US Military Funded TXA Mechanisms Study Update

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Background

• CRASH-2 and MATTERS studies lead to most massive transfusion protocols to incorporate tranexamic acid

• CRASH-2
  – Reduction in death from hemorrhage
  – When given after 3 hours increased risk of death

• MATTERS
  – Survival benefit – Adjusted analysis
  – Thrombosis risk - unadjusted
Questions

• What are mechanisms?
• What is best dose?
• What are risks?
• Prehospital benefit?
• When is it indicated?
  – Empiric or goal directed
• Traumatic brain injury patients?
Tranexamic Acid Clinical Research

• Program Announcement in 2012
  – U. S. Army Medical Research and Materiel Command (USAMRMC)
  – Telemedicine and Advanced Technology Research Center (TATRC)
  – Combat Casualty Care Joint Program Committee (CCCJPC)
  – Directorate for Combat Casualty Care (CCC)
Priorities

• Prospective clinical studies examining the effects of TXA in the treatment of patients with traumatic hemorrhage (polytrauma and TBI).

• Doses up to the range of those published for trauma are recommended.

• Treatment with TXA should begin within 2 hours of injury.
Priorities

- Use of other pro-hemostatic or antifibrinolytic drugs must be carefully documented and should be included only as part of the current local standard of care.
- Use of fluids and blood products for resuscitation and surgery should also be documented.
- Randomized studies and studies that examine more than one dose-level are preferred.
Expectations

• Provide insight into one or more of the following:
  – Safety
    • Deep vein thrombosis
    • Pulmonary thromboembolism
    • Post-operative seizures
  – Mechanism of action
    • Coagulation function/dysfunction
    • Fibrinolysis, Immune function, etc.
  – Pharmacokinetics and pharmacodynamics in trauma
Funding

• The amount currently available for funding Combat Casualty Care Research Program 2012 for this Priority Area is approximately $12 million over three (3) years.

• This Program Announcement is expected to result in approximately 3-5 investigator initiated awards, depending on the quality and number of applications received.

• Funding of Applications received in response to this Program Announcement is contingent upon the availability of Federal funds for this program.
Grants Awarded?

- University of Oregon - YES
  - Marty Schreiber

- University of Pittsburgh - YES
  - Jason Sperry

- University of Washington in St Louis?
  - Phil Spinella and Grant Bochicchio
TXA in TBI

• Study Centers:
  – 10 North American Trauma Centers
• Design: Double Blinded RCT
• Hypothesis:
  – Prehospital administration of TXA in patients with moderate to severe TBI will increase favorable long-term neurologic outcome compared to placebo
Inclusion Criteria

• Blunt or penetrating traumatic mechanism consistent with traumatic brain injury
• Prehospital Glasgow Coma Score (GCS) score ≤ 12 at any time prior to randomization and administration of sedative and/or paralytic agents
• Prehospital systolic blood pressure (SBP) ≥ 90 mmHg prior to randomization
• Prehospital intravenous (IV) or intraosseous (IO) access
• Estimated Age ≥ 15
• Emergency Medicine System (EMS) transport to a participating trauma center
Exclusion Criteria

• Prehospital GCS=3 with no reactive pupil
• Estimated time from injury to hospital arrival > 2 hours
• Unknown time of injury - no known reference times to support estimation
• Clinical suspicion by EMS of seizure activity or known history of seizures, acute myocardial infarction (MI) or stroke
• Cardio-pulmonary resuscitation (CPR) by EMS prior to randomization
Exclusion Criteria

- Burns > 20% total body surface area (TBSA)
- Suspected or known prisoners
- Suspected or known pregnancy
- Prehospital TXA given prior to randomization
- Subjects who have activated the "opt-out" process when required by the local regulatory board
Study enrollment

1. EMS Arrives at scene of accident
2. Patient has Blunt or Penetrating Traumatic Brain Injury TBI
3. Transport Destination Oregon Health & Science University
4. Patient Meets Enrollment Criteria
5. Open Study Kit Give First Dose of Study Drug or Placebo In Ambulance
6. Second dose of study drug or placebo Research blood draws at ED arrival
Study Arms

• Bolus with infusion
  – EMS gives 1 gram TXA IV bolus
  – 1 gram TXA infusion post admission over 8 hrs
• Bolus no infusion
  – EMS gives 2 grams IV bolus
  – Placebo (NS) infusion post admission over 8 hrs
• Placebo
  – EMS gives placebo IV bolus
  – Placebo infusion post admission over 8 hours
TXA in TBI

• Primary Outcome:
  – Glasgow Outcome Scale Extended score (GOS-E)
  – 6 months post-injury

• Secondary Outcomes:
  – Observed volume (absolute and relative) of intracranial hemorrhage (ICH) progression
  – On hospital arrival through 28 days or from hospital admission through the end of the hospital stay, an expected average of 14 days post injury
Secondary Outcomes

