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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 2, all sites were approved by local IRBs and HRPO for CLOTT Part 1 (17 sites) and CLOTT Part 2 (5 sites). All sites are enrolling participants. Due to delays in approvals, sites require additional time to meet enrollment targets. A 12-month extension without funds was requested and approved. All sites will continue to recruit subjects in the third project year.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 1 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. 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.

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 – No cost extension for Year 3 issued to 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, 4,900 subjects have been enrolled. For CLOTT Part 2, 131 subjects have been enrolled.
- Draw blood samples for thromboelastography testing (TEG) (Aim 2 only): Ongoing at all five sites for CLOTT Part 2. Received approval for obtaining consent within 7 days at UT Houston and UCSF.

- 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

e. What do you plan to do during the next reporting period to accomplish the goals?
    i. In the next quarter, all sites will continue enrolling under a 12 month no cost extension. 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. 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

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. The CLOTT Part 2 waiver of consent timeframe was extended to 7 days. This was to allow more time to consent the participant or obtain approval from their legally authorized representative.
    ii. We requested and received a 12-month no cost extension to allow more time to recruit participants.
    iii. There were changes in the site principal investigators at Scripps & Christiana. These changes were due to the previous PI changing roles in the department (Scripps) or leaving the institution (Christiana).

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

1. In the statement of work, we estimated that all sites would have local IRB approval by month 5 and HRPO approval by month six. At the end of Year 1, all 17 CLOTT Part 1 sites had IRB approval. Two sites were under initial review at HRPO. For CLOTT Part 2, four of five sites had IRB and HRPO approval at the end of Year 1. One site was pending IRB approval. There were a couple of factors that slowed the IRB approval process. First, some sites had delays in hiring staff and, therefore, delays in submitting to the IRB. Second, some IRBs expressed concern about the waiver of consent in CLOTT Part 1. Third, some IRBs were concerned about collecting date of birth and date of injury. Fourth, some IRBs wanted Data Use Agreements to be executed with UCSF before giving IRB approval.
2. Subject enrollment was delayed as a result of issues described above. We have received a 12 month no cost extension to continue enrollment.
3. CLOTT Part 2 sites have had difficulty recruiting subjects. Therefore, UCSF and UT Houston obtained approval to extend the waiver of consent to 7 days. This has helped with enrollment somewhat. UT Houston is still having difficulty identifying subjects. Dr. Knudson is going to work with the site PI to ensure the site isn't missing potential enrollees. The target enrollment for the study has been reduced to 180. Sites will continue to enroll during the 12 month no cost extension with the goal of recruiting 40 patients at each site.

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. CLOTT Part 2 waiver of consent was amended to allow for 7 days to obtain consent at UT Houston and UCSF.

6. PRODUCTS

Please see attached slide deck from the 2019 CLOTT Investigator meeting.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. Individuals who have worked on the project:

Prime Award at National Trauma Institute

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)
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. PowerPoint presentation attached

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

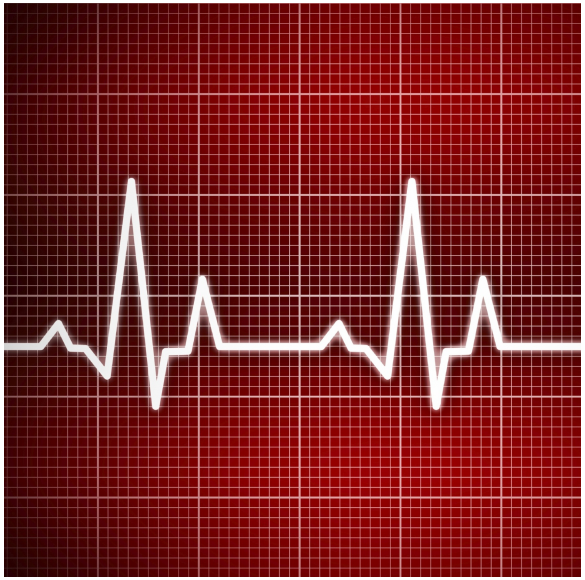
1. To compare the safety of observation versus treatment of asymptomatic peripheral pulmonary clots discovered on computed tomography (CTA).
2. To define the role of post-injury fibrinolysis shutdown in the development of post-traumatic PE.

