TITLE: Hyperbaric Oxygen for Blast-Related Post-Concussion Syndrome: 3-month outcomes

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ABSTRACT

Importance: Mild traumatic brain injury (mTBI) and post-concussion syndrome (PCS) are common among military combatants. Hyperbaric oxygen (HBO_2) is a proposed treatment for these conditions but it has not been rigorously studied.

Objectives: Determine the effects by 3-months post-intervention of HBO_2 at two commonly employed dosing levels to treat PCS. Also determine if specific subgroups may have benefited and if no overall effect is found if benefit is masked by other conditions.

Design: Randomized, double-blind, sham controlled study.

Setting : Naval Air Station, Pensacola, Florida.

Participants: 61 male Marines with history of mTBI and PCS.

Intervention: Forty, once daily, 60 minute, hyperbaric chamber compressions at 2.0 atmospheres absolute (ATA) at one of three randomly pre-assigned oxygen fractions, resulting in respective blinded groups with an oxygen breathing exposure equivalent to 1) surface air (sham), 2) 100% oxygen at 1.5 ATA, or 3) 100% oxygen at 2.0 ATA.

Main Outcome Measure: Rivermead Post-Concussion Questionnaire (RPQ-16) collected pre-compressions and at two later points.

Results: Interaction of time by intervention group was not significant for improvement on the RPQ-16. Nor was there evidence of efficacy on the RPQ-16 for any subgroup. No significant time by intervention interaction was found for any functional, cognitive, or psychomotor secondary outcome measure at an unadjusted 0.05 significance level.

Conclusions: Using a randomized control trial design and analysis including a sham, results show no evidence of efficacy by 3 months intervention to treat the symptom, cognitive, or behavioral sequelae of PCS after combat-related mTBI.

Trial Registry: ClinicalTrials.gov Identifier: NCT01220713

INTRODUCTION

The U.S. has reported nearly 250,000 deployment-related mild traumatic brain injuries (mTBI) in the Global War on Terrorism (GWOT)[1]. Many of these individuals have chronic symptoms consistent with post-concussion syndrome (PCS). Irritability, sleep disturbance, forgetfulness, anxiety, headaches, poor concentration, and other symptoms are reported years after mTBI among GWOT Veterans.[2-6] Blast-induced mTBI has been especially common and may further alter risk of PCS and distribution of individual symptoms,[6-9] particularly when repetitive.[2,10] Co-morbidities often complicate PCS as well,[6,11,12]; most GWOT Veterans with mTBI have chronic pain, post-traumatic stress disorder (PTSD), depression, and/or other mental health conditions,[13] possibly explaining the higher rate of PCS in military personnel.[13,14]

Mild TBI sequelae extend beyond symptom distress. Neurocognitive impairment, pervasive after moderate or severe TBI,[15-18] can persist after mTBI.[19-21,22] Balance deficits are common after mTBI in both civilian and military samples.[23,24 24,25,26,27,] Fine motor speed and dexterity impairment is also common after TBI and its assessment is recommended by the National Institute of Neurologic Disorders and Stroke (NINDS).[28]

The large number of Veterans and servicemembers (SMs) suffering from PCS has led to standardized programs of mTBI evaluation and treatment in respective health care systems. But standard treatment remains a symptom-based approach, since there are no proven medications or other interventions to treat the underlying brain injury. One proposed but unproven intervention is hyperbaric oxygen (HBO_2), the breathing of high levels of oxygen at an increased pressure at least 1.4 times greater than the atmospheric absolute pressure at sea level.[29] Proposed mechanisms of action include; a return to near normal function of neurons, adjacent to damaged or dead neurons, exposed to hyper-oxygenated

blood, reactivated along metabolic or electrical pathways,[30] stem cell mobilization to sites of injury, immune modulation, and impact on fundamental neurotransmitters.[31]

Departments of Defense (DoD) and Veterans Affairs (VA) have developed a clinical research initiative assessing the utility and efficacy of HBO_2.[32]Including this three-arm, randomized, double-blinded, sham-controlled trial of SMs with mTBI and PCS compared the effects of two hyperbaric oxygen breathing dosing regimens. Analyses of 1-week post-compression regimen in this trial revealed no efficacy for the primary outcome measure, PCS symptoms as measured by the Rivermead Post-Concussion Questionnaire (RPQ-16)[33] or on cognitive/psychomotor performance[34]. The current analyses examined for potential delayed or progressive response to HBO_2 at 3 months, whether participant attributes masked efficacy, and whether efficacy was specific to sub-group(s). Repeated measures statistical model, including multiple explanatory variables, was used to analyze PCS symptoms and secondary outcomes. We hypothesized that HBO_2 would lead to improvements in symptoms, function, and cognition/psychomotor performance over time. We further hypothesized that efficacy was specific for or masked by select participant attributes, such as PTSD status or age.

MATERIALS AND METHODS

Defense Advanced Research Projects Agency and U.S. Navy Bureau of Medicine and Surgery (BUMED) sponsored this single center, randomized, three-arm sham-controlled, double-blinded trial of HBO_2 exposure for PCS after mTBI. This study received all institutional review board and governmental approvals. Sample size estimates were calculated using a 10% difference for the primary outcome, which has been reported to be a clinically meaningful improvement.[35] Inclusion criteria included diagnosis of mTBI occurring within the last 3 months to 3 years,[36] diagnosis of PCS, two months stable psychiatric status, one month, stable psychotropic medication history and ability to

undergo testing. The diagnoses of mTBI and PCS were confirmed through interview, physical examination, and review of medical records. Exclusions included previous exposure to or contraindications to hyperbaric exposure (such as "air trapping" pulmonary conditions). Recruitment was primarily from Marine Corps Base Camp Lejeune, North Carolina. Recruitment involved standard techniques, including open, in-person information sessions to medical personnel on the project, medical clinic flyers posted for both medical personnel and potential subjects, medical clinic brochures displayed for both medical personnel and potential subjects, and direct calls to base command and medical leadership requesting identification and access to all potentially eligible subjects.

Using computer-generated random numbers, participants were block randomized to one of three conditions in the hyperbaric chamber (40 total exposures). To ensure subject and investigator blinding to specific treatment exposures, subjects were pressurized inside the chamber to 2.0 ATA. Subjects breathed an oxygen-nitrogen gas blended to achieve the oxygen pressure equivalents to which they were assigned. Three gas mixtures were employed: 1) sham air equivalent of 10.5% oxygen (balance 89.5% nitrogen), 2) 1.5 ATA oxygen equivalent of 75% oxygen (balance 25% nitrogen) and 3) 2.0 ATA oxygen equivalent of pure oxygen (0% nitrogen); referred to as "sham air," "1.5 ATA O2," and "2.0 ATA O2"). Once at 2.0 ATA of pressure, each subject breathed assigned gas mixture for 60 minutes. Exposures were delivered using modifications of established protocols in the U.S. Navy Diving Manual and through consultation with Navy Bureau of Medicine and Surgery, Undersea Medicine and Radiation Health.[31,37] Intervention dosing used in this study was chosen based on consensus opinion of the DoD and VA.[32] Further details on methods of HBO_2 delivery, sham delivery, blinding, and exposures are reported elsewhere[33].

Outcome measures:

Outcome measures were collected pre-exposure (Pre), within the first week following last exposure (Post-1), and at three months following the last exposure (Post-2). Administration time for the battery of self-report and cognitive and psychomotor testing was approximately five hours. RPQ-16 is a widely-used Likert-type symptom inventory of 16 items evaluating somatic, cognitive and emotional symptoms.[35] RPQ-16 is a NINDS recommended outcome measure for mTBI and is analyzed using total score (range 0-84), with higher values indicative of more severe symptoms. Two sub-scales are described, with items 1-3 constituting the RPQ-3 and remaining 13 items constituting the RPQ-13.[35]

Multiple, pre-specified, secondary outcomes were obtained measuring participants' neuropsychological, psychomotor, functional, and behavioral health. Cognitive performance measures were chosen for high sensitivity to attention, memory, processing speed deficits, and efficiency of administration. Selected tests were: Conners's Continuous Performance Test-II (CCPT-II)[38], Paced Auditory Serial Addition Test (PASAT)[39], Halsted-Reitan Trail Making Test A & B (TMT)[40], Stroop Color-Word interference test[41], California Verbal Learning Test-II (CVLT-II)[42], Wechsler Adult Intelligence Scale III (WAIS-III) select items[43], Delis-Kaplan Executive Function Systems (DKEFS) version of the Controlled Oral Word Association Test (COWAT)[44], and Benton Visual Memory Test-Revised (BVMT-R)[45]. All selected tests are recommended by NINDS TBI Comprehensive Evaluation Common Data Elements (CDEs). Psychometric properties are available on the NINDS website.[28] Given the expansive neuropsychological subtest results, we pre-specified a leading outcome for each cognitive domain of interest: verbal fluency (COWAT Letter Fluency); executive function (Trails B); working memory (WAIS III Working Memory Index[46]); visual attention (Stroop Color-Word Interference); sustained visual attention (CCPT-II Detectability Index); auditory attention (PASAT 2.0 pacing); delayed verbal memory (CVLT Delayed Free Recall[47]); and delayed visual memory (BVMT-R Delayed

Free Recall). Except for WAIS and CCPT-II index scores, neuropsychological test raw scores were analyzed.

Fine motor speed/dexterity aspect of psychomotor performance was measured using the Grooved Pegboard test [48]. Balance was measured using computerized posturography on dual-plate force platform, the NeuroCom Smart Balance Master® (NeuroCom; NeuroCom International, Inc, Clackamas, OR), via the composite equilibrium score on the Sensory Organization Test (SOT)[49], a weighted average of equilibrium scores across 6 sensory conditions and index of overall performance.

Behavioral well-being was assessed with RPQ-16 subscales, RPQ-3 and RPQ-13, and the Center for Epidemiological Studies Depression Scale (CES-D)[50]. Functional status was measured across three domains using TBI outcome measures: global outcome using the Glasgow Outcome Scale Extended (GOSE) [51], life activities participation using the Mayo Portland Adaptability Inventory-4 (MPAI-4) Participation Index[52], and life satisfaction using the Satisfaction With Life Scale (SWLS)[53].

Explanatory variables:

Select explanatory covariates previously shown or theorized to influence mTBI outcome were included in the analysis. Dichotomous variables were: self-reported, past mTBIs before deployment (Yes, No); number of military blast exposures as Low (<4) versus High (≥4); time since worst blast exposure as Recent (≤6mos) versus Old (>6mos); loss of consciousness (LOC) and/or post-traumatic amnesia (PTA) after the subject's worst mTBI (Yes, No); post-traumatic stress disorder (PTSD) at baseline using the traditional PTSD Check-List[54,55] (PCL) cutoff of 50 or above (Yes, No)[56]; feigned or invalid effort testing on the Test of Memory Malingering (TOMM) at any data collection point using traditional criteria (Pass, Fail);[57] and alcohol misuse via the Alcohol Use Disorders Identification Test[58] (AUDIT-C) as At-Risk (≥4) versus Not At-Risk (<4)[58]. Scale explanatory variables included: age in years; bodily pain on the Short Form McGill Pain Questionnaire (SF-MPQ), a validated self-rating of

sensory and affective pain descriptors;[59] and estimated premorbid intellectual functioning, assessed using the Wechsler Test of Adult Reading (WTAR)[60,61].

Statistical Methods:

After performing descriptive statistics, a repeated measures mixed-effect model was used to determine efficacy for the primary outcome; whether RPQ-16 scores differed between intervention groups (sham air, 1.5 ATA O2, 2.0 ATA O2) across time points (Pre, Post-1, Post-2). This model included all of the explanatory variables listed, as well as time (Pre, Post-1, Post-2), intervention group (sham air, 1.5 ATA O2, 2.0 ATA O2), and the interaction between time and intervention group. Evidence of intervention efficacy was determined if the parameters corresponding to the interaction term were non-zero at the 0.05 level. This model is adjusted for following subjects longitudinally, through an unstructured covariance structure and a random effect accounting for the cohort.

Several secondary analyses were conducted with similar models. Like the primary analysis, evidence of efficacy was defined as a significant interaction between time and treatment group. Lastly, to assess if the active intervention was superior to sham for a specific subgroup (i.e. participants with or without PTSD) with regard to the primary outcome, a model was fit with time, intervention group, and each covariate, along with all two-way and the three-way interactions. All secondary effects were also evaluated at the 0.05 level. SAS v9.3 was used for all statistical analyses.

RESULTS

Participant Characteristics:

The consort flow diagram is shown in Figure 1. Primary reasons for exclusion were non-confirmation of mTBI diagnosis, active medication changes, and/or schedule conflicts. One of the consenting but ineligible (moderate severity TBI) SMs requested and was permitted to enter the trial, but

was excluded from analysis. The 61 final, fully-eligible participants were distributed among intervention arms as follows: 21 in sham air, 21 in 1.5 ATA O2, and 19 in 2.0 ATA O2.

*****Insert Figure 1 about here*****

All participants within the final sample were male with mean age 23.3 years (SD=3.24). Twenty (33%) were married, 3 (5%) were divorced, and 38 (62%) were single. All were Marines and 97% had E1-E6 pay grades. ANOVA and chi square analysis revealed no between group differences with respect to age, pay grade, or marital status. All deployment-related mTBIs were caused by blast (for those with >1 mTBI, blast caused the worst); 85% from improvised explosive device (IED), 3.0% from rocket propelled grenade, 1.7% from mortar attack, and 10% not categorizable. Baseline assessments occurred a mean of 8.5 months (SD= 6.6 months, range= 3-39 months) after most recent deployment-related mTBI.

As previously reported, symptom severity on the RPQ-16 was high at baseline[33] and none of the outcome measures' distributions at baseline differed between intervention groups[33,34]. The distribution of explanatory variables by group at baseline is shown in Table 1; no between groups differences were found (Chi-square for categorical, ANOVA for scale, all $P>0.05$).

*****Insert Table 1 about here*****

Main Analysis for Primary Outcome (RPQ-16)

Main effects of each RPQ-16 explanatory variable are shown in Table 2. Significant main effects were found for PTA, PTSD, and pain levels (McGill). Not considering secondary interactions with other

explanatory variables, such as intervention group or time point effects, subjects whose worst mTBI resulted in PTA (or LOC) had higher RPQ-16 scores versus those without (*d*=6.61, SE=3.00, 95% CI: 0.57, 12.64). Similarly, those with PTSD at baseline had higher RPQ-16 scores (*d*=6.06, SE=2.24, 95% CI: 1.55, 10.56) than those without. Participants with higher pain levels had worse RPQ-16 scores with mean RPQ-16 increasing by 0.58 (SE=0.10, 95% CI: 0.38, 0.78) per unit increase on the McGill. No other explanatory variables were significantly related to RPQ-16 scores.

*****Insert Table 2 about here*****

The statistical test for efficacy, measuring any interaction between intervention group (sham air, 1.5 ATA O2, 2.0 ATA O2) difference on RPQ-16 score across any time points (Pre, Post-1, Post-2), was not significant (F(4, 63.7)=1.0, *P*=0.410). Intervention group RPQ-16 by time is plotted in Figure 2.

*****Insert Figure 2 about here*****

Secondary Outcomes Analyses

Results of statistical test of efficacy for each secondary outcome, the respective mixed model treatment group by time interaction, are shown in Table 3. No secondary outcomes showed a significant difference over time between the three intervention groups. (all $P > 0.05$).

*****Insert Table 3 about here*****

Although not relevant to assessing intervention efficacy, some secondary outcome analyses did show significant effect(s) with one or more explanatory variables similar to the primary outcome. The following secondary measures demonstrated statistically significant changes irrespective of treatment. Improvements were shown on Trails B (at 12 weeks), CVLT (at 2 weeks), PASAT (at 2 and 12 weeks), BVMT (at 12 weeks) and COWAT (at 2 and 12 weeks), whereas WAIS-III working memory worsened (at 2 weeks). No significant changes were noted on any of the other secondary outcome measures. Complete results of the effects are shown in the Appendix.

Subgroup Analyses for the Primary Outcome:

A model was fit with time, intervention, and each explanatory variable, along with all two-way and the selected three-way interactions to test for any intervention effect within specific participant groups (i.e. PTSD positive and negative groups) with respect to RPQ-16. None of three-way interactions were significant at the 0.05 level (Table 4). Thus, there was no evidence of efficacy on the primary outcome for any of the subgroups examined.

*****Insert Table 4 about here*****

DISCUSSION

This collaborative randomized, double-blinded, sham-controlled trial studying the effects of HBO_2 on PCS after mTBI shows non-efficacy for either 1.5 ATA or 2.0 ATA equivalent oxygen breathing exposures on PCS symptom severity by three months post-compression. We also found no evidence that efficacy was masked by any of the explanatory variables and no evidence of efficacy

within any of the sub-groups we defined. We likewise found no evidence of treatment efficacy for any of the secondary outcomes. This is despite comprehensive testing with measures known to be sensitive to the subtle impairments that are typical of mild TBI and PCS, such as indices of complex attentional control[62,63], delayed recognition memory[47,64], memory proactive interfence,[63] and computerized posturography, and despite running all 16 secondary outcome models at an unadjusted alpha=0.05 level, which increased the odds of spurious findings from Type 1 error.

Analyses showed several significant explanatory variable main effects for both the primary RPQ-16 outcome and the secondary outcomes. Not considering treatment group or time point, RPQ scores were higher for participants with PTA after their worst mTBI, active PTSD, or greater pain levels. For secondary outcomes, the scattered significant main effects findings included: 1) poorer life activities participation for those with greater levels of pain and greater time elapsed from injury date, 2) poorer balance for those with LOC (worst mTBI) and those with lower WTAR, 3) better working memory for those with higher WTAR, and 4) poorer delayed visual memory for those with PTSD. Secondary outcomes analyses showed significant interactions for the main effect of time. For the entire cohort, there was improvement over time for working memory, executive function, delayed verbal memory, delayed visual memory, and verbal fluency. But improvement over time was not accompanied by a significant intervention group by time interaction for any measure and therefore cannot be attributed to HBO_2 exposure. The lack of converging temporal improvement on any of the numerous symptom or functional measures suggest that these findings may be better explained by practice effects or other explanations, such as natural recovery, placebo effect or the non-specific effects of attention and care in the context of study participation. This would also support the notion that the subjects were interested in finding ways to improve their difficulties, and thus not a population that was biased against a positive outcome.

This investigation was part of a series of federally-funded, coordinated research trials to assess the efficacy of HBO_2 for persistent symptoms after mTBI, so that the VA and/or DoD could implement treatment programs based on scientific rigor.[32] The VA and DoD medical heath systems have been established to rapidly and systematically implement any and all scientifically valid and clinically useful modalities to attenuate the sequelae of combat A study strength is the incorporation of features lacking in prior studies outside of the DoD's current coordinated program[32], including randomization, blinding, control groups, and multiple HBO_2 dose levels to assess dose-response effects. A carefully-designed sham control, with all participants receiving the same compression intensity, was employed to ensure effective blinding. By adjusting the oxygen/nitrogen ratio, three well-disguised groups were achieved, equivalent to 1) breathing surface air (sham), 2) 100% oxygen at 1.5 ATA, or 3) 100% oxygen at 2.0 ATA. An additional strength is the use of a mixed-effect model to confer extra statistical control over potential interactions between participant characteristics and outcomes. Use of this design allowed assurance against efficacy being masked by one or multiple known influencers of mTBI outcome. This provided a platform to explore for subgroup efficacy, however none was found for the primary outcome.

The multitude and breadth of analyses of secondary outcomes and covariates in this study could be considered a weakness due to our analysis of multiple (16) outcomes without adjusting alpha levels. This approach was taken due to the pilot nature of the study, but it weakens confidence where differences were found. The significant covariant and secondary outcome main interactions noted are subject to increased threat of Type 1 error. These findings should be considered preliminary and needing further empirical confirmation. Despite this, there was one set of results whose recurring pattern made Type 1 error unlikely: the improvement over time in multiple cognitive performance measures irrespective of treatment group. This pattern is consistent with findings in a separate small (n=16) uncontrolled trial of HBO_2 for PCS, which Harch[65] reported improvement in full-scale IQ, Weschler

Memory Scale (WMS) IV Delayed Memory, WMS-IV Working Memory, Stroop Test, Test of Variables of Attention (TOVA) Impulsivity, TOVA Variability, and Grooved Pegboard one week after 1.5 ATA HBO_2. Harch's lack of a sham control restricted analyses to within group differences only; so as with the current study, these findings cannot be interpreted as evidence of intervention efficacy. Furthermore, even in a published trial without sham control, Churchill failed to find any efficacy from HBO_2 in individuals with brain injury.[66]

This study had several other inherent limitations. Sample was exclusively male; so findings may not generalize to females. Small sample size limits the power of the study. Due to high number of outcomes, there also were some randomly missing data points, including three missed follow-up evaluations. The mixed-effect model allowed us to incorporate subjects that did not complete a given measurement point and include all subjects in all statistical tests. Secondary gain was not directly measured, but could have introduced participant selection bias since study participation was associated with extended time away from military assignment.

In conclusion, this study found no beneficial effect of HBO_2 exposure 3 months post-compression for symptoms, functional status, or cognitive or psychomotor performance at either 1.5 or 2.0 ATA equivalent oxygen breathing compared to sham intervention. Within group changes were noted for the entire sample in both primary and secondary (neuropsychological testing) measures, and interactions were noted between primary and secondary measures and within secondary measures, however none of these were noted to be related to HBO_2.These results parallel those of Wolf[31] and do not support the use of HBO_2 to treat PCS after combat related mTBI even at typical treatment pressures advocated by hyperbaric clinicians for mTBI.[65,67]

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Dr. Walker and Dr. Cifu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Graham was responsible for the data analysis.

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Conflict of Interests:

None of the authors report any conflict of interest.

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Table 1: Explanatory variable distribution by intervention group

Variable	Level	Sham	1.5 ATA O2	2.0 ATA O2	*P*
Blast Exposure	High (≥ 4)	8 (38%)	8 (38%)	6 (32%)	0.887
	Low (< 4)	13 (62%)	13 (62%)	13 (68%)	
LOC	Yes	8 (38%)	12 (57%)	6 (32%)	0.231
	No	13 (62%)	9 (43%)	13 (68%)	
PTA	Yes	13 (62%)	15 (71%)	8 (42%)	0.161
	No	8 (38%)	6 (29%)	11 (58%)	
PTSD	Yes (PCL ≥ 50)	6 (29%)	6 (29%)	10 (53%)	0.359
	No (PCL < 50)	15 (71%)	15 (71%)	9 (47%)	
TOMM	Pass	19 (90%)	18 (86%)	14 (74%)	0.340
	Fail	2 (10%)	3 (14%)	5 (26%)	
Time Elapsed	≤ 6 mos	11 (52%)	9 (43%)	11 (58%)	0.627
	> 6mos	10 (48%)	12 (57%)	8 (42%)	
Drinking Status	High Risk	11 (52%)	11 (52%)	11 (58%)	0.923
	Low Risk	10 (36%)	10 (48%)	8 (42%)	
Previous Head Injury	Yes	3 (15%)	6 (32%)	7 (33%)	0.349
	No	17 (85%)	13 (68%)	14 (67%)	
Age		24 (1.2) [b]	22.9 (2.9) [b]	22.9 (3.3) [b]	0.326[a]
WTAR (baseline)		33.9 (6.1) [b]	32.9 (6.5) [b]	34.0 (6.0) [b]	0.828[a]
McGill Score (baseline)		11.9 (8.3) [b]	12.0 (6.0) [b]	10.4 (8.8) [b]	0.780[a]

Percentages are calculated as percentage of each treatment arm. *P*-values correspond to Pearson chi-square tests, unless indicated by [a], which are calculated from a *F*-statistic. [b] Mean (SD) reported.

Table 2. Explanatory variable main effects on RPQ-16.

Explanatory Variable	F-ratio(df1, df2)	*P*-value
Time	0.9 (2, 55.5)	0.426
Intervention Group	0.5 (2, 47.2)	0.590
Blast Exposure	2.6 (1, 48.2)	0.112
PTA	**4.8 (1, 48.4)**	**0.033**
LOC	0.9 (1, 48.1)	0.350
PTSD	**7.3 (1, 48.5)**	**0.009**
Injury Elapse	2.4 (1, 48.3)	0.131
Alcohol Use	1.5 (1, 129)	0.219
Age	0.0 (1, 50.1)	0.925
Previous Head Injury	0.0 (1, 48.1)	0.937
McGill	**33.4 (1,143)**	**<0.001**
WTART	1.2 (1,119)	0.278
TOMM	0.1 (1, 47.7)	0.730

Note: Explanatory variables having a $P < 0.05$ are highlighted in bold.

Table 3. Hypothesis tests for the treatment by time interaction for the secondary outcomes.

Predictor	F-ratio (df1,df2)	*P*
RPQ-3	0.7 (4, 64.0)	0.592
RPQ-13	1.0 (4, 63.8)	0.400
Mayo	0.6 (4, 62.8)	0.702
Balance (SOT)	1.0 (4, 58.9)	0.443
WAIS	1.8 (4, 59.4)	0.141
Trail-Making B	0.7 (4, 64.9)	0.621
Stroop	0.6 (4, 60.2)	0.664
CPT-II	0.6 (4, 60.9)	0.685
CVLT Long Delay Free Recall	0.8 (4, 63.1)	0.523
PASAT	1.4 (4, 52.9)	0.256
BVMT Delay Recall	0.5 (4, 62.3)	0.753
COWAT	1.6 (4, 64.1)	0.197
Grooved Peg Board	0.5 (4, 47.5)	0.724
SWLS	0.5 (4, 61.2)	0.751
Depression (CESD)	0.5 (4, 63.8)	0.767
GOSE	0.8 (4, 57.7)	0.503

Table 4. Hypothesis tests for subgroup efficacy analysis (RPQ-16 outcome; three way interaction between explanatory variable, time, and treatment group).

Explanatory Variable	F-ratio(df1, df2)	*P*
Blast Exposure	0.57 (4, 62.8)	0.685
PTA	1.00 (4, 62.9)	0.416
LOC	0.20 (4, 63.4)	0.938
PTSD	0.13 (4, 63.9)	0.971
Injury Elapse	0.67 (4, 63.1)	0.618
Alcohol Use	0.27 (4, 65.4)	0.898
Age	0.78 (4, 69.3)	0.539
Previous Head Injury	2.06 (4, 62.1)	0.097
McGill	0.12 (4, 72.6)	0.975
WTAR	0.67 (4, 69.1)	0.618
TOMM	0.83 (4, 66.5)	0.510

Figure 1: Participant Selection and Randomization

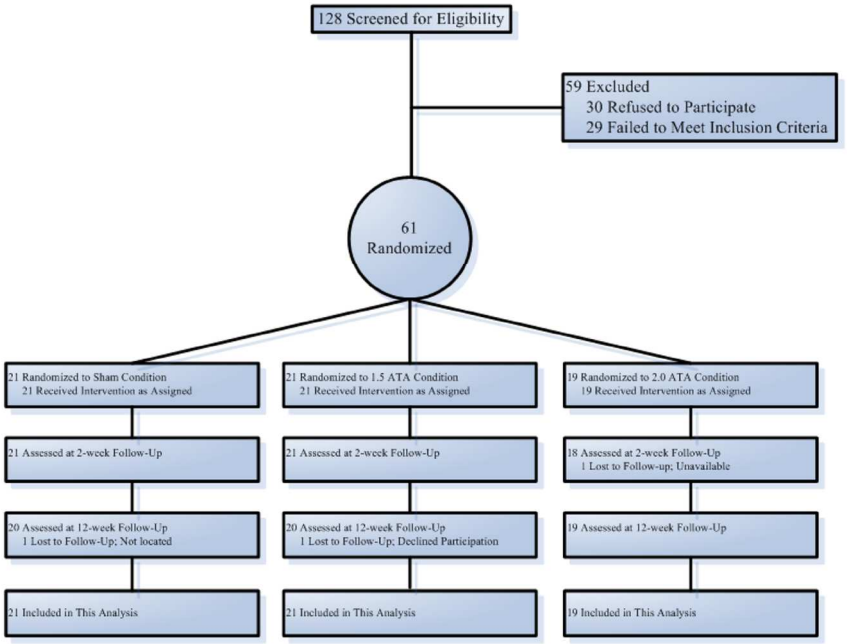

Fig_1
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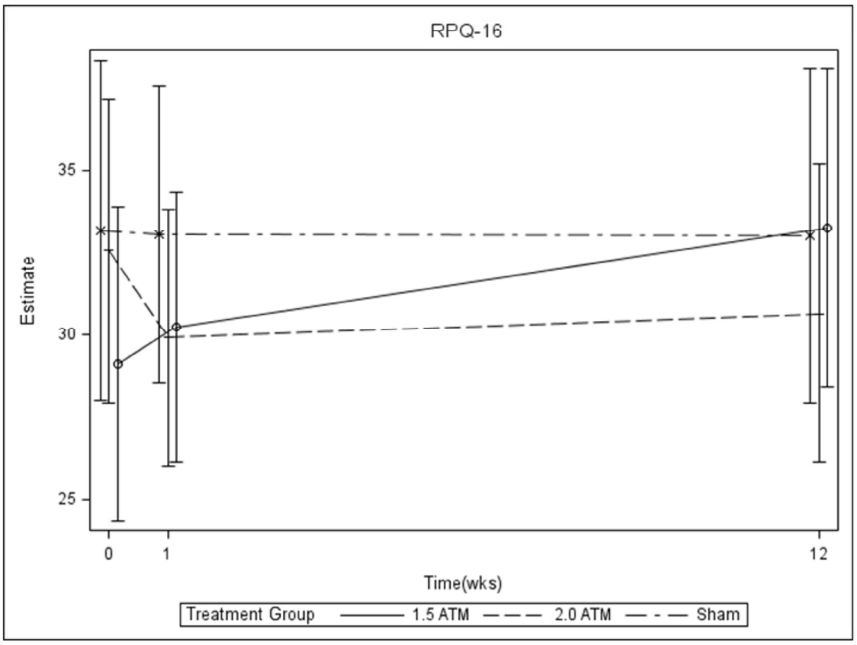
Figure 2. **RPQ-16 by intervention group over time (baseline, 1 week, 3 months)**



[caption] Time by intervention group effect = (F(4, 63.7)=1.0, *P*=0.410).