• 28 day survival
• Seizure, stroke, MI, DVT, PE frequency during hospitalization
• Vent Free days
• Hematologic parameters
  – Fibrinolysis
  – TEG
TXA in TBI

- Sample Size is 1002 (334 per group),
  - Which will allow for 80% power to detect an 8.1% absolute difference in favorable long-term neurological outcome as determined by the GOS-E 6 months after injury, using a one-sided, level 0.1 test.
Exception to Informed Consent

• Life-threatening situation
• Intervention must be administered before consent is feasible
• No reasonable way to identify prospectively individuals at risk
• Patients have the prospect of benefit from the treatment
• The research could not practically be carried out without the waiver of consent
Study of Tranexamic Acid During Air Medical Prehospital Transport Trial (STAAMP Trial)

- Study Centers:
  - U of Pittsburgh, Utah, Rochester
  - UT San Antonio
- Design: Double Blind RCT
- Hypothesis:
  - Prehospital infusion of tranexamic acid in patients at risk for bleeding will reduce the incidence of 30 day mortality.
Inclusion Criteria

• 18-90 years of age
• Blunt or penetrating injured patients being transported via air medical services from the scene of injury or from referring hospital to a definitive trauma center that is participating in the trial AND
• Within 2 hours of time of injury AND
• Hypotension (Systolic Blood Pressure (SBP) < 90mmHg)
• At scene of injury or during air medical transport
Inclusion Criteria

• Documented at referring hospital prior to air medical transport arrival AND

• Tachycardia (heart rate >110 beats per minute)

• At scene of injury or during air medical transport

• Documented at referring hospital prior to air medical transport arrival Inclusion criteria #3. and #4. not required to be simultaneous
Exclusion Criteria

• Age > 90 or < 18 years of age
• Inability to obtain intravenous access
  – (intraosseous access not sufficient)
• Documented cervical cord injury with motor deficit
• Known prisoner or pregnancy
• Traumatic arrest with > 5 minutes CPR without return of vital signs
Exclusion Criteria

- Penetrating cranial injury
- Traumatic brain injury with brain matter exposed
- Isolated drowning or hanging victims
- Wearing an opt out bracelet.
Study Groups

- TXA, 1 Gram IV given prehospital
- Placebo IV given prehospital
- Sample size of 1000 patients
Outcomes

• **Primary Outcome:**
  – 30 Day Mortality

• **Secondary Outcome Measures:**
  – 24 Hour Mortality
  – Acute Lung Injury
  – Multiple Organ
  – Nosocomial Infection
  – 24 Hour Blood Transfusion
  – Hyperfibrinolysis
Tranexamic Acid Mechanisms and Pharmacokinetics In Traumatic Injury (TAMPITI Trial)

• Study Center: Washington University in STL
• Design: Double Blinded RCT
• Hypothesis:
  – We hypothesize that early TXA use in patients with severe traumatic injuries, reduces a pro-inflammatory state.
  – We expect reduced inflammation, and monocyte activation in TXA treated patients compared to placebo.
Secondary Hypothesis

- We hypothesize that the pharmacokinetics of TXA administration are affected by the degree of shock measured by admission base deficit, StO₂, presence of acute renal failure, and blood products administered in patients with severe traumatic injury.

- We expect that the degree of shock and blood products transfused will affect TXA pharmacokinetics.
Study groups

• The three treatment arms will be
  – TXA 2 gram IV bolus
    • 50 patients
  – TXA 4 gram IV bolus
    • 50 patients
  – Placebo
    • 50 patients
• Change in immune parameters, monocyte function, from time 0 to time 72 hours.
Inclusion Criteria

• Hospitalized patients with traumatic injury who can receive study drug < 2 hours from injury
  – And
• Who ordered to receive at least 1 blood product
  – Or
• Patients that have been determined by the physician of record to require directly transfer to the operating room from the ED < 2 hours from injury
Exclusion criteria

- Patients < 18 years of age
- Known inherited coagulation disorders
- Known history of thromboembolic events
- Pregnancy and/or lactating, incarceration
- Futile care
- Risk of immune suppression
- Unknown time of injury
Laboratory Parameters

- Cytokines: TNF-α, IL-6, IL-10, and IFN-γ measured at time 0, 6, 24 and 72 hours.

- Flow cytometric analyses on leukocytes measured at time 0, 6, 24 and 72 hours:
  - CD66+/ROS+ to identify activated polymorphonuclear cells
  - CD4+/CD69+ and CD8+/CD69+ to identify activated lymphocytes
  - CD14+/HLA-DR+ to identify activated monocytes
  - CD4+/Foxp3+ to identify T regulatory cells
Pharmacodynamics

• Compare pharmacokinetic data between patients with varying degrees of shock (base deficit and StO2 measures) and adjusting for acute renal failure and total amount of blood products transfused in the first 12 hours of injury.

• Blood samples will be collected in 50 patients within each TXA treatment group at time 0 (before administration of TXA), then at 10 min, 20 min, 40 min, 1 hr 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 10 hr, 12 hr and 24 hr.
Questions ?