Form "EAST Multicenter Study Proposal"

Study Title	Correlation of Serum Tissue Factor Levels and Thromboembolic Events in Trauma Patients with and without Traumatic Brain Injury.
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Use this area to briefly (1-2 paragraphs only) outline the burden of the problem to be examined	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 (1-2). 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% (3-5). The presence of traumatic brain injury in this setting 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 (6), decreased platelet function (7), and possible consumptive coagulopathy (8). While previous studies have examined the relationship between tissue factor levels and thromboembolic complications, correlation in the setting of traumatic brain injury has not been successfully demonstrated due to lack of specificity or insufficient power (1-2). 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.
Primary aim	This study will determine if traumatic brain injury in the setting of severe trauma alters serum tissue factor levels.
Secondary aims	This study will define the relationship between serum tissue factor levels and thromboembolic events in the setting of severe trauma in patients both with and without traumatic brain injury.
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 tissue factor expression.
Secondary Outcomes	Secondary outcomes will include all cause 30-day mortality, incidence of venous thromboembolic events such as pulmonary embolism, deep venous thrombosis, or cerebrovascular accident, and incidence of sepsis.

List specific variables to be collected & analyzed

Measured variables will include :

demographic data

age

sex

injury data

Abbreviated Injury Score

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 48 hours

management variables

medications given to correct coagulopathy

anti-coagulation medications

mechanical DVT prophylaxis

length of stay

ICU length of stay

transfusion requirement

performance of an operation within 72 hours of admission

outcome variables

level of serum tissue factor

all cause 30-day mortality

incidence of sepsis

incidence of venous thromboembolic events (pulmonary embolism, deep venous thrombosis, or cerebrovascular accident)

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.

Outline the data collection plan and statistical analysis plan succinctly

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.

Outline consent procedures here, if applicable

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. 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.

Succinctly outline a 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.

Include a brief listing of key references

1.Utter GH, Owings JT, Jacoby RC, Gosselin RC, Paglieroni TG. Injury induces increased monocyte expression of tissue factor: factors associated with head injury attenuate the injury-related monocyte expression of tissue factor. J Trauma. 2002 Jun;52(6):1071-7; discussion 1077.

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3.Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. N Engl J Med. 1994;331: 1601 Y 1606.

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5.Haut ER, Garcia LJ, Shihab HM, Brotman DJ, Stevens KA, Sharma R, Chelladurai Y, Akande TO, Shermock KM, Kebede S, et al. The effectiveness of prophylactic inferior vena cava filters in trauma patients: a systematic review and meta-analysis. JAMA Surg. 2014;149:194 Y 202.

6.Owings JT, Bagley M, Gosselin R, Romac D, Disbrow E. Effect of critical injury on plasma antithrombin activity: low antithrombin levels are associated with thromboembolic complications. J Trauma. 1996; 41: 396–406.

7.Jacoby RC, Owings JT, Holmes J, Battistella FD, Gosselin RC, Paglieroni TG. Platelet activation and function after trauma. J Trauma. 2001 Oct;51(4):639-47.

8.Goodnight SH, Kenoyer G, Rapaport SI, Patch MJ, Lee JA, Kurze T. Defibrination after brain-tissue destruction: A serious complication of head injury. N Engl J Med. 1974 May 9;290(19):1043-7.