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TITLE: Hyperbaric Oxygen Therapy in the Treatment of Chronic Mild-Moderate Blast-Induced Traumatic Brain Injury Post-Concussion Syndrome (PCS) and Post Traumatic Stress Disorder (PTSD)

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14. ABSTRACT

The purpose of the study is to see if an eight-week course of forty low-pressure HBOT's can significantly improve symptoms and cognitive function in military veterans and civilians with mild TBI/PPCS. The proposed design is a randomized controlled (non-treatment, non-sham) single-arm crossover single-blind study. The scope of the project is to recruit, enroll, test, treat, re-test and follow-up on 50 subjects at Louisiana State University, New Orleans in 23 months and another 50 subjects at Oklahoma State University in an equivalent period of time. The study received final approval from all regulatory agencies on 5/13/2014. Enrollment began shortly thereafter. By 9/30/2017 150 subjects had been screened, 59 of the allotted 69 subjects had been enrolled, 8 of these had withdrawn prior to completing the post-8-week primary outcome testing, and another 4 withdrawals who did not complete the two-month post-treatment follow-up testing, leaving a total of 51 enrolled. 38 subjects have completed the protocol, 5 were in treatment at the end of September, 1 was in the control period, and 3 are in the two-month follow-up period post-hyperbaric oxygen treatment. A total of 13 subjects were enrolled in the past year since the previous annual report. Due to expected additional dropout/withdrawals the study enrollment limit was increased again from 59 to 69 subjects on 9/12/2017, but this was proven unnecessary. Study enrollment closed on 9/29/2017. The second site for the study, Oklahoma State University Center for Health Sciences, has not participated in the study due to inability to secure funding. There are no study results to report at this time and no significant adverse advents.

15. SUBJECT TERMS

HBOT: hyperbaric oxygen therapy; TBI: traumatic brain injury; PPCS: persistent post-concussion syndrome

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I. INTRODUCTION

Mild-moderate blast-induced traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) affect 11-28% and 13-17%, respectively, of U.S. combat troops returning from Iraq and Afghanistan. Mild TBI affects another 2 million civilians in the United States and far greater numbers worldwide. Approximately 10-15% of mild TBI patients experience the persistent post-concussion syndrome (PPCS). Evidence-based medicine exists for PTSD, but there is no effective treatment for the persistent post-concussion syndrome (PPCS) of mild-moderate TBI nor the combined diagnoses of PPCS and PTSD. Between the Fall of 2008 and end of 2010, the P.I. conducted a non-controlled pilot trial of hyperbaric oxygen therapy (HBOT 1.5 atmospheres absolute/60 minutes, twice/day, 40 treatments in one month) in military veterans with both TBI/PPCS and PTSD that achieved substantial symptomatic, cognitive, and brain imaging improvements in the subjects. Preliminary results were published 11/2011 in the Journal of Neurotrauma (http://www.liebertonline.com/doi/abs/10.1089/neu.2011.1895)[1] and final results in Medical Gas Research (http://www.medgasres.com)[2]. The original purpose of the present study was to replicate the pilot trial in a randomized sham-controlled double-blind design with the sham-control group receiving slightly pressurized air at the beginning and end of each treatment. After further review of the science and discussion with the FDA the study was changed to: 1) a randomized controlled (non-treatment non-sham) single-arm crossover single-blind design, 2) include both military and civilian subjects with the single diagnosis of PPCS from either blast or blunt trauma, and 3) an eight week course of treatment, instead of four weeks.

Therefore, the purpose of the new proposed study is to see if an eight-week course of forty low-pressure HBOT's can significantly improve symptoms and cognitive function in military veterans and civilians with mild TBI/PPCS using a randomized controlled single-arm crossover design. The scope of the project is to recruit, enroll, treat, test, retest, and follow-up test 50 subjects within 23 months at LSU, New Orleans and another 50 subjects at Oklahoma State University Health Sciences Center, Tulsa, Oklahoma.

