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TITLE: Hypothermia for Patients Requiring Evacuation of Subdural Hematoma: Effect on Spreading Depolarizations

PRINCIPAL INVESTIGATOR: Jed A. Hartings, PhD

RECIPIENT:
University of Cincinnati

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Jed A. Hartings, PhD

E-Mail: jed.hartings@uc.edu

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University of Cincinnati
2600 Clifton Ave
Cincinnati, OH 45220-2872

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14. ABSTRACT

This report describes Year 2 progress in clinical studies to determine the impact of temperature management on spreading depolarizations (SD) and outcomes in severe traumatic brain injury (TBI). After DSMB closure of the proposed prospective trial, revised statements of work and budgets were prepared, and through several iterations, resulted in execution of a modified contract in the 3rd quarter to address the research question using existing clinical databases from the W81XWH-08-2-0016 (Objective 1) and TRACK-TBI (NIH U01; Objective 2)studies. New and revised subaward contracts, ethical approvals, and other permissions to conduct these studies were obtained. Studies were inventoried, identifying sample sizes of n=138 ICU-admit patient with SD data and n=1083 without SD data. Preparation of databases, including hourly nursing chart values, for statistical analysis was initiated, including data extraction, organization, and cleaning. Custom programming to import, query, and export data was initiated. Study teams were organized with exploration of initial statistical approaches.

15. SUBJECT TERMS

traumatic brain injury; subdural hematoma; electroencephalography; spreading depression; spreading depolarization; therapeutic hypothermia; craniotomy

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TABLE OF CONTENTS

1. INTRODUCTION:

The ***hypothesis of the originally funded study*** was that a mechanism of therapeutic benefit of hypothermia in TBI patients is through suppression of mass neuronal spreading depolarizations (SD) in cerebral cortex. The ***objective*** was to determine whether very early cooling in the HOPES trial is associated with reduced incidence of spreading depolarizations compared to normothermia treatment. The HOPES trial was a separately funded, prospective, randomized trial to determine the effects of very early cooling in the specific pathoanatomic subgroup of TBI patients undergoing surgical evacuation of acute subdural hematomas (ASDH).

As communicated in the Year 2 Annual Report, completion of the proposed study was not possible since (1) Office of the Secretary of the Army review of the study protocol, which utilized Exception from Informed Consent, was never accomplished, and (2) during this period, at a scheduled interim review on August 27, 2018, the Data Safety and Monitoring Board of the HOPES study recommended to end the trial due futility.

This report describes efforts in Year 3 to develop alternate research plans to address the original hypothesis concerning the role of hypothermia, and SD as a mechanistic target, for improving outcome from TBI. The major goals and scientific progress reported are aligned with the approved, revised Statement of Work.

2. KEYWORDS:

traumatic brain injury; subdural hematoma; electroencephalography; spreading depression; spreading depolarization; therapeutic hypothermia; normothermia; controlled normothermia; temperature management; mass lesion; craniotomy;

3. ACCOMPLISHMENTS:

In this year, following closure of the HOPES study, the PI held discussions with the Science Officer and Contract Specialist to determine whether and how the scientific objectives of the study might still be achieved by alternate research plans. Several revised Statements of Work (SOW) were developed by the PI after additional consultation with collaborators at the University of Pittsburgh, University of Texas at Houston, and other institutions. These were refined and re-drafted until a SOW, dated 10 Dec 18, was given conditional approval from USAMRAA. A revised budget in line with this SOW was subsequently drafted and submitted on 7 Jan 19. Subaward budget documents and other clarifications were submitted to the Contract Specialist on 13 Feb 19, in support of the previously submitted prime award budget. After review, further clarifications and supporting documentation were requested by the Contract Specialist on 3 Mar 19, and the requested materials were returned by UC to the Contract Specialist on 18 Mar 19. A fully executed contract modification was received June 28, 2019.

Major goals of the project

It is recognized that fever contributes to secondary injury after TBI and should be avoided. However, it is uncertain how aggressively therapy should be applied, and whether there is benefit to controlled normothermia, targeted temperature management, or hypothermia. Hypothermia,

for instance, remains attractive as a treatment for elevated intracranial pressure, despite mixed results and several failures in clinical trials.

Under the revised SOW, we aim to refine understanding of optimal practices for temperature management in TBI by examining patient temperatures and temperature management therapies and their relationship to functional and cognitive outcomes in a large national, observational TBI cohort. In a more focused study, we will further investigate spreading depolarizations (SDs) as a hypothesized neuronal mechanism for the adverse effects of fever. SDs are pathologic waves in cerebral cortex that recur for days following TBI and are an independent factor in worse patient outcomes. We hypothesize that temperature management is effective due to suppression of SDs, and that the limit and extent of outcome benefit of lower patient temperatures is similar to the impact of temperature on SD risk.

