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TITLE: The Pathogenesis of Post-Traumatic Pulmonary Embolism: A Prospective Multi-center Investigation by the CLOTT Study Group

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14. ABSTRACT

Venous thromboembolism, which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially mortal complication after injury in both civilian and military settings. To date, there are no methods that have been definitively demonstrated to prevent post-traumatic pulmonary embolism (PE) which carries a mortality of 11% and is the third leading cause of death following injury. PE is particularly common among combat casualties due to the prevalence of certain risk factors such as multiple amputations, traumatic brain injury, the need for transfusions, and prolonged immobilization during evacuation. In Year 3, all sites were enrolling participants except when restricted due to COVID-19 (as reported to HRPO). Due to COVID-19, CLOTT Part 2 sites require additional time to meet enrollment targets. A 12-month extension without funds was requested and approved. Four CLOTT Part 2 sites will complete recruitment in Year 4. CLOTT Part 1 sites closed recruitment September 29, 2020. In Year 4, all CLOTT sites (17) will close protocols with the IRB & HRPO, complete data collection, cleaning and analyses. There are no significant findings to report at this time.

15. SUBJECT TERMS

Venous thromboembolism, pulmonary embolism, combat casualty, trauma, clots, thromboelastography, fibrinolytic shutdown, clot lysis, surveillance bias

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YEAR 3 ANNUAL REPORT

1. INTRODUCTION

Venous thromboembolism, which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially mortal complication after injury in both civilian and military settings. To date, there are no methods that have been definitively demonstrated to prevent post-traumatic pulmonary embolism (PE) which carries a mortality of 11% and is the third leading cause of death following injury. PE is particularly common among combat casualties due to the prevalence of certain risk factors such as multiple amputations, traumatic brain injury, the need for transfusions, and prolonged immobilization during evacuation. However, due to the liberal use of computed tomography following injury, many patients are found to have small clots in the chest that may not be PE at all and may in fact not need to be treated. Additionally, recent laboratory investigations suggest that some severally injured patients develop a hypercoagulable state due to failure to break down clot once formed and that platelets contribute to the strength of the clot. This failure of clot lysis may set the stage for true PE events. For Aim 1, patients aged 18-40 years who are admitted to any of 17 major trauma centers will be considered eligible for enrollment. Data are collected on all patients who develop PE in order to characterize the risk factors for those with symptomatic, central PE versus those with asymptomatic, peripheral thrombi. The safety of observing patients with peripheral thrombi versus treatment (full-dose anticoagulation or placement of a vena cava filter) will be compared. All 17 sites closed enrollment into CLOTT 1 as planned on September 29, 2020. For Aim 2, five trauma centers are enrolling a cohort of patients admitted to their intensive care unit and collect blood samples that can be subjected to thromboelastography (TEG) in order to identify patients with failure of clot lysis (fibrinolytic shutdown). The association between fibrinolytic shutdown and the subsequent development of PE will be explored. Four of these sites will continue enrolling during the no-cost extension (extension without funds - EWOF) period (9/30/20 - 9/29/21).

2. KEY WORDS

Venous thromboembolism, pulmonary embolism, combat casualty, trauma, clots, thromboelastography, fibrinolytic shutdown, clot lysis, surveillance bias

3. ACCOMPLISHMENTS

a. What were the major goals of the project?

- **i.** Study Specific Aims: (1) To compare the safety of observation versus treatment of asymptomatic peripheral pulmonary clots discovered on computed tomography (CTA) (2) To define the role of post-injury fibrinolysis shutdown in the development of post-traumatic PE.

- ii. CLOTT Aim 1/Part 1:
    1. Main Hypothesis: Peripheral asymptomatic pulmonary thrombi (PT) seen on chest computed tomography (CTA) can be safely

observed without specific treatment.

2. Secondary Hypothesis: Risk factors for asymptomatic PT will differ from risk factors for symptomatic pulmonary emboli (PE) with or without associated deep vein thrombosis (VTE).
3. Sub-Aim 1: To compare the safety of observation versus treatment of asymptomatic peripheral pulmonary thrombi discovered on computed tomography of the chest with contrast (CTA)
4. Sub-Aim 2: To evaluate the efficacy of various prophylactic measures in their ability to prevent PE
5. Sub-Aim 3: To determine the magnitude of surveillance bias on the incidence of PE based on the frequency with which chest CTA is utilized.

iii. CLOTT Aim 2/Part 2:

1. Main Hypothesis: Fibrinolytic shutdown after injury will be detected frequently in critically injured patients.
2. Secondary Hypothesis: Fibrinolytic shutdown is associated with an increased incidence of VTE after injury.
3. Sub-Aim 1: To describe the incidence of and the timing for the development of fibrinolytic shutdown in critically injured patients
4. Sub-Aim 2: To identify the risk factors for the development of fibrinolytic shutdown after injury
5. Sub-Aim 3: To investigate the association between fibrinolytic shutdown and the development of DVT and/or PE

b. What was accomplished under these goals?

