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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

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Kimbra Kenney, M.D.

E-Mail: Kimbra.kenney@usuhs.edu

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The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.
6720-A Rockledge Drive
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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 ensure 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 ensure adherence to the protocol and that all study procedures are being carried out uniformly and efficiently.

Subtask 3c. Complete biochemical assays on participants enrolled in the first half of the study. Prepare first manuscript for publication on the association of baseline PTH characteristics with plasma levels of bioactive lipid mediators.

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 ensure 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.

Subtask 6c. Prepare manuscripts for publication for 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 DSMB 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. Modifications to the protocol allow pick up and direct shipping of food to participants due to COVID-19 pandemic.
11. Blood collection, processing, and storage is on-going per protocol. Modifications due to COVID-19, allowing alternative self-administered finger stick by participants and collection of small blood samples on a droplet card.
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. No further movement on this issue in 2020.
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, 2019, and 2020 were approved by the WRNMMC for all sites.
18. Recruitment and enrollment of patients began at all enrolling sites in year 2 and continue into year 4. One hundred and sixty participants have signed consents, 100 have been randomized, and 82 have completed the study with 17 withdrawals after randomization, none as a result of AEs. See table below:

Enrollment by site to Sept. 1, 2020:

Site	***WRNMMC***	***WAMC***	***FBCH***	***TOTAL***
Consented	***30***	***68***	***57***	***145***
Randomized	***20***	***43***	***37***	***100***
Withdrew	***1***	***12***	***4***	***17***
Completed	***19***	***30***	***33***	***82***
In baseline:*	***4***	***3***	***5***	***12***

*As of 3/16/2020 when face-to-face research restriction imposed

19. Monitoring of the Headache Diary and protocol adherence is done bi-weekly by dieticians and research staff who monitor on-line and by telephone/video conference with participants.
20. 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.
21. 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 these assays in one batched analysis, since results can be affected by season, humidity, etc.
22. An NCE was approved in Sept. 2019 for 18 months to allow more time for enrollment and completion of study procedures.
23. We are just now slowly opening up from COVID restrictions after 6 months of no enrollment from COVID-related Research Restriction of all Face-to-Face research at all e enrolling sites and halt of non-COVID related bench lab restriction at NIH. We anticipate that we will need an additional 6 months beyond the current NCE expiration of 29 March 2021 to fully enroll the study and analyze the samples. **As requested previously, we anticipate requesting an extension of our NCE in 12/2020 to extend the study to 9/30/2021 as funds remain available to continue and fully staff the study through that time.**
24. Continue patient recruitment and enrollment for full study enrollment.
25. We are preparing 3 manuscripts, one of the overall study methods, one of the dietary methods and a final one of the baseline PTH clinical characteristics.
26. Dr. Guerra, PI at FBCH, has left and Dr. Chae has taken the position of PI at FBCH.

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:

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. Since the occurrence of COVID-19, the study has instituted modified procedures during times when in-person contact is inadvisable or not allowed. The study was placed on institutional hold at the beginning of the pandemic outbreak and is becoming active again at the end of Sept. 2020 with modified procedures, respecting the safety of the patients and staff.

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. **Delay/abrupt stop required in enrollment due to COVID 19 since March until September 2020. We anticipate requesting an extension of our NCE in 12/2020 to extend the study to 9/30/2021 as funds remain available to continue and fully staff the study through that time and we estimate that we should be fully enrolled by 3/31/2021 with the last participant completing the study by June 30, 2021 and having a final quarter (7/1/2021-9/30/2021) for study close-out, final analysis and manuscript preparation and submissions.**

Changes that had a significant impact on expenditures

Nothing to Report. Study was on hold for 6 months during no in-person contact period of COVID-19. The study is starting recruiting and enrolling again but the PI is aware that the situation is fluid and the study could be shut down again if the pandemic situation worsens.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

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

Journal publications.

Nothing to Report.

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

Nothing to Report.

Other publications, conference papers and presentations.

1. Cora Davis - oral presentation about the study at the National Capital Region-Medical Quality Symposium - March 26-27, 2019.
2. 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, M.D.*
No change

Name: *Keturah Faurot PA, Ph.D.*
No change

Name: *Chris Ramsden, M.D.*
No change

Name: *Heechin Chae, M.D.*
Project Role: *FBCH PI*
Researcher Identifier: *N/A*
Nearest person month worked: *0.5*
Contribution to Project: *Dr. Chae will lead the study at FBCH.*
Funding Support: *Federal*

Name: *Beth MacIntosh*
No change

Name: *Carol Moore, MA, CCRC*
No change

Name: *Cora Davis*
No change

Name:	*Margaret Dunlap*
Project Role:	*Clinical Research Assistant*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*12*
Contribution to Project:	*Ms. Dunlap screens and identifies patients suitable for enrollment and obtains consent.*
Name:	*Wanda Rivera*
No change	
Name:	*J. Douglass Mann, M.D.*
No change	

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

PI change at FBCH. Dr. Guerra left at the end of May and Dr. Chae took over June 1, 2020 as PI.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHART: See attached.

APPENDICES: See attached.