

AWARD NUMBER: W81XWH-14-1-0373

TITLE: Tranexamic Acid and Pharmacokinetics in Severe Traumatic Injury

PRINCIPAL INVESTIGATOR: Philip C. Spinella, MD

CONTRACTING ORGANIZATION: Washington University  
SAINT LOUIS MO 63130-4862

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14 Abstract The major accomplishments have been the completion of patient enrollment and analysis of the data for the primary manuscript. We are currently writing the manuscript and in the process of considering which secondary analyses to work on after the submission of the primary manuscript. Preliminary major findings are the pharmacodynamics results indicate a volume of distribution of 15.6 L/70kg and clearance of 113 ml/min/70kg. There were no differences in organ failure or mortality between the 3 study groups, but there was an increase in VTE. VTE was increased in the 2 and 4 gram TXA dose groups compared to placebo. This relationship was maintained after adjusting for potential confounders. There were no differences between immune and hemostatic parameters measured between the three study groups.					
<b>15. SUBJECT TERMS</b> Trauma, hemorrhage, transfusion, fibrinolysis, immune suppression, pharmacokinetics, outcomes, adverse events.					
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**Title: Tranexamic Acid Mechanisms and Pharmacokinetics In Traumatic Injury**

**(TAMPITI Trial)**

**Annual Report YR 3**

Award Number: W81XWH-14-1-0373

Log Number: 13335005

Philip C. Spinella, MD

Grant V. Bochicchio, MD, MPH

## **1. INTRODUCTION:**

This single center randomized controlled trial in adult patients with severe traumatic injury will determine if the use of tranexamic acid within 2 hours of injury is associated with less immune suppression compared to placebo. Tranexamic acid doses of 4g and 2g will be analyzed. In addition the pharmacokinetics of tranexamic acid will be established in addition to outcome and safety measures. We will also develop a biorepository of plasma samples for future analysis of coagulation and endothelial injury parameters.

## **2. KEYWORDS:**

Trauma, hemorrhage, transfusion, fibrinolysis, immune suppression, pharmacokinetics, outcomes, adverse events.

## **3. ACCOMPLISHMENTS:**

### **What were the major goals of the project?**

Task 1: Obtain FDA IND and Community Consent for trial. (Timeframe: 1-6 months).

Task 2: Conduct a multi-center, double-blinded, Randomized Controlled Trial (RCT) of 150 patients with three study groups; TXA 2 gram IV bolus, TXA 4 gram IV bolus, and placebo. (Timeframe: months 7-36).

### **What was accomplished under these goals?**

Task 1: Obtain FDA IND and Community Consent for trial. (Timeframe: 1-6 months).

FDA IND initial approval was received 20-FEB-2015 (letter received 19-MAY-2015)

- Community Consultation Activities took place between 28-MAR-2015 and 18-MAY-2015 and the results of the activities were reported to the WU IRB and were reviewed by a full board on 23-SEP-2015. WU IRB approval was received 16-OCT-2015.
- WU IRB review and approval was contingent on the Barnes Jewish Hospital Emergency Medicine Research Committee's approval which had been previously granted on 09-APR-2015.
- Secretary of the Army Approval was granted on 11-SEP-2015.
- Public Disclosure activities began 22-OCT-2015 and are planned to continue throughout the performance of this trial.

Task 2: Conduct a multi-center, double-blinded, Randomized Controlled Trial (RCT) of 150 patients with three study groups; TXA 2 gram IV bolus, TXA 4 gram IV bolus, and placebo. (Timeframe: months 7-36).

Enrollment began 01- MAR-2016 and was completed on 02-JUL-2017. 150 total patients were enrolled per protocol. Due to some delays with pharmacokinetic sample processing and analysis, we have not yet completed all of the data analysis and are currently working on finalizing those analyses in addition to analyzing the immunology, and outcome data Once our data analyses are complete, we will disseminate the information to the public via public disclosure efforts.

Therefore, our goal is to complete these analyses with a plan for public disclosure of the study results to begin in early 2019. We also plan to prepare manuscripts for peer review and presentation at that time

**What opportunities for training and professional development has the project provided?**

Nothing to report.

**How were the results disseminated to communities of interest?**

We provided information to the community throughout the trial regarding the investigation, risk and benefits, and information pertaining to the exception from informed consent for emergency research through community consultation efforts. We have utilized local, and regional broadcasting, newspapers, town hall meetings, as well as posters and signage.

In addition, our website remains active but has been updated to reflect enrollment completion. Research team members continue to promptly answer questions posed on-line about the study a. Clinicaltrials.gov has also been updated to reflect enrollment completion. Finally, a public disclosure plan is currently being drafted to provide a comprehensive and robust effort to share the results of our study once our data analysis is complete.

**What do you plan to do during the next reporting period to accomplish the goals?**

Nothing to Report

**4. IMPACT:**

**What was the impact on the development of the principal discipline(s) of the project?**

The impact of the results from this trial will be the first pharmacokinetic data of TXA published in patients with severe traumatic bleeding. If optimal serum concentrations are ever determined in this population then our PK data can be used to determine appropriate dosing. The results indicating increased VTE in patients treated with TXA with a dose response will also impact the field by highlighting the potential risk of VTE when TXA is used. The results need to be taken in context though, because there was no difference in organ failure or mortality in those who developed a VTE. Therefore the clinical significance of these VTE events is questionable. We are still analyzing the data and will provide more context to the increased VTE findings in the manuscript we are in the process of developing.