OBJECTIVE 1: Determine the impact of patient temperature and temperature management practices on the variable incidence and timing of SDs after severe TBI.

Specific Aim 1A: Determine the impact of patient temperature on SD probability.
Specific Aim 1B: Determine whether patients without SDs (n=55) differ from those with SDs (n=83) in temperature values and temperature management practices.
Specific Aim 1C: Determine the impact of temperature management on 6-month clinical outcomes.

OBJECTIVE 2: Determine the impact of patient temperature on long-term functional and cognitive outcomes in a large national cohort.

Specific Aim 2A: Determine the impact of patient temperature on functional outcomes.
Specific Aim 2B: Determine the impact of patient temperature on cognitive outcomes.
Specific Aim 2C: Determine the impact of temperature mangement practices on 6-month clinical outcomes.

Accomplishments toward these goals in Year 3, aligned with SOW Milestones

Preparatory Work

Subaward Contracts: A revised subaward contract with the University of Pittsburgh has been fully executed, and a new subcontract with the University of California-San Francisco has also been fully executed. The revised contract with University of Texas at Houston is awaiting countersignature.

Ethical approvals: For objective 1, a protocol was submitted to the University of Cincinnati for study of an existing database. The IRB determined that the protocol meets requirements for exemption from IRB review in accordance with 45 CFR 45.104 (secondary research on data or specimens; no consent required). For objective 2, all collaborating sites have approved IRB protocols in place. Separate HRPO submissions will be made for each objective, following recent DOD guidance.

TRACK-TBI Collaboration: For objective 2, it was necessary to submit a project proposal/declaration to the TRACK-TBI Executive Committee to permit data use/access for our intended purpose. The collaboration request was submitted on 4 Sept 19 and approval was received on 3 Oct 19.

Objective 1

1. Write MATLAB code for import of hourly physiologic values and SD times

2. Write MATLAB code to analyze SD rates in relation to physiologic values

3. Perform analysis of Aim 1A

4. Perform analysis of Aim 1B

Progress: Work on tasks 1-4 has proceeded in parallel.

- The database from the SD-1 study (W81XWH-08-2-0016) was organized into worksheets for analysis. This includes hourly data (e.g. patient temperature) from more than a dozen monitoring modalities throughout the time-course of SD monitoring (Figure 1). The data are organized identically for each patient, with one worksheet per patient, in Excel. Data from 138 patients are included. The formatting is consistent with capabilities to import the data in bulk into MATLAB for subsequent computations.

Time	SBP	DBP	MAP	Heart rate	ICP	CPP	CVP	Temp	Temp. unit	Temp method	Brain temp	PbrO2	SaO2
14:00	128	51	74	105	7	68	999	36.6	C	R	999	999	100
15:00	123	50	73	97	8	65	999	36.6	C	R	999	999	100
16:00	122	64	131	83	9	73	999	37.8	C	R	999	999	100
17:00	142	59	86	81	10	74	999	37.7	C	R	999	999	100
18:00	133	53	79	84	11	68	9	999	C	R	999	999	100
19:00	127	57	82	78	12	70	13	37.5	C	R	999	999	100
20:00	126	58	82	77	12	70	12	37.4	C	R	999	999	100
21:00	117	53	75	76	10	65	9	37.3	C	R	999	999	100
22:00	117	53	75	76	10	65	8	37	C	R	999	999	100

Figure 1. Sample spreadsheet of hourly nursing chart values.

- A similar organization was performed in Excel for the previously completed scoring of SD events. Data from both the hourly nursing chart values and the SD scoring will be imported into MATLAB for cross-computation and analysis.
- We reviewed MATLAB programming goals for computational analysis. These include (1) import of all data into comprehensive structures that allow easy identification of patients and alignment of time points on a common axis, and which precludes the need to track multiple datasets, (2) identification and coding of missing values, (3) computation of various measures for a given variable (e.g. maximum, median, variance, % time above threshold), (4) capabilities to easily query and export requested data.
- Established collaboration with a biostatistic faculty member, Roman Jandarov, PhD, to develop a statistic approach to addressing the objectives. A biostatistics PhD student, Koffi Wima, under the supervision of Dr. Jandarov, was also identified to work on the study as a thesis project. All project goals were discussed and Excel data files were shared.

5. Perform analysis of Aim 1C — Not started

6. Manuscript preparation and publication — Not started

Objective 2

1. Completion of data entry

2. Data cleaning and extraction

   Progress: To initiate work on tasks 1-2, we identified the TRACK cohort with eligible data. All primary data points required to conduct and report studies have been collected, monitored, and locked for the main TRACK cohort (excluding subsequent auxillary studies). This includes 2997 patients, of which 1083 are adults admitted to the ICU, and therefore eligible for inclusion in our analysis. The hourly nursing chart data (including temperatures) have been downloaded, and are ready for examination and cleaning.

