Progress of the Brain Injury and Mechanisms of Action of Hyperbaric Oxygen (HBO_2) for Persistent Post-Concussive Symptoms after Mild Traumatic Brain Injury (BIMA) Study

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The EMMES Corporation

LOGO

Abstract

INTRODUCTION/BACKGROUND: The BIMA study, sponsored by the Department of Defense (DoD), presents a unique opportunity to gain information about hyperbaric oxygen (HBO2) mechanisms of action. A randomized, double-blind, sham-controlled clinical trial, BIMA is differentiated from recently published DoD-sponsored HBO2 studies because of its longer duration of follow-up (12 months) and its ambitious assessment battery allowing for investigation of symptomatic as well as functional responses to HBO2.
MATERIALS/METHODS: BIMA initiated September 2012 and will complete enrollment May 2014. Randomized Active Duty military personnel and Veterans receive HBO2 at 1.5 ATA or sham chamber sessions at 1.2 ATA, air, for 60 minutes daily for 40 sessions. Outcome measures include neuropsychological, neuroimaging (MRI, fMRI, MR Spectroscopy, DTI; CT perfusion), neurological, vestibular, autonomic function, EEG, and visual systems domains (e.g. static/dynamic visual acuity, eyetracking, fundus photography) evaluated at baseline, 13 weeks, and 6 months with only computerized self-report questionnaires performed at 12 months.
RESULTS: As of March 06, 2014 147 participants have been enrolled and 56 (target = 72) randomized. Characteristics include: Median age 32 years (range 21 - 49), 98% male, 84% Caucasian, 45% diagnosed PTSD, 29% with most recent qualifying injury 3 months to 1 year prior to enrollment, 79% >1 blast injury, and 71% with multiple injuries. Forty have completed chamber sessions and the first follow-up visit at 13 weeks, 24 have completed the 6-month follow-up visit, and 10 have completed the final 12-month follow-up visit. Of those who have completed chamber sessions, 83% (33/40) have completed 40 chamber sessions and 95% have completed >20. Adherence to follow-up visits is high with 97% completing all expected visits.
SUMMARY/CONCLUSIONS: BIMA will provide detailed characterization of potential outcome measures for persistent post concussive symptoms following mTBI. Independent of a therapeutic role of HBO2, the information from BIMA will aid understanding of mTBI.

Introduction

- Traumatic brain injury (TBI) referred to as "signature injury" of war on terrorism
- US Army Medical Research and Materiel Command (USAMRMC) holds FDA-IND, planned multi-year research effort to study HBO_2 on mild TBI (mTBI)
- Objectives of ongoing BIMA trial to select endpoints for potential Phase III efficacy trial, describe brain function and anatomy of military mTBI across time and between intervention groups

Study Design

- Double-blind, sham-controlled RCT
  - Sham (1.2 ata air) v. HBO_2 (1.5 ata O2) x 60 mins, 5 days/week to 40 sessions
- N=72, Active Duty and Veterans with mTBI
- Visit schedule: Baseline, 3 months, 6 months; self-report outcomes at 12 months
- Sites: Outcomes Assessment Center, Colorado; Ft. Carson, Colorado; Joint Base Lewis McChord, Washington; Camp Lejeune, North Carolina
- Study Timeline: 2012-2015, enrollment complete May 2014

Department of Defense Study Comparison

	Air Force[1]	Navy-VA-VCU[2]	HOPPS[3]	BIMA	NORMATIVE
Timeframe	2009-2011	2011-2013	2011-2012	2012 - Present	2013 - Present
Design	Prospective, Double Blinded, Sham-Controlled	Prospective, Double Blinded, Sham-Controlled	Prospective, Double Blinded, Sham-Controlled	Prospective, Double Blinded, Sham-Controlled	Prospective
N	50	60	72	72	75
Intervention	1.3 ata room air; 2.4 ata 100% O_2 x 90 mins/30 sessions	2.0 ata 10.5% O_2; 2.0 ata 75% O_2; 2.0 ata 100% O_2; x 40 sessions	Control; 1.2 ata room air; 1.5 ata 100% O_2 x 60 mins/40 sessions	1.2 ata room air 1.5 ata 100% O_2 x 60 mins/40 sessions	N/A
Outcomes	Symptom inventory, Neuropsych battery, ANAM, ImPACT, TOVA	Symptom inventory, Neuropsych battery, CDP, Eye Tracking	Symptom inventory, Neuropsych battery,	Symptom inventory, Neuropsych battery, see table above	Same as BIMA
Visit Schedule	Pre-trial, Post-intervention Post-intervention	Pre-trial, Post-intervention, 3-months	Pre-trial, Post-intervention,	Pre-trial, Post-intervention, 6-months, 12-months	Same as BIMA
Results	No diff between intervention and sham group*	No diff among intervention and sham groups*	No diff between intervention and sham groups*	TBD	N/A

*Chamber intervention seemed associated with improved outcomes

Outcome Assessments

Neuropsychological	Neurobehavioral Symptom Inventory (NSI), Rivermead Post Concussive Symptoms Questionnaire (RPQ), PTSD Checklist Civilian (PCL-C), Automated Neuropsychological Assessment Metrics (ANAM), World Health Organization Quality of Life (WHOQOL-BREF)
Neurological Function	Neurological Exam, EEG, qEEG, Dynamometer, Sharpened Romberg Test, Romberg Test, Berg Balance Scale
Audiology and Vestibular	Peripheral and Central Auditory Examination, Videonystagmography, Computerized Dynamic Posturography, Dynamic Visual Acuity, Rotational Vestibular Test, Dynavision
Visual Systems	Visual Acuity, Dynamic Visual Acuity, Refractive Error, Oculomotor Exam, Retinal Fundoscopy, Eye Tracking
Autonomic Function	24 Hour Holter Monitor
Lab	CBC, HbA1c, COHb, Creatinine, Pregnancy, Stem Cells, Neuro-endocrine, Banked DNA, RNA, Serum, Plasma
Sleep	Actigraph, Pittsburgh Sleep Quality Index
Neuroimaging	MRI, fMRI, CT Perfusion Angiography, ASL, Detailed Volumetric Anatomical Imaging, DTI, MR Spec

