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TITLE: Safety and Feasibility of Emergency Preservation and Resuscitation for Cardiac Arrest from Trauma (EPR-CAT)

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CONTRACTING ORGANIZATION: University of Maryland, Baltimore, MD

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

During this fourth year of the project, we have remained on clinical hold because of concerns about the local blood supply due to the COVID-19 pandemic. In addition, the FDA has raised concerns about whether or not the study meets the requirements for the Exception from Informed Consent for emergency research. Specifically, they are not convinced that EPR provides the potential for benefit for individual subjects based upon the current data, which includes only 6 EPR subjects and 5 controls. We have submitted 2 written responses to their concerns and held a video conference with them to clarify the issues. They have now asked for a comprehensive report of the background of the study, the clinical data, our response to the unexpected clotting issues, and our explanation for why we believe the study should continue. This report, along with some additional background information they requested, will be reviewed by their Exception from Informed Consent panel. This panel has not yet been involved in the EPR review by the FDA.
Stroger Hospital of Cook County has received approval for the study from their IRB and the Army HRPO. Given the issues noted above, we have held off on moving forward with training or enrollment at Stroger Hospital of Cook County.

15. SUBJECT TERMS
Trauma, hemorrhagic shock, cardiac arrest, cardiopulmonary resuscitation, hypothermia

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1. INTRODUCTION:

Cardiopulmonary resuscitation (CPR) can save victims of non-traumatic cardiac arrest (CA), e.g., ventricular fibrillation. During exsanguination CA from trauma, however, CPR, even with an emergency department (ED) thoracotomy and open chest CPR, results in unacceptably low survival rates (<5%). *Emergency Preservation and Resuscitation (EPR)* was developed to rapidly preserve the whole body during ischemia, using hypothermia, drugs, and fluids, to "buy time" for transport and resuscitative surgery. Laboratory research has only demonstrated efficacy with hypothermia. The purpose of this study is to test the feasibility of rapidly inducing profound hypothermia (10ºC) with an aortic flush in trauma victims that have suffered CA and failed standard resuscitative efforts to enable resuscitative surgery and delayed resuscitation with cardiopulmonary bypass. The primary outcome variable will be survival to hospital discharge with minimal neurologic dysfunction.

2. KEYWORDS:

Trauma, hemorrhagic shock, cardiac arrest, cardiopulmonary resuscitation, hypothermia

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aims

1. Rapidly identify appropriate candidates for EPR
2. Initiate EPR and achieve goal temperature within 25 minutes of subject identification
3. Compare the rate of hospital discharge without major neurologic disability in the EPR group with the concurrent control group
4. Compare the rates of 28-day survival, 1-year neurologic functional outcome, and the development of multiple organ dysfunction in the EPR group with the concurrent control group
5. Document direct complications of the EPR technique

Major Task 1: Regulatory approvals

1. Local IRB approval of community consultation and public disclosure plan
2. Conduct community consultation/public disclosure
3. Local IRB Approval
4. US Army HRPO Approval

Major Task 2: Training

1. IACUC Approval
2. ACURO Approval
3. Complete animal training
4. Complete cadaver training

Major Task 3: Retrospective review of trauma registries

1. Review of patients who have undergone a resuscitative thoracotomy

Major Task 4: Enroll patients in first 2 cohorts

1. Develop specific logistics with involved disciplines
2. Assure that all necessary equipment is ready
3. Subject enrollment at Site 1
4. Subject enrollment at Site 2
5. Enroll 10 EPR subjects and 10 control subjects

Major Task 5: Revise protocol

1. Evaluate data from first cohorts of 10 EPR and 10 control subjects
2. Revise protocol based upon data from first cohorts
3. Obtain approvals for second set of cohorts from DSMB, FDA, IRBs, and US Army HRPO

Major Task 6: Enroll patients in second 2 cohorts

1. Enroll 10 EPR subjects and 10 control subjects
2. Evaluate data from second set of cohorts of 10 EPR and 10 control subjects

What was accomplished under these goals?

Major Task 1: Regulatory approvals

All approvals have been completed at the University of Maryland and the John H. Stroger Hospital of Cook County. The subcontract with the John H. Stroger Hospital of Cook County (Hektoen Institute for Medical Research) as a second site is also complete.

Major Task 2: Training

Training has been completed at the University of Maryland, which has IACUC and ACURO approval. Animal and cadaver training for the team at Stroger Hospital will be completed at the University of Maryland, rather than at Stroger Hospital, after the issues with the FDA have been resolved.

1. IACUC Renewal: completed
2. ACURO Renewal: completed
3. Complete animal training: pending for Stroger Hospital
4. Complete cadaver training: pending for Stroger Hospital

Major Task 3: Retrospective review of trauma registries

1. Review of patients who have undergone a resuscitative thoracotomy: we are still analyzing this data for any correlations that my help guide recruitment. Overall, however, the survival rate, as noted in previous reviews, remains approximately 5%.