**What was the impact on other disciplines?**

Nothing to Report

**What was the impact on technology transfer?**

Nothing to Report

**What was the impact on society beyond science and technology?**

Nothing to Report

## 5. CHANGES/PROBLEMS:

### Changes in approach and reasons for change

Nothing to Report

### Actual or anticipated problems or delays and actions or plans to resolve them

We experienced delays in PK sample processing analysis but have been able to move the analysis further in the past few weeks and expect the analysis to be complete in early next quarter.

### Changes that had a significant impact on expenditures

Nothing to Report

### Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

## 6. PRODUCTS:

- **Publications, conference papers, and presentations**

There have been formal (power point presentation at a variety of organized community meetings in addition to a presentation to the Barnes Jewish Hospital Emergency Medicine Research Committee) and informal presentations made to the community as part of our community consultation and public disclosure efforts. In addition, members of the DSMB have been presented interim data during their quarterly meetings.

### Journal publications.

Nothing to Report

### Books or other non-periodical, one-time publications.

Nothing to Report

### Other publications, conference papers, and

presentations. Nothing to Report

- **Website(s) or other Internet site(s)** [www.tampiti.wustl.edu](http://www.tampiti.wustl.edu)

- Our website provides detailed information regarding the study (Investigators, design, sponsor, the problem, purpose, etc). The website also provided links to “opt out forms”, “request information forms”, contact information for the study team, links to our Facebook and Twitter pages, feedback forms, our community power point presentation, and the NIH video explaining

emergency research and the EFIC, in addition to relevant references supporting the purpose of this study.

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

Nothing to Report.

## 7. PARTICIPANTS & OTHER COLLABORATING

**ORGANIZATIONS** What individuals have worked on the project?

Name:	Philip C. Spinella, MD
Project Role:	PI
Research Identifier	ORCID ID: 0000-0003-1721-0541
Nearest person month worked	1
Contribution to Project:	Dr. Spinella has led the protocol and methods development for this trial in addition to the FDA IND renewal submission. He assisted with several community consultation activities, conferred with the WU HRPO leadership to continue the successful execution of this trial. Dr. Spinella assists with the oversight of the study, reviewing AEs/SAEs, DSMB reports, and data collection/entry questions.

Funding Support:	During the reporting period, Dr. Spinella has received funding support from NIH/NHLBI (U01HL116383, R21HD089131, R21HL128863, R01HD092471), Children's Discovery Institute (CDI-EI-2015-499), DoD (W81XWH-13-C-0160, WX81XWH-14-1-0373, N00014-13-C-0260, W81XWH-16-C-0162, W81XWH-17-1-0668)
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Name:	Grant V. Bochicchio, MD, MPH
Project Role:	Co-PI
Research Identifier:	ORCID ID: 0000-0002-8313-

1449 Nearest person month worked 1

Contribution to Project:

Dr. Bochicchio has assisted with protocol modifications, FDA IND renewal submission, and has worked with the study team and WU IRB Leadership for guidance and developing processes and procedures for unplanned enrollment of prisoners and minors. He has participated in and has led several community consultation and public disclosure activities. Dr. Bochicchio has met with

key stakeholders regarding this project (including the Emergency Medicine Leadership, HRPO leadership, Trauma Surgery Faculty, Ortho Spine Faculty, Trauma Anesthesia Faculty, etc.) and continues to oversee study execution logistics and patient safety.

Funding Support:

During the reporting period, Dr. Bochicchio had funding support from, NIH- KaloCyte (R42HL135965, R21HD086784-01A1), Foundation for Barnes -Jewish Hospital, and DoD (W81XWH-14-1-0373, DM140394, W81XWH1510504, W81XWH-17-1-0668).

Name:

Kelly Bochicchio, RN, MS

Project Role:

Project Manager

Research Identifier

unknown

Nearest person month worked

3

Contribution to Project:

Ms. Bochicchio has functioned as the overall project manager for this trial. She has prepared all regulatory documents for submission, review, and approval to the WU IRB and DoD HRPO. She assisted with the FDA IND renewal submission and organized and led the Community Consultation and Public Disclosure Plan activities. She has trained the research team regarding data collection and entry, and all study related procedures. She is responsible for the overall research team management.

Funding Support:

During the reporting period, Ms. Bochicchio had funding support from Department of Defense (W81XWH1210550, W81XWH-14-0373).

Name:

Anja Fuchs

Project Role:

Sub-Investigator

Research Identifier

ORCID ID: 0000-0002-0186-4308

Nearest person month worked

1

Contribution to Project:

Dr. Fuchs has developed and validated laboratory techniques associated with the cytokine and PK/PD

Funding Support:

procedures being performed for this trial. During this reporting period, she had trained all study staff regarding bench SOPs for laboratory work and has begun to analyze patient samples. During the reporting period, Dr. Fuchs had funding support from the DoD W81XWH-14-1-0373), and The Foundation for Barnes-Jewish Hospital.

Name:	Avril Adelman
Project Role:	Biostatistician
Research Identifier	
own Nearest person month worked	1
Contribution to Project:	Ms. Adelman has finalized the case report form and
	RedCap database for this trial. She has run reports for the DSMB and has prepared reports for the FDA IND renewal, developing case report forms and the database for this trial. In addition, she has assisted with deciding the randomization plan and reports to be presented to the DSMB.

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to Report

**What other organizations were involved as partners?**

The Children's Hospital of Philadelphia  
Perelman School of Medicine at the University of Pennsylvania  
Athena F. Zuppa, MD, MSCE

**5. SPECIAL REPORTING REQUIREMENTS:**

None

**6. APPENDICES:**

None