Fig_2.
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Appendix

Table A1: Primary and Secondary Outcome Measures listed with their abbreviation, scale metrics, and direction of relation to participant well-being

Tables A2-A17: Efficacy test results (Time* Treatment interaction) along with Main effects of explanatory variables for each of the pre-specified Secondary Outcomes

Table A1: Primary* and Secondary Outcome Measures and their relation to well-being

Measure	Abbr.	Scale	Positive Values [a]
Rivermead Post-Concussion Symptoms Questionnaire-16*	RPQ-16	Scale (0-84)	Low
Rivermead Post-Concussion Symptoms Questionnaire-13	RPQ-13	Scale (0-72)	Low
Rivermead Post-Concussion Symptoms Questionnaire-3	RPQ-3	Scale (0-12)	Low
Wechsler Adult Intelligence Scale (Working Memory Index)	WAIS	Scale (50-150)	High
Trail Making Test-B	Trails B	Time (Continuous)	Low
Stroop Test	Stroop	Count	High
Conners's Continuous Performance Test II (d')	CPT-II	Continuous (0+)	High
California Verbal Learning Test (Long D Free Recall)	CVLT	Scale (0-16)	High
Paced Auditory Serial Addition Test	PASAT	Scale (0-60)	High
Brief Visuospatial Memory Test (Delayed Recall)	BVMT	Scale (0-12)	High
Controlled Oral Word Association Test	COWAT	Count	High
Grooved Peg Board Test	Peg Board	Time (Continuous)	Low
Sensory Organization Test	SOT	Scale (0-100)	High
Mayo-Portland Adaptability Inventory	MAYO	Scale (0-111)	Low
Center for Epidemiological Studies Depression Scale	CES-D	Scale (0-60)	Low
Satisfaction with Life Scale	SWLS	Scale (0-35)	High
Glasgow Outcome Scale-Extended	GOSE	Scale (3-15)	High

[a] Positive values describes the direction of the outcome that is reflective of positive outcomes. For example, RPQ has a 'Low' value as patients with lower scores on the RPQ are healthier than patients with high scores.

Table A2: RPQ-13

Predictor	F-ratio(df1, df2)	*P*
Time	1.2 (2, 55.7)	0.316
Treatment	0.7 (2, 47.6)	0.523
Blast Exposure	3.0 (1, 48.1)	0.088
PTA	3.6 (1, 48.4)	0.066
LOC	1.0 (1, 48.1)	0.333
PTSD	**7.0 (1, 48.4)**	**0.011**
Injury Elapse	2.9 (1, 48.3)	0.094
Alcohol Use	2.3 (1, 132)	0.128
Age	0.4 (1, 50.0)	0.533
Previous Head Injury	0.4 (1, 48.0)	0.950
McGill	**26.4 (1,145)**	**<0.001**
WTAR	0.5 (1,121)	0.477
TOMM	0.0 (1, 47.6)	0.964
Time*Treatment	1.0 (4, 63.8)	0.400

Highlights:

- There are no differences in the profiles of the treatment groups.
- Subjects with PTSD had higher RPQ13 scores (*d*=5.44, SE=2.06, 95% CI: 1.30, 9.58) than subjects without PTSD.
- Subjects with higher pain (McGill) had higher RPQ13 scores (*b*=0.47, SE=0.09, 95% CI: 0.29, 0.65).

Table A3: RPQ-3

Predictor	F-ratio(df1, df2)	*P*
Time	0.3 (2, 55.5)	0.710
Treatment	0.1 (2, 45.3)	0.879
Blast Exposure	0.1 (1, 46.6)	0.812
PTA	**5.7 (1, 45.2)**	**0.021**
LOC	0.2 (1, 45.0)	0.640
PTSD	3.1 (1, 47.3)	0.087
Injury Elapse	0.1 (1, 24.1)	0.781
Alcohol Use	2.0 (1, 122)	0.166
Age	3.9 (1, 50.1)	0.055
Previous Head Injury	0.1 (1, 43.7)	0.821
McGill	**23.1 (1, 133)**	**<0.001**
WTAR	3.2 (1, 99.1)	0.076
TOMM	1.4 (1, 46.8)	0.238
Time*Treatment	0.7 (4, 64.0)	0.592

Highlights:

- There are no differences in the profiles of the treatment groups.
- Subjects with PTA had higher RPQ3 scores (*d*=1.36, SE=0.57, 95% CI: 0.21, 2.51) than subjects without PTA.
- Subjects with higher pain (McGill) had higher RPQ3 scores (*b*=0.10, SE=0.02, 95% CI: 0.06, 0.15).

Table A4: Computerized Posturography SOT Balance Composite

Predictor	F-ratio(df1, df2)	*P*
Time	0.2 (2, 52.2)	0.856
Treatment	3.2 (2, 48.2)	0.051
Blast Exposure	1.2 (1, 47.2)	0.286
PTA	4.0 (1, 46.4)	0.052
LOC	**4.7 (1, 45.5)**	**0.035**
PTSD	0.2 (1, 46.6)	0.700
Injury Elapse	1.2 (1, 45.8)	0.276
Alcohol Use	1.0 (1, 104)	0.113
Age	0.4 (1, 48.0)	0.516
Previous Head Injury	0.1 (1, 46.9)	0.733
McGill	3.6 (1,92.0)	0.061
WTAR	**9.2 (1,95.6)**	**0.003**
TOMM	**8.0 (1, 46.6)**	**0.007**
Time*Treatment	1.0 (4, 58.9)	0.443

Highlights:

- There are no differences in the profiles of the treatment groups. The *p*-value for the treatment suggests a difference, but this difference is between the active treatment groups and persists for all time points, including baseline. This does not give evidence for efficacy.
- Subjects with a loss of consciousness following their most severe TBI have lower balance than those with no loss of consciousness (*d*=7.84, SE=3.60, 95%CI: 0.57, 15.10).
- Subjects with high WTAR have lower balance (*b*=-0.30, SE=0.10, 95% CI: -0.50, -0.11).
- Subjects with high TOMM have lower balance (*b*=-9.80, SE=3.46, 95% CI: -16.75, -2.84).

Table A5: Grooved Pegboard (fine motor speed/dexterity)

Predictor	F-ratio(df1, df2)	*P*
Time	2.2 (2, 49.8)	0.118
Treatment	0.6 (2, 49.4)	0.550
Blast Exposure	0.4 (1, 47.2)	0.520
PTA	0.0 (1, 46.3)	0.836
LOC	0.7 (1, 47.2)	0.416
PTSD	1.0 (1, 47.7)	0.333
Injury Elapse	0.1 (1, 46.8)	0.802
Alcohol Use	0.2 (1, 101)	0.695
Age	0.5 (1, 54.7)	0.464
Previous Head Injury	0.2 (1, 47.0)	0.656
McGill	0.8 (1, 109)	0.373
WTAR	0.5 (1, 85.0)	0.477
TOMM	**4.3 (1, 47.5)**	**0.043**
Time*Treatment	0.5 (4, 58.9)	0.724

Highlights:

- There are no differences in the profiles of the treatment groups.
- Subjects who failed the TOMM had slower (*d*=8.11, SE=3.89, 95%CI: 0.27, 15.94) scores that subjects who have passed.