Major Task 4: Enroll patients in first 2 cohorts

Enrollment is on hold at the University of Maryland.

1. Develop specific logistics with involved disciplines: Discussions are on hold at Stroger Hospital
2. Assure that all necessary equipment is ready: Discussions are on hold at Stroger Hospital
3. Subject enrollment at Site 1: Enrollment has remained on hold because of COVID-19 related effects on the blood supply and the recent issues raised by the FDA.
4. Subject enrollment at Site 2: pending resolution of the FDA issues and local training
5. Enroll 10 EPR subjects and 10 control subjects: in progress. We currently have 6 EPR subjects and 5 control subjects.

Major Task 5: Revise protocol

Pending completion of enrollment of the first cohort of 10 EPR and 10 control subjects.

1. Evaluate data from first cohort of 10 EPR and 10 control subjects
2. Revise protocol based upon data from first cohorts
3. Obtain approvals for second set of cohorts from DSMB, FDA, IRBs, and US Army HRPO

Major Task 6: Enroll patients in second 2 cohorts

1. Enroll 10 EPR subjects and 10 control subjects
2. Evaluate data from second cohorts of 10 EPR and 10 control subjects

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

Nothing to report for this period. Once we resolve the FDA and blood supply issues, we will need to conduct refresher training since the study has been on hold for so long. Training of the Stroger Hospital team members may begin once the FDA issues have been resolved.

How were the results disseminated to communities of interest?

Nothing to report.

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

We will restart recruitment of subjects at the University of Maryland as soon as our clinical hold is lifted by the blood bank and we have resolved the issues with the FDA.

We will consider initiating training for the Stroger Hospital team after the FDA issues have been resolved. Training should occur as close to the time of planned enrollment as possible.

IACUC and ACURO renewal have been completed.

4. **IMPACT:**

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

Nothing to report.

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

The cause for low enrollment at the University of Maryland is unclear. We are continuing to review our trauma registry and screening procedures with the research staff to be sure we are not missing potential subjects. This will be difficult to assess given that we have been on hold for >2 years.

Bringing on the John H. Stroger Hospital of Cook County as a second site could help with overall study enrollment. On the other hand, given the unanticipated adverse events and the scrutiny by the FDA, we may hold off on adding Stroger Hospital for this initial feasibility study.

Changes that had a significant impact on expenditures

The study has remained on clinical hold. Consequently, we have minimized any expenditures.

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

Significant changes in use or care of human subjects

There have been no changes to the care of human subjects or vertebrate animals.

IRB approval date: 14-May-2019

IACUC approval date: 05-Sept-2019

Maryland State Anatomy Board approval date: 08-Jun-2015.

USAMRMC Office of Research Protections cadaver approval: 16-Jul-2015 under Proposal Log Number 07152001, Award Number W81XWH-07-1-0682.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

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

Journal publications.

1. Tisherman SA: Emergency preservation and resuscitation for cardiac arrest from trauma. Ann NY Acad Sci. 2022;1509(1):5-11.

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

Nothing to report.

Other publications, conference papers and presentations.

Presentations regarding the background and protocol. No data has been presented.
"A cool way to save patients", 10th Congress for Emergency Medicine, Graz, Austria, 2022

- **Website(s) or other Internet site(s)**

The following website was developed for disseminating information about the study as part of the public disclosure process. There is currently no information regarding results on this site.

https://www.umms.org/ummc/health-services/shock-trauma/news/body-cooling-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:	Samuel A. Tisherman, MD
Project Role:	Principal investigator
Researcher Identifier (e.g. ORCID ID):	0000-0003-3810-3729
Nearest person month worked:	2
Contribution to Project:	Manages all aspects of the study, including training, readiness for enrollment, data management and analysis, submission of regulatory documents, and coordination with all sites. Dr. Tisherman is the sponsor of the Investigation Device Exemption.
Name:	Thomas Scalea, MD
Project Role:	Co-investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Training of surgeons involved in the project. Revisions to the clinical protocol. Identification of clinical sites.
Name:	Leslie Sult, RN
Project Role:	Research coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Assists with training. Assures that equipment is available and personnel are prepared for subject enrollment. Supervises data collection.
Name:	Faran Bokhari, MD
Project Role:	Site principal investigator at John H. Stroger Hospital of Cook County
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Manage all aspects of the study at Stroger Hospital, including team oversight, data management, and submission of regulatory documents.

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?

Organization Name: Stroger Hospital of Cook County
Location of Organization: Chicago, IL
Partner's contribution to the project: Collaboration as second site for conducting the study.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: