, if present?
Hyperbilirubinemia with serum total bilirubin >2.5 mg/dL within 30 days of admission?

Length of stay
Length of ICU stay
Length of overall stay

Mortality
Did the patient survive 30 days from the date of injury?

For Lab Use
Serum Tissue Factor levels

Admission
24 hours
72 hours
120 hours
168 hours
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Data Dictionary

**Head Injury:** Glasgow Coma Scale score of 9 or less, *and* Abbreviated Injury Scale (AIS) Head/Neck score of 3 or greater.

**Hepatic injury:** Hyperbilirubinemia with serum total bilirubin >2.5 mg/dL within 30 days of admission

**Lung injury:** PaO2/FIO2 ratio <300

**Oliguria:** less than 400 ml urine output over 24 hours