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TITLE:	**Targeted Alteration of Dietary Omega-3 and Omega-6 Fatty Acids for the Treatment of Post-Traumatic Headaches**
PRINCIPAL INVESTIGATOR:	**Kimbra Kenney, M.D.**
CONTRACTING ORGANIZATION:	**The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. Bethesda, MD 20814**
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14. ABSTRACT

Post-traumatic headache (PTH) is a common problem in military personnel due to their high rate of traumatic brain injury (TBI). From a prior study in migraine we demonstrated that a high Omega-3/low Omega-6 (H3-L6) diet intervention reduced headache pain, altered circulating anti- and pro-nociceptive lipid mediators and their precursor fatty acids, reduced psychological distress and improved quality-of-life in a chronic headache population. We propose to carry out a 2-arm, parallel group, randomized, controlled 12-week dietary intervention trial to evaluate the biochemical effects and therapeutic efficacy of two dietary interventions (one high in Omega-3 and the other high in Omega-6, reflecting the usual US diet) in patients with PTH that are migrainous. We hypothesize that compared to the Control Diet (high Omega-6, low Omega-3), the H3-L6 intervention will produce significant increases in anti-nociceptive n-3 metabolites including 17-hydroxy DHA (Primary Biochemical Aim), and reductions in pro-nociceptive n-6 metabolites. Further, we hypothesize that compared to the Control Diet, the H3-L6 intervention will produce significant improvement in the Headache Impact Test-(a headache-specific quality of life measure-Primary Clinical Outcome), mean total Headache Hours per day, and mean Severe Headache Hours per day.

15. SUBJECT TERMS

Post-traumatic headache (PTH), traumatic brain injury (TBI), nociceptive neurotransmission, migraine, chronic inflammation, biomarker, Omega-3, Omega-6, Headache Impact Test (HIT), nutritional intervention

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1. INTRODUCTION:

Post-traumatic headache (PTH), a common and debilitating secondary headache disorder, is a common problem in military personnel due to their high rate of traumatic brain injury (TBI). Most PTHs have a phenotype indistinguishable from primary headache disorders and have similar responses to therapy. Recent studies indicate that migraine is the most common headache type after trauma, accounting for 50-60% of all PTH, while tension-type headaches account for less than 20%. The mechanisms of PTH are complex and incompletely understood but recent studies emphasize the role of inflammation, cytokine modulation, microglial activation, and abnormalities in neurotransmitter activity in mediating PTH. These observations provide one mechanism underlying the proposed use of dietary interventions designed to reduce chronic inflammation and promote anti-nociceptive neurotransmission, and biomarker data we will obtain will provide direct support for the role of inflammation in PTH. From a prior study in migraine we have preliminary data demonstrate that a high Omega-3/low Omega-6 (H3-L6) diet intervention reduced headache pain, altered circulating anti- and pro-nociceptive lipid mediators and their precursor fatty acids, reduced psychological distress and improved quality-of-life in a chronic headache population. These compelling preliminary data also help establish the feasibility of implementing this dietary intervention in TBI populations with chronic pain. We propose to carry out a 2-arm, parallel group, randomized, controlled 12-week dietary trial to evaluate the biochemical effects and therapeutic efficacy of two dietary interventions (one high in Omega-3 and the other reflecting the usual US diet, high in Omega-6) in patients with PTH with migrainous phenotype. We hypothesize that compared to the Control Diet (high Omega-6, low Omega-3), the H3-L6 intervention will produce significant increases in anti-nociceptive n-3 metabolites including 17-hydroxy DHA (Primary Biochemical Aim), and reductions in pro-nociceptive n-6 metabolites. Further, we hypothesize that compared to the Control Diet, the H3-L6 intervention will produce significant improvement in the Headache Impact Test—a headache-specific quality of life measure-Primary Clinical Outcome); mean total Headache Hours per day; and mean Severe Headache Hours per day.

2. KEYWORDS:

Post-traumatic headache (PTH), traumatic brain injury (TBI), nociceptive neurotransmission, migraine, chronic inflammation, biomarker, Omega-3, Omega-6, Headache Impact Test (HIT), nutritional intervention

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Task 1: Planning and Regulatory Review (Months 1-5)

Subtask 1a. Complete the detailed protocol, Standard Operating Procedures (SOP) manual, develop Case Report Forms (CRFs), create and beta test Database, create study website. Trial registration in Clinicaltrials.gov. Advertise for and hire study staff.

Subtask 1b. Obtain IRB approvals at WRNMMC, USUHS, NIH, UNC-Chapel Hill, and Womack Army Medical Center.

Subtask 1c. Training of dietitians and standardize preparation of diets.

Subtask 1d. Training of study staff at all sites.

