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

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14. ABSTRACT This report describes Year 2 progress in a sub-study of the HOPES trial to assess the effects of hypothermia on the pathologic mechanism of spreading depolarizations (SD). HOPES is a randomized multi-center clinical study of very early hypothermia in patients with traumatic brain injury who require emergent surgical evacuation of a subdural hematoma. In this period, no progress was made as the study remained under ethical review by the Secretary of the Army, as a requirement for a study conducted under Exception from Informed Consent (EFIC). Alternatives to use of EFIC were explored. At the end of this period, the HOPES Data and Safety Monitoring Board conducted a scheduled interim review and recommended to stop the trial due to futility, which precludes any possibility to conduct the study as presently described in the HOPES protocol. The investigators are formulating a proposed revision of the Statement of Work with alternate plans to achieve the objectives of the study.					
15. SUBJECT TERMS traumatic brain injury; subdural hematoma; electroencephalography; spreading depression; spreading depolarization; therapeutic hypothermia; craniotomy					
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1. INTRODUCTION:

HOPES (Hypothermia for Patients Requiring Evacuation of Subdural Hematoma) is a privately funded, prospective, multi-center randomized trial to determine the effects of very early cooling in the specific pathoanatomic subgroup of traumatic brain injury (TBI) patients undergoing surgical evacuation of acute subdural hematomas (ASDH). The study is conducted under Exception From Informed Consent (EFIC) due to the short time window for patient enrollment (5 hr post-TBI). Patients requiring evacuation of ASDH are randomized 1:1 to (a) normothermia at 37 C, or (b) hypothermia induced to 35 C before surgery and maintained at 33 C for at least 48 hr. Temperatures are managed in both groups by intravascular catheters and neurologic outcomes are assessed using the Glasgow Outcome Score-Extended at 6 months. The ***hypothesis of the present study*** is that a mechanism of therapeutic benefit of hypothermia is through suppression of spreading mass neuronal depolarizations, a mechanism of secondary damage in injured cerebral cortex. The ***objective*** is to determine whether very early cooling in the HOPES trial is associated with reduced incidence of spreading depolarizations compared to normothermia treatment. To achieve this objective, spreading depolarizations will be monitored by electrocorticography at four centers in the HOPES trial, as an optional observational monitoring component of the HOPES protocol. Electrocorticography electrode arrays will be placed on the brain after surgical ASDH evacuation, and spreading depolarizations will be monitored during the post-operative period of temperature management in the intensive care unit for a minimum of 48 hr. Recordings will then be scored for the occurrence and severity of spreading depolarizations by off-line, off-site review that is blinded to randomization and patient outcomes. The results will be compared with 6-month neurologic outcomes and between normothermia and hypothermia treatment arms.

2. KEYWORDS:

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

3. ACCOMPLISHMENTS:

Major goals of the project

The major goals of the project are to determine:

- 1) Whether spreading depolarizations are less common in patients treated with hypothermia compared to normothermia (a) during temperature management and (b) after temperature management
- 2) Whether the burden of spreading depolarizations (during and after temperature management and in total) is associated with long-term neurologic outcome, and whether such association is dependent or independent of temperature management protocol

These goals will be accomplished by implementing electrocorticography (ECoG) monitoring at 4 study sites of the HOPES trial: University of Cincinnati (UC), University of Pittsburgh (UP), University of Texas at Houston (UT-H), and University of Miami (UM). UC is the coordinating center for the ECoG component of the study and will work closely with UT-H as the coordinating center for HOPES. The work is organized into major tasks to be accomplished in a 4-year

performance period. These are shown in the chart below with expected and actual times of task completion.