Oklahoma State University was not able to secure funding and was dropped from the study.

II. BODY

The research accomplishments associated with the tasks in the Statement of Work of 12/18/2013 are as follows:

A. Obtain TATRC IRB and scientific reviews/approvals: IRB approval was obtained from LSU School of Medicine 12/18/2013. Second level (final) ORP approval was obtained on 5/13/2014. VA IRB submission was planned after ORP approval, but abandoned due to the high probability of inestimable further delays as described in previous reports.

B. Recruit sufficient numbers of appropriate subjects to complete the study within project period: This has not occurred. Recruitment and enrollment was much slower than expected, despite continued advertisement and dissemination of information about the study, necessitating a final No Cost Extension through 3/28/2018. A variety of reasons were enumerated in past reports, but the primary reason was the unexpected dearth of referrals from local VA sources and of active duty and retired service men and women. In the past year, 13 subjects were enrolled and one of these withdrew or dropped out with no post-treatment testing. None have withdrawn for medical reasons. To achieve the sample size necessary for one of the co-primary outcome instruments an increase in the enrollment limit was sought and obtained in September, 2016 from 50 to 59 subjects and again in September, 2017 from 59 to 69 subjects. Enrollment closed on 9/29/2017.

C. Enroll, test, and treat 50 subjects within 17 months from award date: Based on the final ORP approval date of 5/13/2014 this task was not accomplished on time and necessitated two No Cost Extensions through 3/28/2018. The last subject was enrolled in September, 2017 and the study will now finish before expiration of the latest No Cost Extension. Tasks 3.a.-f. in the Statement Of Work have not changed. Each subject is adhering to this schedule. They are renumbered C.1-6 with appropriate change of dates:

1. Recruit subjects, beginning the end of May 2014. Patients in the HBOT Group will complete the protocol in 18 weeks while patients in the Control Group will complete the protocol in 27 weeks. **IN PROCESS.**

2. Obtain consent, take hyperbaric medicine history, and conduct physical exam at the hyperbaric facility (Family Physicians Center). This sub-task will be completed during the week of recruitment, most likely on the day the subject is recruited. **DONE.**

3. Perform psychometric testing and questionnaires at Neuro-psychological and Psychological Services for Children and Adults, LLC, 3925 I-10 Service Road, West, Suite 224, Metairie, LA, 70002 which is 10 miles from the hyperbaric facility. The collaborator performing this task is Dr. Susan Andrews. This task will be accomplished during the first week of recruitment, most likely on the second day. **DONE.**

4. Post-treatment physical exam conducted by the PI at the hyperbaric facility on or about the day of the 40th hyperbaric treatment**. IN PROCESS**

5. Repeat psychometric testing and questionnaire completion by Dr. Andrews the day following the 40th hyperbaric treatment. **IN PROCESS**

6. Repeat NSI and QOLIBRI eight weeks following the 40th hyperbaric treatment. **IN PROCESS.**

D. Analyze data and submit a manuscript for peer-reviewed publication within 24 months of funding and within 8 months of completion of the study: Given the timeline in C. a more accurate statement of this goal would be a publication by September, 2018.

III. KEY RESEARCH ACCOMPLISHMENTS

Enrollment of the final subject by the pre-determined deadline at the end of September, 2017

IV. REPORTABLE OUTCOMES

There are no reportable outcomes. No data has been analyzed.

V. CONCLUSION

The study is closed to enrollment. 150 subjects have been screened, 59 of the allotted 69 subjects have been enrolled, 8 of these had withdrawn prior to completing the post-8-week primary outcome testing, and another 4 withdrawals who did not complete the two-month post-treatment follow-up testing, leaving a total of 51 enrolled. 38 subjects have completed the protocol. 5 were in treatment at the end of September, 1 was in the control period, and 3 were in the two-month follow-up period post-hyperbaric oxygen treatment. A total of 13 subjects were enrolled in the past year since the previous annual report. Due to a larger number of dropouts than expected the enrollment limit was increased to meet sample size estimates from 50 to 59 subjects in September, 2016 and again in September, 2017 from 59 to 69 subjects. The final subjects will be completing treatment and testing, finishing the protocol in January, 2018. Data analysis and publication will follow. There are no study results to report at this time and no significant adverse advents.