Task 2. Start recruitment and enrollment of patients at all sites (Months 6-12)

*Subtask 2a***.** Target is that all sites will have enrolled at least 1 participant by the end of Year 1. Target is that all sites combined have enrolled at least 20 participants.

Subtask 2b. All sites will have had 1 monitoring visit to insure adherence to protocol and that all study procedures are being carried out uniformly and efficiently.

Subtask 2c. At the end of Year 1, biochemical assays on participants enrolled over the first 6 months will be performed to ensure that sample quality is excellent and that anticipated values are obtained.

Task 3. Continue patient recruitment and enrollment (Months 13-24)

Subtask 3a. Anticipate that at the end of Year 2, 70 participants will have been enrolled at the three clinical sites.

Subtask 3b. Once enrollment is active at each site, monitoring visits q 6 months to insure adherence to the protocol and that all study procedures are being carried out uniformly and efficiently.

Subtask3c. Complete biochemical assays on participants enrolled in the first half of the study. Prepare first *s*cript for publication on the association of baseline PTH characteristics with plasma levels of bioactive

Task 4. Continue patient recruitment and enrollment (Months 25-36)

Subtask 4a. Anticipate that at the end of Year 3 110 participants will have been enrolled at the three clinical sites.

Subtask 4b. Continue monitoring visits q 6 months to insure adherence to the protocol and that all study procedures are being carried out uniformly and efficiently.

Subtask 4c. Complete biochemical assays on participants enrolled in the first three years of the study. Prepare second manuscript for publication on the association of baseline post-concussive symptoms, mood, affective, and cognitive problems, and plasma levels of bioactive lipids.

Task 5. Complete all study procedures (Months 36-40)

Subtask 5a. Complete enrollment of 120 participants, including follow-up after 12 weeks of dietary intervention.

Subtask 5b. Resolve all data queries originating from data monitoring visits.

Subtask 5c. Complete biochemical assays for entire study.

Task 6. Data analysis and preparation of primary manuscripts. (Months 40-48)

Subtask 6a. Complete data cleanup and database lock.

Subtask 6b. Complete analysis of primary and secondary outcomes.

What was accomplished under these goals?

1. Received full WRNMMC parent/shell multi-site protocol approval 16 FEB 2016
2. First level IRB approval for all site-specific protocols, including WRNMMC, FBCH and WAMC and UNC as the data center was approved by the WRNMMC IRB, with modifications approved 9-23-2017.
3. Second level HRPO approval for all site-specific protocols, including WRNMMC, FBCH, WAMC and UNC approved 25 JUL 2016, 10 JAN 2016, 10 JAN 2017 and 22 DEC 2016, respectively. HRPO Second Level Approval from: Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US) Date: Jan 10, 2017 Subject: A-18878.d Approval Memorandum (Proposal Log Number PR141560, Award Number W81XWH-15-2-0059)

4. FITBIR and UDEs for study CRFs and FITBIR transfer complete.
5. A DSMC with stoppage rules established at UNC and has conducted bi-annual monitoring at each site. The monitor's reports were sent to the DSMB. No safety concerns.
6. Research personnel were hired and trained.
7. The study is enrolling at a steady pace. There was a late start due to lengthy time for IRB approvals partly due to the initiation of IRIS.
8. Registered on ClinicalTrials.org, NCT03272399.
9. Monthly conference calls continue among the 5 campuses lead by Dr. Kenney.
10. Food purchases, storage, and distribution is coordinated and running without problems.
11. Blood collection, processing, and storage is on-going per protocol.
12. Web-based randomization and data entry system (RedCap) are working well.
13. A CRADA has been completed between WRNMMC and HJF.
14. An MTA has been executed for transfer of samples from WRNMMC to NIA, NIH for planned study analysis.
15. A newly required (WRNMMC DRP) Data Sharing Agreement DHA has been signed with WRNMMC but is on hold with NIH as the two institutions determine how to proceed. No data is being entered into FITBIR as we wait to learn the outcome of the discussions.
16. The MOP is continually updated as questions arise on procedures in order to insure uniformity among the institutions. All updates are discussed with the teams and the study monitor.
17. The Continuing Review for 2018 was approved by the WRNMMC for all sites.
18. The Continuing Review for 2019 was approved by the WRNMMC for all sites.
19. Recruitment and enrollment of patients began at all enrolling sites in year 2 and continue into year 3. One hundred and thirty-two signed consents, 80 participants have been randomized, and 63 have completed the study as of Sept. 30, 2019 with 11 withdrawals after randomization, none as a result of AEs.

