

AWARD NUMBER: W81XWH-14-2-0177

TITLE: Topical Application of Tranexamic Acid to Reduce Blood Loss during Complex Combat-Related Spine Trauma Surgery

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REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE (DD-MM-YYYY)		2. REPORT TYPE		3. DATES COVERED (From - To)	
October 2016		Annual		30Sept2015 - 29Sept2016	
4. TITLE AND SUBTITLE Topical Application of Tranexamic Acid to Reduce Blood Loss during Complex Combat-Related Spine Trauma Surgery				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-14-2-0177	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Lehman, Ronald A., MD Messer, Zachary M., MPH Email: rl2781@cumc.columbia.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Washington University St. Louis, MO 63110-1010 Columbia University Medical Center: New York, NY 10034; Harborview Medical Center Seattle, WA 98104; Henry M. Jackson Bethesda Maryland 20817				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Shortly after IRB approval was obtained at Washington University, the PI, Dr. Ronald Lehman, transferred to Columbia University. No other study-related procedures have taken place, as the transfer of the grant continues to be processed. Two issues have slowed the completion of this transfer. First, Columbia University does not encounter patients that meet inclusion criteria at nearly the same volume as the original institution. Thus, new sub-sites needed to be added to ensure that recruitment would follow the time course described in the statement of work. Second, over the course of the transfer, it was discovered that one of the sub-sites originally listed had applied for a grant in direct competition to this one. Subsequently, that site was removed from the grant and a replacement was needed to cover the associated loss in anticipated patient enrollment. We apologize for this delay, and have every anticipation that the transfer application will be submitted shortly and successfully.					
15. SUBJECT TERMS Spine; Tranexamic Acid; Perioperative blood loss; Trauma; Antifibrinolytic; Postoperative drain output; Allogenic transfusion; Hemorrhage; Spinal injuries; Back injuries; Wounds					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	10	19b. TELEPHONE NUMBER (Include area code)

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1. **INTRODUCTION:** The purpose of this prospective, randomized, double-blind, placebo-controlled study is to study the role and cost-effectiveness of topical tranexamic acid as a therapeutic tool, applied intraoperatively into the surgical wound for five minutes before closure, to reduce perioperative blood loss in patients undergoing surgery for complex combat-related and civilian spine trauma.
2. **KEYWORDS:** Spine; Tranexamic acid; Perioperative blood loss; Trauma; Antifibrinolytic; Postoperative drain output; Allogenic transfusion; Hemorrhage; Spinal injuries; Back injuries; Wounds
3. **OVERALL PROJECT SUMMARY:** Shortly after IRB approval was obtained at Washington University, the PI, Dr. Ronald Lehman, transferred to Columbia University. No other study-related procedures have taken place, as the transfer of the grant continues to be processed. Two issues have slowed the completion of this transfer. First, Columbia University does not encounter patients that meet inclusion criteria at nearly the same volume as the original institution. Thus, new sub-sites needed to be added to ensure that recruitment would follow the time course described in the statement of work. Second, over the course of the transfer, it was discovered that one of the sub-sites originally listed had applied for a grant in direct competition to this one. Subsequently, that site was removed from the grant and a replacement was needed to cover the associated loss in anticipated patient enrollment. We apologize for this delay, and have every anticipation that the transfer application will be submitted shortly and successfully.

Below, please find the original aims and tasks as outlined in the original statement of work, along with percent completions and explanatory text as needed.

IRB HUC submission/review/approval (February – July 2014)

Task 1. Submit clinical protocol to Walter Reed National Military Medical Center IRB for review and approval, to be completed by WRNMMC PI. (February – July 2014)

Completed, although insufficient as lead site has changed. IRB approval at Columbia University is 50% complete.

Task 2. Submit clinical protocol to the Thomas Jefferson University Medical Center and Washington University in St. Louis Medical Center IRB for review and approval, to be completed by each sites PI. (February – July 2014) *Not completed, as the lead site and sub-sites have changed. The IRB requires an up-to-date list of all sites on a multi-center trial, thus this was on hold and will resume as soon as the transfer is complete and Columbia University IRB approval is obtained. In addition, Washington University is no longer part of this study.*

Task 3. Submit clinical protocol to the Department of Defense (DoD) Human Research Protection Office for review and approval, to be completed by Project PI. (February – July 2014) *100% Completed, though updates will be submitted once the transfer application is complete.*

Task 4. An IND application will be submitted to the FDA for review and approval, to be completed by Project PI (February – July 2014) *100% complete. The IND is in good order, and the FDA has been made aware of the project status and provided with all necessary documentation.*

Specific Aim 1: Evaluate the efficacy of topical tranexamic acid to reduce perioperative blood loss and allogenic transfusion requirements. *0% completed for all tasks below. No patients have been recruited due to the aforementioned issues, thus, no evaluation of tranexamic acid's effectiveness could be performed. In addition, Walter Reed and Washington University are no longer part of this project.*

Task 1. Recruit military combat casualties and civilian patients after high-energy trauma that have sustained thoracic or lumbar spinal column with or without neurologic deficit requiring surgical fixation when they are admitted to each institution within 21 days of injury; complete screening procedures. **(August 2014 – July 2016)**

1a) WRNMMC will enroll a minimum of twenty-six (26) military patients to complete task 1, with a quarterly enrollment target of 3 to 4 patients per quarter.

1b) Washington University will enroll a minimum of 176 patients, with a quarterly enrollment target of 22 patients per quarter in Year 1 and Year 2.