VI. REFERENCES

1. Harch PG, Andrews SR, Fogarty EF, et al. A phase I study of low-pressure hyperbaric oxygen therapy for blast-induced post-concussion syndrome and post-traumatic stress disorder. J Neurotrauma, 2012;29(1):168-85.
2. Harch PG, Andrews SR, Fogarty EF, Lucarini J, Van Meter KW. Case control study: hyperbaric oxygen treatment of mild traumatic brain injury persistent post-concussion syndrome and post-traumatic stress disorder. Med Gas Res. 2017;7(3):156-174.

VII. APPENDICES

There are no appendices.

VIII. SUPPORTING DATA

There is no supporting data.

Hyperbaric Oxygen Therapy in the Treatment of Chronic Mild Traumatic Brain Injury Post-Concussion Syndrome
W81XWH-10-1-0962; USAMRMC

PI: Paul G. Harch, M.D. **Org:** Louisiana State University Health Sciences Ctr-New Orleans

Problem, Hypothesis and Military Relevance

- mTBI/PCS are major problems in the military, Veterans Affairs Healthcare System, and society, causing significant personal suffering, disability, and costs.
- Mild (m)TBI causes wounds in the brain, HBOT treats wounds. HBOT has duplicated human success in chronic TBI in an animal model, therefore, HBOT should help chronic mTBI/PCS in Veterans.
- Effective treatment for mTBI/PCS could have a profound impact on patients suffering from this condition.
- Hypothesis: an 8 week course of HBOT can improve symptoms and cognitive function in military veterans and civilians with mild Traumatic Brain Injury (TBI)/Post-Concussion Syndrome (PCS).

Proposed Solution

- Randomized single-blinded control-group crossover study of forty daily, 5d/week 1.5 ATA (atmospheres absolute) hyperbaric oxygen treatments vs. eight weeks of continued medication and/or counseling in adult veterans or civilians with mTBI/PCS of 6 months-15 years duration.
- Will assess symptoms, cognitive and emotional function, and quality of life in Veterans and civilians using standard accepted instruments.
- Primary outcomes: Working Memory and the Neurobehavioral Symptom Inventory.

Timeline and Total Cost (direct and indirect)

Activities FY	'12	'13	'14	'15	'16	'17	'18
Regulatory approval: FDA, TATRC, LSU, IRB							
Recruit, enroll, study 50 subjects							
Analyze data and publish							
Estimated Budget ($K)	0	23	326	392	200	125	25

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PI: Paul G. Harch, M.D. **Org:** Louisiana State University Health Sciences Ctr-New Orleans

DMRDP

Award Information

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Period of Performance: 9/30/2010-3/30/2016
Award Amount: $1,054,000
GOR: Dr. Brenda Bart-Knauer
Collaborators: None.

Problem Areas

- Failure of Oklahoma State to secure funding. Lack of participation by OSU necessitated reliance on sole recruitment at single site.
- Recruitment of subjects;
  - Continued inability to recruit from the VA and military sources.
  - Flawed DoD HBOT/TBI studies with negative conclusions likely contributing to VA/military recruitment problem and medical profession-wide mis-perception of ineffectiveness of HBOT in TBI.

Key Research Accomplishments

- Final No Cost Extension (NCE) granted through 3/28/2018 study end date.
- Oklahoma State University, Tulsa, OK, dropped as second site due to inability to secure funding.
- Have enrolled 51 subjects, 47 actively completed or completing study, 8 withdrawals/dropouts.
- No significant adverse events.

Next Steps

- Study closed to enrollment 9/29/2017
- Completion of treatment of final five study subjects.
- Final testing of subjects in January, 2018
- Data Analysis in February and March, 2018
- Publication of results by Fall, 2018.