Table A6: WAIS-III Working Memory Index

Predictor	F-ratio(df1, df2)	*P*
Time	**6.8 (2, 52.8)**	**0.002**
Treatment	2.0 (2, 39.1)	0.145
Blast Exposure	3.5 (1, 41.5)	0.067
PTA	0.0 (1, 40.3)	0.995
LOC	0.3 (1, 40.7)	0.605
PTSD	2.7 (1, 42.1)	0.106
Injury Elapse	1.4 (1, 24.9)	0.245
Alcohol Use	0.8 (1, 138)	0.367
Age	0.0 (1, 42.3)	0.989
Previous Head Injury	0.1 (1, 39.7)	0.742
McGill	1.5 (1,119)	0.222
WTAR	**11.3 (1, 108)**	**0.001**
TOMM	1.2 (1, 40.4)	0.279
Time*Treatment	1.8 (4, 59.4)	0.141

Highlights:

- There are no differences in the profiles of the treatment groups.
- Baseline measurements were lower than the 2 week (*d*=0.49, SE=0.21, 95%CI=0.07, 0.90) and 12 week (*d*=0.78, SE=0.21, 95% CI: 0.36, 1.20) measurements.
- After adjusting for TOMM, subjects with and without PTSD did not have different WAIS means.
- Subjects with high WTAR have higher WAIS scores (*b*=0.07, SE=0.02, 95% CI: 0.03, 0.11).

Table A7: Trails B (executive function)

Predictor	F-ratio(df1, df2)	*P*
Time	**13.6 (2, 56.3)**	**<0.001**
Treatment	0.0 (2, 51.9)	>0.999
Blast Exposure	**5.3 (1, 45.9)**	**0.026**
PTA	1.0 (1, 44.6)	0.315
LOC	2.3 (1, 44.2)	0.141
PTSD	1.2 (1, 46.6)	0.281
Injury Elapse	0.0 (1, 44.6)	0.937
Alcohol Use	0.0 (1, 105)	0.944
Age	**4.2 (1, 47.5)**	**0.046**
Previous Head Injury	0.3 (1, 45.7)	0.614
McGill	1.4 (1, 82.2)	0.243
WTAR	0.1 (1, 71.7)	0.777
TOMM	0.7 (1, 45.4)	0.398
Time*Treatment	0.7 (4, 64.9)	0.621

Highlights:

- There are no differences in the profiles of the treatment groups.
- 12 week measurements were lower than baseline (*d*=13.57, SE=2.80, 95%CI=7.98, 19.17) and 2 week (*d*=8.27, SE=2.23, 95% CI: 3.80, 12.74) measurements.
- Subjects with a high number of blast exposures *lower* Trails scores (*d*=10.32, SE=4.50, 95% CI: 1.28, 19.37) than subjects with a low number of blast exposures.
- Older subjects have higher scores than younger patients (*b*=1.47, SE=0.72, 95% CI: 0.03, 2.92).

Table A8: Stroop Color-Word Interference (visual selective attention)

Predictor	F-ratio(df1, df2)	*P*
Time	0.1 (2, 52.3)	0.881
Treatment	0.1 (2, 47.3)	0.925
Blast Exposure	2.8 (1, 45.1)	0.103
PTA	0.0 (1, 43.2)	0.912
LOC	0.0 (1, 41.4)	0.893
PTSD	0.2 (1, 45.3)	0.700
Injury Elapse	0.9 (1, 42.0)	0.359
Alcohol Use	0.0 (1, 123)	0.939
Age	1.9 (1, 44.2)	0.171
Previous Head Injury	0.1 (1, 43.3)	0.782
McGill	2.7 (1, 116)	0.101
WTAR	1.0 (1, 95.6)	0.316
TOMM	2.3 (1, 42.6)	0.136
Time*Treatment	0.6 (4, 60.2)	0.664

Highlights:

- There are no differences in the profiles of the treatment groups.
- There is no relationship between the Stroop Test and any other variables.

Table A9: CPT-II 2.0 Discrimination Index (sustained visual attention)

Predictor	F-ratio(df1, df2)	*P*
Time	0.9 (2, 53.2)	0.433
Treatment	0.3 (2, 48.2)	0.734
Blast Exposure	0.6 (1, 51.2)	0.456
PTA	0.1 (1, 43.5)	0.736
LOC	2.6 (1, 45.9)	0.111
PTSD	0.1 (1, 45.8)	0.756
Injury Elapse	0.1 (1, 32.4)	0.818
Alcohol Use	1.0 (1, 117)	0.314
Age	1.4 (1, 57.3)	0.249
Previous Head Injury	0.0 (1, 49.6)	0.840
McGill	2.7 (1, 122)	0.102
WTAR	0.0 (1, 121)	0.952
TOMM	0.2 (1, 46.5)	0.697
Time*Treatment	0.6 (4, 60.9)	0.685

Highlights:

- There are no differences in the profiles of the treatment groups.
- There is no relationship between the CPT-II and any other variables.

Table A10: CVLT Long Delayed Recall (delayed verbal memory)

Predictor	F-ratio(df1, df2)	*P*
Time	**4.4 (2, 55.2)**	**0.017**
Treatment	0.5 (2, 51.3)	0.617
Blast Exposure	2.2 (1, 49.0)	0.146
PTA	0.2 (1, 50.1)	0.632
LOC	0.5 (1, 48.4)	0.499
PTSD	1.0 (1, 49.1)	0.330
Injury Elapse	1.9 (1, 48.5)	0.175
Alcohol Use	1.1 (1, 132)	0.288
Age	0.4 (1, 49.1)	0.535
Previous Head Injury	1.1 (1, 48.7)	0.310
McGill	2.2 (1, 140)	0.139
WTAR	1.0 (1, 131)	0.316
TOMM	**5.1 (1, 47.7)**	**0.028**
Time*Treatment	0.8 (4, 63.1)	0.523

Highlights:

- There are no differences in the profiles of the treatment groups.
- The CVLT score at 2 weeks was higher (*d*=1.23, SE=0.41, 95%CI: 0.40, 2.06) than at baseline.
- Subject failing the TOMM had lower scores (*d*=2.81, SE=1.24, 95%CI: 0.31, 5.32) that subject who have passed.