3. Adapt MATLAB code for data import and analysis Not started

4. Perform analysis of Aim 1A

5. Perform analysis of Aim 1B

6. Perform analysis of Aim 1C

   Progress: For tasks 4-6, we also held a conference call with the primary TRACK statistician, Nancy Temkin, PhD, to review the aims of the study and brainstorm requirements and possible approaches. It was determined that it will be necessary to conduct separate analyses for different injury severities, or at least include severities as an adjustment factor in outcome analysis. It was decided to exclude patients with <3 days of ICU stay. It was decided that a sensitivity analysis should be conducted to determine the effect of including patients with only partial or sporadic data documentation. The occurrence of hypothalamic injury, infection, anemia, and blood-loss anemia will be examined as confounders. Statistical approaches to hour temp data were discussed, including proportion over/under threshold, time-severity burden, and use of the trapezoidal rule.

7. Manuscript preparation and publication Not started

Opportunities for training and professional development
Nothing to Report

Dissemination of results to communities of interest
Nothing to Report

Next reporting period

In the next quarter, we will:

- Execute the final subcontract with UT-H
- Complete MATLAB programming for data import and basic computations in Objective 1.
- Identify an initial statistical approach to address Objective 1 and perform initial tests to identify pitfalls and successes.

- Review TRACK cases for any missing data from hourly nursing charts, and contact sites for data completion. Once data completion is verified, we will proceed with data cleaning and then formatting for analysis.

4. IMPACT

Impact on the development of the principal discipline(s) of the project
Nothing to report

Impact on other disciplines
Nothing to report

Impact on technology transfer
Nothing to report

Impact on society beyond science and technology
Nothing to report

5. CHANGES/PROBLEMS

Changes in approach and reasons for change
Nothing to report since the contract modification was executed

Actual or anticipated problems or delays and actions or plans to resolve them
Nothing to report since the contract modification was executed

Changes that had a significant impact on expenditures
Nothing to report since the contract modification was executed

Significant changes in use or care of human subjects
Nothing to report since the contract modification was executed

Significant changes in use or care of vertebrate animals
Not applicable

Significant changes in use of biohazards and/or select agents
Not applicable

6. PRODUCTS

Publications, conference papers, and presentations

A manuscript that provides a comprehensive description of the patient dataset to be analyzed in Objective 1 was accepted for publication. This work is not reported as progress from the present contract, but will facilitate subsequent publication of the more detailed analysis we are now undertaking.

Hartings JA, Andaluz N, Bullock MR, Hinzman JM, Mathern B, Pahl C, Puccio A, Shutter LA, Strong AJ, Vagal A, Wilson JA, Dreier JP, Ngwenya LB, Foreman B, Pahren L, Lingsma H, Okonkwo DO.

Prognostic value of spreading depolarizations in severe traumatic brain injury. ***JAMA Neurology***, in press (anticipated publication December 30, 2019).

Website(s) or other Internet site(s)
Nothing to report

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: Jed Hartings, PhD
Project Role: Principal Investigator
Nearest person month worked: 2
Contribution to Project: Corresponded with DOD and all collaborating partners to determine new SOW. Organized the initiation of this work and planning of objectives. Reviewed and prepared data for analysis. Supervised submission of protocols and obtained research permissions. Supervised budget preparation and establishment of new subawards.

Changes in other support of the PD/PI(s) or senior/key personnel since the last reporting period
Nothing to report

Other organizations involved as partners
Organization Name: University of Texas at Houston
Location of Organization: Houston, TX
Partner's contribution to the project: Data curation, analysis, writing, and intellectual contribution in approach to Objective 2
Financial support to project: None
In-kind support: None
Facilities, Collaboration, or Personnel Exchange outside contribution noted above: None

Organization Name: University of Pittsburgh
Location of Organization: Pittsburgh, PA
Partner's contribution to the project: Data curation, analysis, writing, and intellectual contribution in approach to Objective 2
Financial support to project: None
In-kind support: None
Facilities, Collaboration, or Personnel Exchange outside contribution noted above: None

Organization Name: University of California San Francisco
Location of Organization: San Francisco, CA

Partner's contribution to the project: Data management, curation, and extraction in support of Objective 2
Financial support to project: None
In-kind support: None
Facilities, Collaboration, or Personnel Exchange outside contribution noted above: None

8. SPECIAL REPORTING REQUIREMENTS

Quad Chart is submitted separately.

9. APPENDICES

None