TASK / MILESTONE	EXPECTED TIMELINE (months)	COMPLETION
1. Develop Case Report Forms (CRFs) and implement web-based database in RedCap (Research Electronic Capture, Vanderbilt University) utilizing TBI Common Data Elements.	Prior to start date	Completed prior to start date
2. Community consultation and notification for Exception from Informed Consent (EFIC) at study sites.	Prior to start date	Completed prior to start date
3. Edit Manual of Procedures and Standard Operating Procedures for addition of ECoG.	Prior to start date	Completed prior to start date
4. Approval of protocol and informed consent forms, with EFIC, at study site IRBs.	3	UT-H: prior to start UP: prior to start UC: month 5 UM:
5. Approval of protocol and informed consent forms by Department of Defense Human Research Protections Office.	1-3	Expected: Nov 2017
6. Establish subaward contracts with Miami, UT-H, and Pittsburgh	3	UT-H: month 6 UP: month 11 UM:
7. Installation of Moberg CNS monitors for ECoG recordings at study sites.	1-2	Completed by month 9 at UT-H, UP, and UC
8. Site initiation visits and training.	1-2	UP: month 10 UT-H: pending UM:
9. Patient enrollment and data collection.	4-36	Not started
10. Assessment of 6-month neurologic outcomes.	10-42	Not started
11. Scoring of spreading depolarizations from patient recordings.	5-39	Not started
12. Interim efficacy analysis after 60 patients accrued.	22	Not started
13. Analysis of intracranial ECoG data in hypothermia vs. normothermia groups (Objective 2).	40-45	Not started
14. Final analysis of neurologic outcomes of 120 patients (Objective 1).	43-45	Not started
15. Manuscript preparation and publication.	45-48	Not started

Accomplishments toward these goals in Year 2

The above table provides an overview of major study milestones and tasks with their projected times of completion compared with current status/progress.

There was essentially no change and no progress in Year 2, as the study protocol remained with the Office of the Secretary of the Army, pending review and approval as a requirement of EFIC studies.

When it became clear that the SecArm review might be indefinitely delayed, alternate plans for conducting the study without EFIC were explored. However, during this period, the Data Safety and Monitoring Board of the HOPES study conducted an scheduled interim review after enrollment of 30 patients. Their finding on August 27, 2018, was a recommendation to end the trial due to futility.

As a result of this finding, conduct of the present study as described above is no longer possible. The DSMB findings were communicated to the sponsor and a stop work order was issued on September 20, 2018.

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:

- Terminate subaward contracts with UT-Houston and University of Pittsburgh
- Close the University of Cincinnati IRB study protocol. Protocols at Houston and Pittsburgh will remain open for follow-up and analysis of HOPES data that is not associated with the present award.
- Submit revised Statement of Work for alternate plan to accomplish the objectives of the study and, with approval, will initiate alternate studies

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

See above "Accomplishments towards these goals in Year 2". We are presently working with co-investigators to develop an alternate plan to address the core hypothesis that "a mechanism of therapeutic benefit of hypothermia is through suppression of spreading mass neuronal

depolarizations.” One possibility is a retrospective study of a large cohort of 138 patients who underwent spreading depolarization and temperature monitoring after surgical treatment of severe TBI. In this cohort, 2,837 spreading depolarizations were recorded in 58 patients (60%) and temperature management practices, including the use of hypothermia, varied between centers. These data could be analyzed to determine the impact of patient temperature, and temperature management practices, on the occurrence of spreading depolarizations. Another possibility is a prospective study with similar objectives.

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

See above

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

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

Nothing to report

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 site PIs and sponsor, managed relationship with HOPES study, supervised regulatory coordinator, maintained study readiness.

Name: Gigi Hergenroeder, MHA, RN

Project Role: Co-PI, HOPES

Nearest person month worked: 1

Contribution to Project: Dr. Hergenroeder has been principally responsible for coordinating and implementing DOD-requested changes to the study protocol at study sites and in preparing documentation for Secretary of the Army review. She coordinates with Dr. Hartings in preparing study procedures and implementing the study database.

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: Overall management and integration of the study within the context of the HOPES trial. Study site enrolling subjects.

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: Study site enrolling subjects.

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