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
Adapt CLOTT Protocol for DoD Funded Status			
Subcontract with all study sites			
Patient enrollment			
Data Analysis and Knowledge Translation			

Timeline adjusted for 12mo NCE

Updated: 10/1/2019

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 and 19 Goal – Patient Enrollment
☐ Aim 1 enrollment completed (n=9,000)
☐ Aim 2 enrollment completed (n=800)
CY19 Goal – Data Analysis and Knowledge Translation
☐ Analyze data
☐ Disseminate findings

Budget Expenditure to Date

Projected Expenditures: $3,735,922
Actual Expenditures: $2,331,515

The Pathogenesis of Post-Traumatic Pulmonary Emboli

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Enrollment At Year 2: Part 1

Center	# Enrolled	Center	# Enrolled
UCSF	441	Hopkins	151
U Texas Houston	562	U. Florida-Jacksonville	283
U. Maryland	540	Lancaster General	164
UCSD	195	MGH	105
Stanford	161	U. Oregon	211
Denver	371	Christiana	157
Utah	218	MUSC	
U. Florida Gainesville	261		
MC Wisconsin	530	Total # Patients	4,665
Scripps	315		

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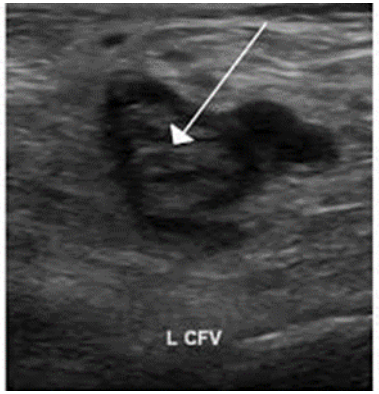
DVT Data

1,505 duplex exams recorded in REDCap

Symptoms: 29%
Positive: 18%

Surveillance: 71%
Positive: 7.4%

Overall DVT rate: 3.7%



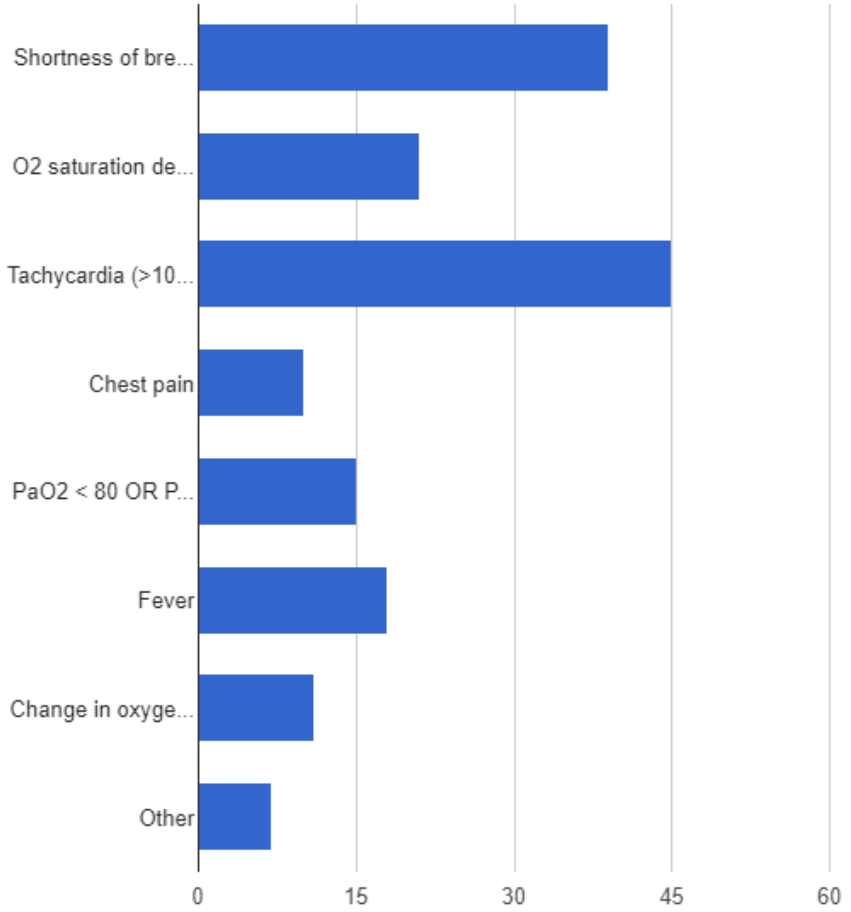
CTA Scans

1,908 scans recorded in REDCap

Symptoms: 16%
Positive: 17%

Surveillance: 84%
Positive: 1.6%
Observation only: 30%

Overall PE rate: 1.8%



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Enrollment at Year 2: Part 2

Center	# Enrolled
UCSF	11
Denver	56
Oregon	19
Houston	22
Maryland	10
Total # Patients	118

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CLOTT 2 DATA

- Patients with TEG data in REDCap: 43
- Patient's exhibiting shutdown at some time-point: 72%
- Shutdown + DVT: 4.7%
- Shutdown + PE: 2.3%

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With gratitude to ALL for Patience and Persistence

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