Major Task 1: Adapt CLOTT protocol for DoD funded status

- Coordinate with sites for annual IRB report for continuing review – Ongoing; NTI assisted the sites with their local IRB submissions and HRPO application and continuing reviews.
- Prepare and submit Quarterly progress reports to the DoD – Ongoing
- *Milestone Achieved: Local IRB approval at all sites*
- *Milestone Achieved: HRPO approval for all protocols*

Major Task 2: Subcontract with all study sites

- *Milestone Achieved: Subawards issued for all sites*

Major Task 3: Patient enrollment

- Identity patients during daily rounds at all 17 sites for study inclusion and collect data during the total length of stay (Aim 1 & Aim 2): Ongoing: For CLOTT Part 1, at least 7,922 subjects have been enrolled. (Note: The actual number of enrolled patients is higher because some centers do not enter their data into the electronic data base until all of their data collection is complete and all enrolled patients are either discharged or

have met the 30-day follow-up period,. For CLOTT Part 2, 223 subjects have been enrolled.
- Draw blood samples for thromboelastography testing (TEG) (Aim 2 only): Ongoing at all five sites for CLOTT Part 2.
- Complete a duplex venous examination (Aim 2 only): Ongoing at five sites for CLOTT Part 2.
- Validate data collected quarterly on a sample of 3% of enrollees: Ongoing
- Coordinate with sites and NTI for monitoring data collection rates and data quality: Ongoing

c. What opportunities for training and professional development has the project provided?
    i. Surgical research associates participated in web-based and in-person protocol training.

d. How were the results disseminated to communities of interest?
    i. Nothing to report (Note: the PI plans to publish the sentinel CLOTT Part 1 paper as soon as the data can be analyzed. A publications committee has already been formed and will assist in providing data to other CLOTT investigators at their request once the sentinel paper is accepted for publication.

e. What do you plan to do during the next reporting period to accomplish the goals?
    i. In the next quarter, with the closure of CLOTT Part 1 enrollment and data collection at all 17 sites we begin data clean up and analysis. Notifications to the site IRBs and close out documentation will be submitted to HRPO as these are completed. Most sites intend to leave their protocol open for data analyses but will inform that IRB that DoD is no longer funding any activities associated with the study. Four CLOTT Part 2 sites will continue enrolling under a second 12 month no cost extension (EWOF). IRB and HRPO continuing review application will be submitted as scheduled. Investigator/research team teleconferences will be held to manage research activities at all sites. UCSF will conduct data assurance checks on 3% of completed cases. Sites will submit quarterly progress reports to the National Trauma Institute d/b/a Coalition for National Trauma Research. These reports will be compiled and submitted to the Department of Defense as scheduled.

4. IMPACT

a. What was the impact on the development of the principal discipline(s) of the project?
    i. Nothing to report. Because of the success of CLOTT, the PI was invited to join the NIH Network of Networks and the steering committee for ACTIV (Accelerating COVID-17 Therapeutic Interventions and Vaccines) focusing on the clotting disorders in COVID patients which are very similar to those in trauma patients. All 17 CLOTT centers are invited to participate in the ACTIV anticoagulation trials depending upon their interest and the number of COVID-17 positive patients at their centers.

b. What was the impact on other disciplines?
    i. Nothing to report

c. What was the impact on technology transfer?
    i. Nothing to report

d. What was the impact on society beyond science and technology?
    i. Nothing to report

5. CHANGES/PROBLEMS

a. Changes in approach and reasons for change
    i. We requested and received approval for a second 12-month no cost extension to allow more time to recruit participants in CLOTT Part 2.

b. Actual or anticipated problems or delays and actions or plans to resolve them

    1. Some sites had to suspend enrollment in CLOTT Part 1 and 2 due to COVID-19 research activities restrictions. These events were reported to HRPO. These suspensions particularly impacted CLOTT Part 2 - which included face-to-face consenting of the patient. Therefore, we applied for and received approval of an addition no-cost extension to continue enrollment at four CLOTT Part 2 sites for as long as financially feasible.

c. Changes that had a significant impact on expenditures
    i. Nothing to report

d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
    i. Nothing to report

6. PRODUCTS

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. Individuals who have worked on the project:

Prime Award at National Trauma Institute d/b/a Coalition for National Trauma Research

