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AWARD NUMBER: W81XWH-13-2-0080

TITLE: Study of Tranexamic acid during Air Medical Prehospital transport (STAAMP) trial

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CONTRACTING ORGANIZATION: University of Pittsburgh, PITTSBURGH, PA 15213

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6. AUTHOR(S)

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12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The enrollment for this study has not yet begun. Pittsburgh site plans to start training of the protocol and research procedures. The remaining sites are in the early phase of submission to their IRB of record for this protocol.

University of Pittsburgh site concluded all community consultation (questionnaires and telephone surveys) in Sep-14. Jason Sperry, the PI for this project, was interviewed by local media and explained the purpose of this study to Pittsburgh local and surrounding area.

15. SUBJECT TERMS
Prehospital ; Tranexamic acid

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a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
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1. **INTRODUCTION:**

   - The primary hypothesis will be that prehospital infusion of tranexamic acid in patients at risk for bleeding will reduce the incidence of 30 day mortality. The secondary hypotheses include that prehospital tranexamic acid will reduce the incidence of hyperfibrinolysis, acute lung injury, multiple organ failure, nosocomial infection, mortality, early seizures, pulmonary embolism and early resuscitation needs, reduce or prevent the early coagulopathy as demonstrated by improving presenting INR and rapid thromboelastography parameters, reduce the early inflammatory response, plasmin levels, leukocyte, platelet and complement activation, and determine the optimal dosing of tranexamic acid post-injury.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

   - Prehospital
   - Tranexamic acid

3. **OVERALL PROJECT SUMMARY:** Summarize the progress during appropriate reporting period (single annual or comprehensive final). This section of the report shall be in direct alignment with respect to each task outlined in the approved SOW in a summary of Current Objectives, and a summary of Results, Progress and Accomplishments with Discussion. Key methodology used during the reporting period, including a description of any changes to originally proposed methods, shall be summarized. Data supporting research conclusions, in the form of figures and/or tables, shall be embedded in the text, appended, or referenced to appended manuscripts. Actual or anticipated problems or delays and actions or plans to resolve them shall be included. Additionally, any changes in approach and reasons for these changes shall be reported. **Any change that is substantially different from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc.) requires review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.**

   - Coordinating Center submitted the initial IND protocol to the FDA on 05-Dec-13.
   - The PI and Project Manager sent response to comments on 21-Jan-14 and 23-Jan-14
   - We received FDA authorization to proceed was granted on 24-Jan-14
   - The PI and Project Manager sent response to non-clinical hold on 18-Feb-14 and 21-Feb-14
   - We received the initial University of Pittsburgh IRB approval for the coordinating center on 06-Aug-14
   - The University of Pittsburgh Coordinating Center received approval for Protocol Modification Version 1.3 by IRB on 18-AUG-14
   - The University of Pittsburgh sites community consultation plan was approved on 28-MAY-14
   - The PI and Project Manager are preparing the community consultation results to present to the University of Pittsburgh IRB
   - The Coordinating Center protocol was distributed to following participating sites on 24-SEP-14 so that they may start on their local IRB submissions: University of Rochester Medical Center, University of Texas San Antonio and University of Utah.

4. **KEY RESEARCH ACCOMPLISHMENTS:** Bulleted list of key research accomplishments emanating from this research. Project milestones, such as simply completing proposed experiments, are not acceptable as key research accomplishments. Key research accomplishments are those that have contributed to the major goals and objectives and that have potential impact on the research field.

- University of Pittsburgh site concluded all community consultation (questionnaires and telephone surveys) in SEP-14.
- Jason Sperry, the PI for this project, was interviewed by local media and explained the purpose of this study to Pittsburgh local and surrounding area.
- Co-I, Frank Guyette presented and was approved by EMSI and is on the agenda to present to the PA State Emergency Board

5. **CONCLUSION:** Summarize the importance and/or implications with respect to medical and /or military significance of the completed research including distinctive contributions, innovations, or changes in practice or behavior that has come about as a result of the project. A brief description of future plans to accomplish the goals and objectives shall also be included.

- The enrollment for this study has not yet begun. Pittsburgh site plans to start training of the protocol and research procedures. The remaining sites are in the early phase of submission to their IRB of record for this protocol.
- Our plan is to have all sites approved by their IRB of records at the time of Department of Army final approval to start the enrollment for this study.

6. **PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:**

a. List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts. Each entry shall include the author(s), article title, journal name, book title, editors(s), publisher, volume number, page number(s), date, DOI, PMID, and/or ISBN.

(1) Lay Press:
(2) Peer-Reviewed Scientific Journals:
(3) Invited Articles:
(4) Abstracts:

- ***Nothing to report***

b. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

- ***Nothing to report***

7. **INVENTIONS, PATENTS AND LICENSES:** List all inventions made and patents and licenses applied for and/or issued. Each entry shall include the inventor(s), invention title, patent application number, filing date, patent number if issued, patent issued date, national, or international.
   - ***Nothing to report***

8. **REPORTABLE OUTCOMES:** Provide a list of reportable outcomes that have resulted from this research. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. This list may include development of prototypes, computer programs and/or software (such as databases and animal models, etc.) or similar products that may be commercialized.
   - ***Nothing to report***

9. **OTHER ACHIEVEMENTS:** This list may include degrees obtained that are supported by this award, development of cell lines, tissue or serum repositories, funding applied for based on work supported by this award, and employment or research opportunities applied for and/or received based on experience/training supported by this award.
   - ***Nothing to report***

   For each section, 4 through 9, if there is no reportable outcome, state "Nothing to report."

10. **REFERENCES:** List all references pertinent to the report using a standard journal format (i.e., format used in *Science*, *Military Medicine*, etc.).

11. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.
   - ***Protocol Summary/Abstract Attached***

NOTE:

TRAINING OR FELLOWSHIP AWARDS: For training or fellowship awards, in addition to the elements outlined above, include a brief description of opportunities for training and professional development. Training activities may include, for example, courses or one-on-one work with a mentor. Professional development activities may include workshops, conferences, seminars, and study groups.
- ***Nothing to report***

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

MARKING OF PROPRIETARY INFORMATION: Data that was developed partially or exclusively at private expense shall be marked as "Proprietary Data" and Distribution Statement B included on the cover page of the report. Federal government approval is required before including Distribution Statement B. The recipient/PI shall coordinate with the GOR to obtain approval. REPORTS NOT PROPERLY MARKED FOR LIMITATION WILL BE DISTRIBUTED AS APPROVED FOR PUBLIC RELEASE. It is the responsibility of the Principal Investigator to advise the GOR when restricted limitation assigned to a document can be downgraded to "Approved for Public Release." DO NOT USE THE WORD "CONFIDENTIAL" WHEN MARKING DOCUMENTS. See term entitled "Intangible Property – Data and Software Requirements" and https://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting for additional information.

PROJECT SUMMARY/ABSTRACT
Study of Tranexamic acid during Air Medical Prehospital transport (STAMP) trial
PI – Jason L. Sperry MD, MPH, Co-PI- Frank X. Guyette MD, MS, MPH

Background: Traumatic injured patients continue to be plagued with uncontrolled hemorrhage resulting in significant morbidity and early mortality. A primary driving force for this unbridled hemorrhage is known to be the early coagulopathy which complicates severe injury. Trauma induced coagulopathy has been postulated to be an equilibrium imbalance between pro and anticoagulant factors, platelets, endothelium and fibrinolysis soon after injury. Recent evidence demonstrates that the early use of the antifibrinolytic agent tranexamic acid after trauma center arrival results in improved survival in patients at risk for bleeding. Bringing this proven treatment to the prehospital arena and intervening earlier in those patients who would otherwise not be candidates for treatment has the real potential to further reduce or prevent the vicious hemorrhagic cascade, improve clinical outcomes and provide insight into the underlying mechanisms responsible for and which maximize its benefit.
Objective/Hypothesis: The primary hypothesis will be that prehospital infusion of tranexamic acid in patients at risk for bleeding will reduce the incidence of hyperfibrinolysis and associated morbidity. The secondary hypotheses include that prehospital tranexamic acid will reduce the incidence of acute lung injury, multiple organ failure, nosocomial infection, mortality, early seizures, pulmonary embolism and early resuscitation needs, reduce or prevent the early coagulopathy as demonstrated by improving presenting INR and rapid thromboelastography parameters, reduce the early inflammatory response, plasmin levels, leukocyte, platelet and complement activation, and determine the optimal dosing of tranexamic acid post-injury.
Specific Aims:
Aim#1: Determine whether prehospital tranexamic acid as compared to placebo reduces hyperfibinolysis, lowers the incidence of acute traumatic coagulopathy and improves early markers of coagulopathy.
Aim#2: Determine whether prehospital tranexamic acid as compared to placebo results in a lower incidence of mortality, acute lung injury, multiple organ failure, nosocomial infection and improved shock parameters and early resuscitation and transfusion requirements.
Aim#3: To explore novel mechanisms by which prehospital tranexamic acid alters the inflammatory response independent of effects on hyperfibrinolysis including analysis of platelet and leukocyte activation, plasmin levels and plasmin mediated complement activation and the early cytokine response to trauma.
Aim#4: Determine whether different dosing regimens of tranexamic acid upon arrival in the hospital are associated with improvements in hyperfibrinolysis, coagulopathy, clinical outcomes and the early inflammatory response.
Study Design: Multi-center, prospective, randomized, blinded, controlled interventional trial over 3 years focusing on patients with concern for bleeding who are transported via air medical transport to definitive care.
Population: Blunt or penetrating injured patients transported via air ambulance with concern for bleeding with 1.) a documented systolic blood pressure < 90 mmHg en route at outside/referral facility OR 2.) documented tachycardia (> 110 bpm) en route or at outside/referral facility. Stage 1 Intervention: 1gm of tranexamic acid or placebo will be infused in a 100ml saline bag by air medical staff over 10 minutes once inclusion criteria are met. Prehospital providers and trauma center arrival staff will be blinded to the treatment given. Stage 2 Intervention: After arrival enrolled patients who received tranexamic acid will undergo a second randomization to one of three different arms: 1.) repeat tranexamic acid dosing, 2.) standard dosing or 3.) abbreviated dosing. Placebo infusion bags will be used for blinding in all arms. Patients and all treatment staff will be blinded to the intervention arm given for both stages. Randomization: Predetermined randomized allocation sequences using block sizes of 8 and 9 respectively for stage 1 and stage 2 interventions will be utilized.
Relevance: Few interventions exist alter the morbidity and mortality that inherently follows traumatic injury. By extrapolating the beneficial effects of tranexamic acid found in the hospital to the prehospital setting will allow intervention at an earlier point promoting a cascade of consequences with positive effects, in a cohort of patients who otherwise would not benefit due to the early administration requirement for tranexamic acid. The results provided by the successful completion of this proposal will have paramount implications for both civilian and military injured patients as control of coagulopathy and hemorrhage and delay to definitive care represent major impediments. The current proposal will add needed understanding and insight into improving outcomes when these impediments exist and will promote focus on the mechanisms responsible and the dosing requirements of tranexamic acid that maximize its benefit.