HBO_2 Chambers

HBO_2 Chamber Trailer Site

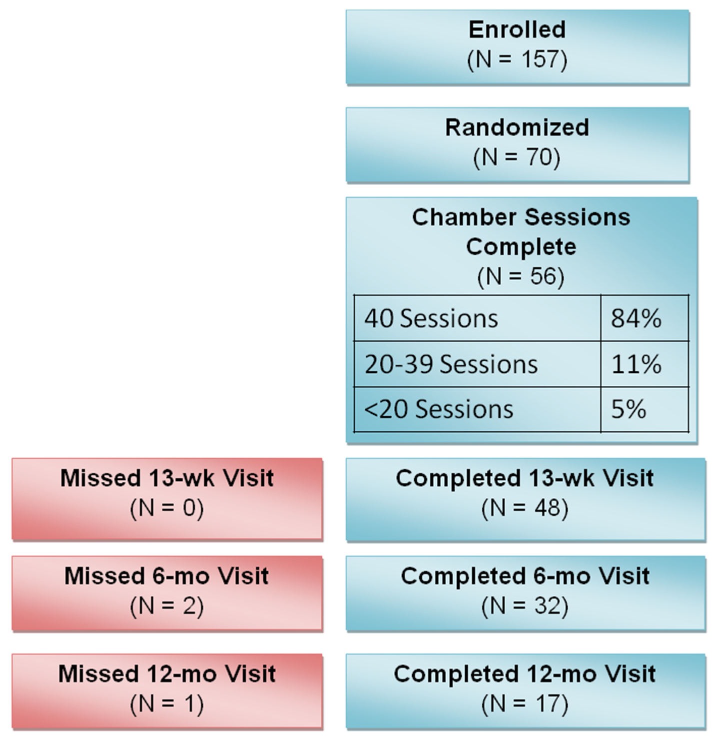
Inside HBO_2 Chamber

Recruitment and Study Progress

Pre-Screen Failure Reason (N = 135)	N (%)
Second Party Inquiry	11 (8)
Outside Recruitment Area	9 (7)
No Interest	31 (23)
Drug Screen Fail	4 (3)
Claustrophobia	2 (1)
TBI Not on Active Duty	2 (1)
Non-Eligible Brain Injury	59 (44)
Other	17 (13)

Randomized Ppt Recruitment Sources (N = 70)	N (%)
Physician / Health Care Provider / Clinic	31 (44)
Flyer / Poster / Brochure	12 (17)
E-mail	9 (13)
Other/Unknown	6 (9)
Case Manager	3 (4)
Family / Friend / Co-worker / Word of Mouth	3 (4)
Study Staff	3 (4)
Town Hall Meeting	1 (1)
Medic from Unit	1 (1)
Media	1 (1)

Enrollment Diagram



Inclusion/Exclusion Criteria

- Active Duty or Veteran, ages 18-65, with history of one or more mTBIs
  - mTBI occurred on active duty, caused by non-penetrating trauma or blast
  - mTBI resulted in loss of consciousness (up to 30 mins); loss of memory; or alteration in mental state
  - Post-concussive symptoms 3 months to 5 years after last injury
- No contraindications to hyperbaric pressurization and oxygenation
- No characteristics that may confound outcome measures

Baseline Characteristics

BIMA Randomized Participants (N = 70)		N (%)
Site	Evans Army Community Hospital	33 (47)
	Madigan Army Medical Center	24 (34)
	Naval Hospital Camp Lejeune	13 (19)
Age	21-30	29 (41)
	31-40	30 (43)
	Over 40	11 (16)
Gender	Male	69 (99)
Race	White or Caucasian	58 (83)
Education Status	Some college or more	57 (81)

BIMA Randomized Participants (N = 70)		N %
PTSD Diagnosis	PTSD	35 (50)
Time Since Injury	Less than 1 Year	17 (24)
Type of Injury	Blast Injuries Only	23 (33)
Number of Injuries	More than 1 Injury	51 (73)
Combat experience	Yes	63 (90)
Years in Military	5 or more	54 (77)

Self-Reported Medical History

All (n = 70) randomized participants reported neurologic conditions

Chronic Pain	86%
Migraines	63%
Motor Weakness	46%

Nearly all (99%, n = 69) randomized participants reported psychiatric conditions

Sleep Problems	97%
Anxiety	71%
Depression	51%

Medications and Therapies

All participants reported medications (Avg meds = 8, SD=5; Range = 1-21)

Antidepressants	xx%
Sedatives	xx%
Narcotics	xx%
Antimigraine Medications	xx%

62 participants reported therapies (Avg therapies = 2, SD=1; Range 1-7)

Counseling	37%
Physical Therapy	36%
Psychotherapy	26%
Occupational Therapy	21%
Behavioral Therapy	9%
Occupational Therapy	7%
Cognitive Rehabilitation	4%
Speech Therapy	4%

Discussion

- Excellent adherence to intervention and study visit schedule
- Less than 5% completed fewer than 20 sessions or missed a 6-month visit
- Ambitious assessment battery
- Potential to gain information about relationship between functional and symptomatic outcomes in mTBI population
- Study results will provide evidence for or against a Phase III trial

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