Enrollment by site to Sept. 1, 2019

Site	WRNMMC	WAMC	FBCH
Consented	28	59	45
Randomized	19	36	25
Withdrew	1	7	3
Completed	18	26	19

20. Monitoring of the Headache Diary and protocol adherence is done bi-weekly by dieticians and research staff who monitor on-line and by telephone with participants.
21. The DSMB reviews all available data, aggregate and differential, for safety issues between and within groups. Severity and frequency of the documented AE/UPs are being reviewed at these times. Subsequently, reports are submitted to the DSMB every 6 months to review safety and efficacy data and any other issues raised by the research team.
22. It was decided that biochemical assays on participants will be conducted at the end of the study in batch assays for economy of finances and effort. We will run batched lipid analyses of all samples when the study is completed, using LC-MS/MS because it is best to run LC-MS/MS assays in one batched analysis, since results can be affected by season, humidity, etc.
23. An NCE was approved in Sept. 2019 for 18 months to allow more time for enrollment and completion of study procedures.
24. Continue patient recruitment and enrollment.

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

The research dietician at UNC-Chapel Hill, the head dietician for the study, trains the dieticians at each of the sites. The study coordinator trained all study RAs about the protocol and procedures and the monthly conference calls have time for instruction by Dr. Kenney and the monitor about unique situations and questions about AEs and procedures.

How were the results disseminated to communities of interest?

Nothing to report. No results. Study is actively enrolling.

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

Recruit and enroll study participants and execute the protocol.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

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**

The sites have instituted broader recruitment tactics, talking with clinic physicians and disseminating new brochures approved by the IRB in order to help boost enrollment numbers. We are also waiting to hear about the data sharing agreement with NIH for the FITBIR database which is on hold at this time.

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

As noted earlier in this annual report and prior quarterly reports, there was a significant delay in IRB approvals for this study through the multi-site study IRB process since the termination of IRBNet. This delay significantly impacted launching of this study.
The DSMB and Investigators and monitor are closely keeping track of enrollment numbers.
In September 2019 the study received approval for a No Cost Extension for 18 months during which time the study anticipates completion of enrollment and all study procedures.

Changes that had a significant impact on expenditures

No Changes to Report

Significant changes in use or care of human subjects

No Changes to Report

Significant changes in use or care of vertebrate animals

No Changes to Report

Significant changes in use of biohazards and/or select agents

No Changes to Report

6. PRODUCTS:

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

  Nothing to Report

- **Journal publications.**

  Nothing to Report

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

  Nothing to Report

- **Other publications, conference papers and presentations**.

  Cora Davis - oral presentation about the study at the National Capital Area-Traumatic Brain Injury Symposium - March 26-27 and Dr. Kenney presented a poster at the MHSRS conference in Kissimmee, FL
  Aug. 19-2019. (pre-approvals from the publications dept.)

- **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:	Kimbra Kenney MD
Project Role:	Grant PI
Nearest person month worked:	1.2
Contribution to Project:	Dr. Kenney assumed role of PI and directed development and submission of protocol through the WRNMMC multi-site eIRB, IRIS
Funding Support:	HJF through 31 May 2016 and DoD civilian employee from 1 June 2016

Name:	Keturah Faurot PA, PhD
Project Role:	NIH PI
Nearest person month worked:	2
Contribution to Project:	Dr. Faurot developed and submitted UNC protocol, established study DSMB and developed CRFs for the Study; study monitor
Funding Support:	HJF

Name:	Chris Ramsden MD
Project Role:	WAMC PI
Nearest person month worked:	1
Contribution to Project:	Dr. Cole developed and submitted WAMC protocol,
Funding Support:	HJF

Name:	Melissa Guerra, MD
Project Role:	FBCH PI
Nearest person month worked:	0.5
Contribution to Project:	Dr. Guerra will lead the study at FBCH.
Funding Support:	Federal Employee

Name:	Beth MacIntosh
Project Role:	UNC AI and study dietician
Nearest person month worked:	1
Contribution to Project:	Ms. MacIntosh assisted with dietician portions of study protocols, participated in monthly conference calls, and is training study dieticians.
Funding Support:	HJF

Name:	Carol Moore MA, CCRC
Project Role:	USUHS AI
Nearest person month worked:	2
Contribution to Project:	Ms. Moore assumed primary role of protocol submission and WRNMMC IRB navigation, Quarterly and Annual reports, training for RAs, MOP.
Funding Support:	HJF

Name:	Cora Davis, BA
Project Role:	Research Associate
Nearest person month worked:	1
Contribution to Project:	Assisted Ms. Moore in protocol submission and navigation.
Funding Support:	The Center for Neuroscience and Regenerative Medicine.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Two dietitians have left and two hired to replace them, one at WRNMMC and one at FBCH.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS: See Attached

9. APPENDICES:

1. Approved Continuing Review (CR)
2. CR Approval Letter - WRNMMC, FBCH, WAMC
3. Currently Approved Protocol
4. Currently Approved Consent
5. CR Approval Letter, UNC (University of North Carolina)
6. NCA-TBI 2019 Symposium Abstract
7. NCA-TBI 2019 Symposium Oral Presentation
8. MHSRS 2019 Poster