Name	Project Role	Nearest person month worked	Contribution to the project
Mary Knudson	Principal Investigator	1	Oversight of entire project (in addition to the effort on the UCSF subaward)
Eric Vittinghoff	Biostatistician	1	Biostatistical support for the entire project (in addition to the effort on the UCSF subaward) Dr. Vittinghoff retired during Year 3. An investigator at Denver Health is providing statistical support for this project.
Ernest Moore	Co-Investigator	1	Lead site investigator for Part 2 (in addition to the effort on the Denver Health subaward)
Michelle Price	Project Manager	1	Oversight and management of daily project activities across 17 data collection sites
Lizette Villarreal	Research Coordinator	1	Assists with regulatory oversight and coordination; maintains research materials; assists with DoD report submissions
Amy Flores	Project Support	1	Manage subawards

Other Collaborating Organizations

Site	Institution	PI
1	UC San Francisco	Mary Knudson
2	Christiana Healthcare	Mark Cipolle – Changed to Sherry Sixta on Sept 11, 2019
3	Medical College of Wisconsin	David Milia
4	Medical University of South Carolina Charleston	Bruce Crookes
5	Johns Hopkins University	Elliot Haut
6	UTHSC Houston	Michelle McNutt
7	University of Florida Health - Jacksonville	Andrew Kerwin
8	University of Florida – Gainesville	Alicia Mohr
9	Oregon Health and Science University	Laszlo Kiraly
10	Denver Health Medical System	Ernest Moore
11	University of Utah	Raminder Nirula
12	Lancaster General Hospital	Frederick Rogers
13	Stanford University	David Spain
14	University of Maryland-R. Adams Cowley Shock Trauma	Brandon Bruns
15	UC San Diego-Hillcrest	Todd Costantini
16	Massachusetts General Hospital	George Velmahos
17	Scripps Mercy Hospital	Michael Sise - Changed to Matthew Martin on Aug 15, 2019

8. SPECIAL REPORTING REQUIREMENTS

a. Quad Chart – Attached

9. APPENDICES

a. None

The Pathogenesis of Post-Traumatic Pulmonary Embolism: A Prospective Multi-center Investigation by the CLOTT Study Group

ERMS/Log Number: BA160400
Award Number: W81XWH-17-1-0673

PI: Mary Knudson Org: National Trauma Institute Award Amount: $4,262,854

Study

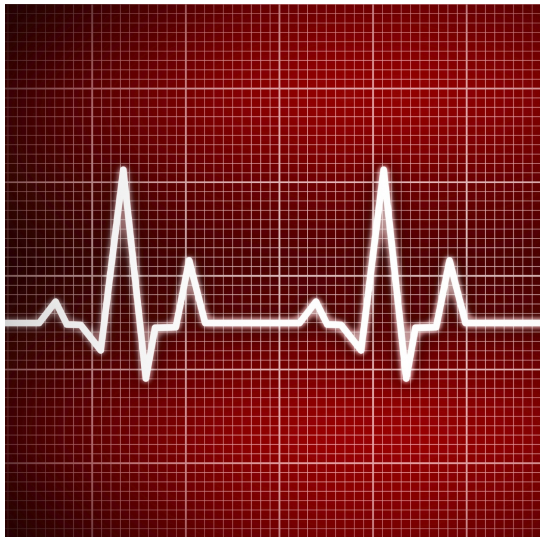
1. To compare the safety of observation versus treatment of asymptomatic peripheral pulmonary clots discovered on computed tomography (CTA).
2. To define the role of post-injury fibrinolysis shutdown in the development of post-traumatic PE.

Approach

This is a multi-center, prospective, observational trial performed at 17 level I trauma centers. All injured civilian adult patients in the age range of 18-40 years will be screened and those who are found to have PE on a CTA will be enrolled. Data will be collected and uploaded into REDCap to characterize the risk factors for those with symptomatic, central PE versus those with asymptomatic, peripheral thrombi. Furthermore, five of these trauma centers will enroll a cohort of patients admitted to their ICU and collect blood samples that can be subjected to thromboelastography (TEG) in order to identify patients with failure of clot lysis (fibrinolytic shutdown).

The Pathogenesis of Post-Traumatic Pulmonary Emboli

THE CLOTT STUDY GROUP



Activities CY	18	19	20	21
Adapt CLOTT Protocol for DoD Funded Status				
Subcontract with all study sites				
Patient enrollment				
Data Analysis and Knowledge Translation				

Timeline adjusted for 2nd 12mo NCE

Updated: 10/30/2020

Goals/Milestones

CY18 Goal – Adapt Protocol
☑Obtain IRB and HRPO approval for lead site
☑ Obtain IRB and HRPO approval for all sites
CY18 Goal – Subcontracts
☑ Sub Awards issued for all sites
CY18 - 21 Goal – Patient Enrollment
☑ Aim 1 enrollment completed (n=9,000 – pending final)
☐ Aim 2 enrollment completed (n=300)
CY21 Goal – Data Analysis and Knowledge Translation
☐ Analyze data
☐ Disseminate findings

Budget Expenditure to Date

Projected Expenditures: $4,262,853
Actual Expenditures: $3,741,214