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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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13. SUPPLEMENTARY NOTES

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 By 9/30/2016 124 subjects had been screened, 46 of the allotted 50 subjects have been enrolled, and 10 of these have withdrawn, leaving a total of 36 enrolled. 27 subjects have completed the protocol. 1 was in treatment at the end of September, 3 were in the control period, and 5 are in the two-month follow-up period post-hyperbaric oxygen treatment. 1 additional subject is scheduled to be screened in October 2016 and 3 are awaiting first appointment for enrollment. A total of 17 subjects have been enrolled in the past year since the previous annual report. Due to the dropout/withdrawals the study enrollment limit was increased from 50 to 59. At the current pace of recruitment a No Cost Extension will be necessary to complete the study. 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). 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.

To date the University of Oklahoma researchers has not been able to secure funding for their half of 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 has been much slower than expected and continues at a reduced pace despite continued advertisement and dissemination of information about the study. A variety of reasons have been enumerated in past reports, but the reality is that recruitment is at a slow steady pace. The primary reason for delayed recruitment has been the unexpected dearth of referrals from local VA sources and active duty and retired service men and women. In the past year 17 subjects have been enrolled and five of these have withdrawn or dropped out with either partial or 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. At the present pace of recruitment of 4 subjects/quarter and 1 dropout/withdrawal per 5 enrolled subjects three additional quarters will be necessary to achieve the 59 allotted subjects for the study. To meet total study enrollment a No Cost Extension will be necessary until 3/2018. The NCE application will be submitted in the next two weeks.

Co-researchers at Oklahoma State University Center for Health Sciences have been unable to secure funding for their half of the study. There are currently no prospects to secure funding in the future.

C. Enroll, test, and treat 50 subjects within 17 months from award date: Based on the final ORP approval date of 5/13/2014 and the current pace of enrollment, enrollment should be completed by the end of May/2017. Final data entry on the last enrolled subject would be early October, 2017 if the last subject was randomized to Control Group first. To do so will require a No-Cost-Extension from the current study expiration date of 3/28/2017 to 3/28/2018. 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.

2. Obtain consent, take hyperbaric medicine history, and conduct physical exam at the hyperbaric facility (Family Physicians Center) and additional study site. This subtask will be completed during the week of

recruitment, most likely on the day the subject is recruited.

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. The same task will be completed at the second study site on the same timeline.

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

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

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

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 June, 2018, assuming a No-Cost-Extension can be obtained through 3/2018.

III. KEY RESEARCH ACCOMPLISHMENTS

The key research accomplishment was the enrollment of 46 subjects by 9/30/2016 without any significant adverse events.

IV. REPORTABLE OUTCOMES

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

V. CONCLUSION

The study is actively recruiting. 124 subjects have been screened, 46 of the allotted 50 subjects have been enrolled, and 10 of these have withdrawn, leaving a total of 36 enrolled. 27 subjects have completed the protocol. 1 was in treatment at the end of September, 3 were in the control period, and 5 are in the two-month follow-up period post-hyperbaric oxygen treatment. One additional subject is scheduled to be screened in October 2016 and 3 are awaiting first appointment for enrollment. A total of 17 subjects have been enrolled in the past year since the previous annual report. Due to 10/46 total dropouts/withdrawals before final testing the limit of enrolled subjects necessary to meet sample size goals was increased from 50 to 59 subjects in September, 2016. At the pace of

4 enrolled subjects/quarter and a dropout/withdrawal rate of 1/5 subjects enrolled the study will enroll it's final subject by May, 2017, at the latest, necessitating a No Cost Extension through 3/2018. An NCE application will be submitted in the next two weeks.

VI. REFERENCES

There are no references.

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

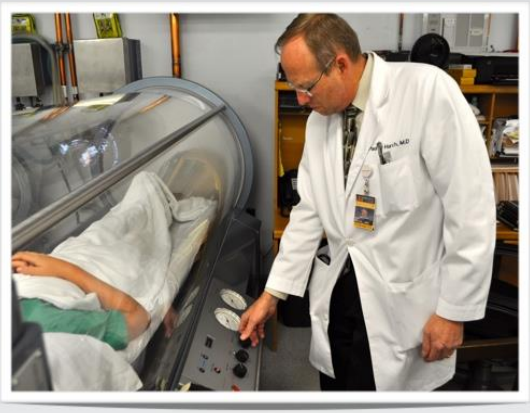
W81XWH-10-1-0962; USAMRMC

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

DMRDP

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	150	

Hyperbaric Oxygen Therapy in the Treatment of Chronic Mild Traumatic Brain Injury Post-Concussion Syndrome.
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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 necessitates 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

- No cost extension obtained through 3/2017. Additional NCE application 10/2016 for 3/2018 study end date.
- No funding source identified for second study site at Oklahoma State University, Tulsa. Pre-application submitted, not invited for full application. No source of funding in sight.
- Have enrolled 46 subjects, 36 actively completed or completing study, 10 withdrawals/dropouts.
- No significant adverse events.

Next Steps

- Continued aggressive marketing and recruiting.
- Continued attempts to reach the veteran population through the VA and military.
- NCE application for study extension through 3/2018 to accommodate recruitment rates of 4 subjects/quarter.