1c) Thomas Jefferson University will enroll a minimum of 50 patients, with a quarterly enrollment target of 6 to 7 patients per quarter.

1d) The PI or AI will perform a complete evaluation of the patient, including clinical examination and review of imaging studies, documenting in the medical record per standard of care a complete neurologic examination using the ASIA impairment scale, and the location and severity/pattern of spinal column injury. The surgeon investigator will obtain informed consent for the surgical procedure.

1e) Research coordinators will identify patients with spinal column injuries requiring surgical intervention and will perform an interview to determine if the patient meets inclusion or exclusion criteria. The research coordinator will review the study goals and consent form with the patient and family, when applicable.

1d) When a patient with a spinal column injury requiring surgical fixation demonstrates interest in the clinical study, the research coordinator will provide education material, discuss the details of the study, and then allow privacy and time to allow decision making for up to 72 hours after recruitment or if surgical intervention is required earlier up to the morning of surgery.

1e) Screening blood laboratory specimens will be drawn after patient recruitment and consent is obtained to determine eligibility for the study and for pre-operative planning to evaluate baseline complete blood count, complete metabolic panel to evaluate renal and hepatic function and electrolyte balance, and coagulation panel to evaluate for pre-existing coagulopathy.

1f) Patients will complete clinical outcome surveys to determine baseline, pre-intervention/baseline outcome scores.

Task 2. Randomization and Intervention. **(August 2014 – July 2016)** *0% completed for all tasks below. No patients have been recruited, randomized, or participated in interventions.*

2a) On the morning of surgery, the patient will be randomized and a sealed envelope carrying the randomization information will be taken to the research pharmacist to prepare the study medication.

2b) Patients will be taken to the operating room for planned surgical intervention, and the study medication will be applied per protocol.

Task 3. Patient follow-up and Study termination (August 2014 – July 2018) 0% completed for all tasks below, due to aforementioned situation.

3a) Research coordinators will obtain patient data at 1 hour post-op in the recovery area, ensuring laboratory specimens are drawn and sent for processing. Data will be recorded every morning on POD#1 through POD#4 by the research coordinator regarding drain output, laboratory values, VAS pain scale, and neurologic examination using the ASIA impairment scale.

3b) Research coordinators will schedule and ensure appropriate patient follow-up after discharge from the hospital at Week 2, Week 16, Year 1 and Year 2 post-operative visits. At each follow-up visit, clinical outcome surveys will be completed, and radiographs will be taken at Week 16, Year 1 and Year 2 post-operative visits.

3c) Each site principal investigator and research coordinator will be responsible for submitting annual interim report, and to report any adverse events during the follow-up period.

3d) Study termination will occur two-years after final subject enrollment. Each site principal investigator and research coordinator will be responsible for appropriately closing out the study at their local IRB and providing final study summaries/reports. All hardcopy documents and information stored on electronic devices will be stored for 2 years and then destroyed.

Specific Aim 2: Determine the effect of topical tranexamic acid on the rate of surgical site infection *0% completed for all tasks below. No patients have been recruited due to the aforementioned situation.*

Task 1. Patient follow-up (August 2014 – July 2018)

1a) Research coordinators will be responsible for documenting the occurrence of deep surgical site infection at each follow-up visit

1b) If deep surgical site infection is treated by a non-study surgeon at another institution, the non-study surgeon will be contacted and the research coordinator will request complete medical records regarding the patient's treatment course for deep surgical site infection.

Specific Aim 3: Evaluate the safety and systemic absorption following topical application of tranexamic acid in a surgical wound *0% completed for all tasks below. No patients have been recruited due to the aforementioned situation.*

Task 1. Patient follow-up (August 2014 – July 2018)

1a) Research coordinators will ensure plasma tranexamic level laboratory specimens are drawn within 1 hour post-op in the recovery area and then sent for processing.

1b) Patients will have screening duplex ultrasound of bilateral lower extremities on POD#3. Research coordinators will be responsible for documenting the occurrence of deep vein thrombosis or pulmonary embolism at each follow-up visit

1c) If deep vein thrombosis or pulmonary embolisms is treated by a non-study physician at another institution, the non-study physician will be contacted and the research coordinator will request complete medical records regarding the patient's treatment course.

Specific Aim 4: Evaluate patient health-related quality of life outcomes measures and perform a cost analysis based on and determined the use of tranexamic acid for blood loss management and prevention of surgical site infection *0% completed for all tasks below. No patients have been recruited due to the aforementioned situation.*

Task 1. Data analysis (August 2018 – October 2018)

1a) After patient enrollment, research coordinators will collect completed patient health-related quality of life questionnaires/surveys (SF-36 and ODI), these will be collected again at the 16 week, 1 year and 2 year follow-up clinic visits.

1b) After termination of the study, the biostatistician will perform cost analysis using regressive and normative methods to establish a decision model of cost resulting from use of topical tranexamic acid with posterior spinal fusion surgery in complex spine trauma surgery.

- 4. KEY RESEARCH ACCOMPLISHMENTS:** Nothing to report.
- 5. CONCLUSION:** Nothing to report.
- 6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:** Nothing to report.
- 7. INVENTIONS, PATENTS AND LICENSES:** Nothing to report.
- 8. REPORTABLE OUTCOMES:** Nothing to report.
- 9. OTHER ACHIEVEMENTS:** Nothing to report.
- 10. REFERENCES:**

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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.

NOTE:

TRAINING OR FELLOWSHIP AWARDS: Not applicable.

COLLABORATIVE AWARDS: Not applicable.

QUAD CHARTS: Not applicable.