Table A11: PASAT 2.0 second pacing (sustained auditory attention)

Predictor	F-ratio(df1, df2)	*P*
Time	**18.0 (2, 46.1)**	**<0.001**
Treatment	0.2 (2, 42.4)	0.854
Blast Exposure	3.3 (1, 45.1)	0.075
PTA	0.3 (1, 42.6)	0.580
LOC	2.9 (1, 43.1)	0.095
PTSD	0.7 (1, 44.0)	0.401
Injury Elapse	1.0 (1, 41.7)	0.333
Alcohol Use	0.1 (1, 134)	0.726
Age	0.0 (1, 47.0)	0.984
Previous Head Injury	0.8 (1, 45.1)	0.388
McGill	0.0 (1, 123)	0.841
WTAR	3.0 (1, 123)	0.084
Time*Treatment	1.4 (4, 52.9)	0.256

Highlights:

- There are no differences in the profiles of the treatment groups.
- The PASAT score at baseline was lower than both the scores at 2 weeks (*d*=4.92, SE=0.97, 95% CI: 2.97, 6.86) and 12 weeks (*d*=7.19, SE=1.32, 95% CI: 4.54, 9.84).

Table A12: BVMT Delayed Recall (visual delayed memory)

Predictor	F-ratio(df1, df2)	*P*
Time	**7.7 (2, 53.9)**	**0.001**
Treatment	0.1 (2, 25.5)	0.929
Blast Exposure	0.2 (1, 38.2)	0.651
PTA	0.3 (1, 33.8)	0.611
LOC	1.8 (1, 35.5)	0.185
PTSD	2.8 (1, 36.2)	0.103
Injury Elapse	0.2 (1, 44.2)	0.677
Alcohol Use	0.1 (1, 79.9)	0.727
Age	1.9 (1, 44.0)	0.180
Previous Head Injury	1.9 (1, 39.6)	0.181
McGill	0.0 (1, 82.0)	0.849
WTAR	0.4 (1, 62.4)	0.508
TOMM	1.2 (1, 39.3)	0.290
Time*Treatment	0.5 (4, 62.3)	0.753

Highlights:

- There are no differences in the profiles of the treatment groups.
- The BVMT score at 12 weeks was higher than both the scores at baseline (*d*=0.97, SE=0.40, 95% CI: 0.17, 1.78) and 2 weeks (*d*=1.53, SE=0.43, 95% CI: 0.67, 2.39).
- After adjusting for TOMM, subjects with PTSD were not significantly different than subjects without PTSD.

Table A13: COWAT letter fluency (verbal fluency)

Predictor	F-ratio(df1, df2)	*P*
Time	**9.1 (2, 57.0)**	**<0.001**
Treatment	0.7 (2, 49.9)	0.515
Blast Exposure	3.0 (1, 49.3)	0.088
PTA	0.6 (1, 49.7)	0.450
LOC	1.9 (1, 49.1)	0.175
PTSD	0.0 (1, 49.3)	0.957
Injury Elapse	0.0 (1, 49.2)	0.858
Alcohol Use	0.1 (1, 146)	0.832
Age	0.0 (1, 49.4)	0.880
Previous Head Injury	0.4 (1, 49.1)	0.513
McGill	0.2 (1, 116)	0.638
WTAR	3.2 (1, 120)	0.076
TOMM	0.0 (1, 48.4)	0.857
Time*Treatment	1.6 (4, 64.1)	0.197

Highlights:

- There are no differences in the profiles of the treatment groups.
- The COWAT score at 2 weeks was higher than both the scores at baseline (*d*=4.39, SE=1.02, 95% CI: 2.34, 6.43) and 12 weeks (*d*=2.09, SE=1.03, 95% CI: 0.02, 4.16). The COWAT score at 12 weeks was higher (*d*=2.30, SE=1.03, 95%CI: 0.24, 4.36) than the score at baseline.

Table A14: GOSE (global outcome)

Predictor	F-ratio(df1, df2)	*P*
Time	2.2 (2, 50.9)	0.117
Treatment	0.0 (2, 38.4)	0.972
Blast Exposure	0.4 (1, 31.8)	0.560
PTA	0.1 (1, 37.7)	0.814
LOC	0.2 (1, 48.9)	0.650
PTSD	0.7 (1, 40.4)	0.649
Injury Elapse	0.3 (1, 12.4)	0.411
Alcohol Use	2.2 (1, 117)	0.140
Age	1.0 (1, 44.1)	0.323
Previous Head Injury	0.1 (1, 28.7)	0.725
McGill	**6.7 (1, 119)**	**0.011**
WTAR	0.0 (1, 93.5)	0.926
TOMM	0.1 (1, 37.2)	0.777
Time*Treatment	0.8 (4, 57.7)	0.503

Highlights:

- There are no differences in the profiles of the treatment groups.
- Subjects who had higher pain had lower (*b*=-0.04, SE=0.02, 95%CI: -0.07, -0.01) GOSE scores than subjects who have passed.

Table A15: MAYO (life particpation)

Predictor	F-ratio(df1, df2)	*P*
Time	2.7 (2, 54.9)	0.079
Treatment	0.3 (2, 49.7)	0.781
Blast Exposure	0.4 (1, 47.2)	0.529
PTA	0.0 (1, 47.7)	0.944
LOC	0.0 (1, 47.9)	0.920
TSD	1.9 (1, 48.5)	0.177
Injury Elapse	**4.3 (1, 47.7)**	**0.043**
Alcohol Use	2.0 (1, 118)	0.162
Age	0.2 (1, 51.9)	0.625
Previous Head Injury	0.8 (1, 48.5)	0.370
McGill	**16.7 (1,127)**	**<0.001**
WTAR	0.7 (1,109)	0.400
TOMM	0.4 (1,48.2)	0.541
Time*Treatment	0.6 (4, 62.8)	0.702

Highlights:

- There are no differences in the profiles of the treatment groups.
- Subjects with 6 months or less elapse since last TBI have better MAYO than those with more than 6 months elapsed time (*d*=1.80, SE=0.86, 95%CI: 0.06, 3.55).
- Subjects with higher pain (McGill) have higher MAYO scores (*b*=0.19, SE=0.05, 95% CI: 0.10, 0.28).

Table A16: SWLS (Life Satisfaction)

Predictor	F-ratio(df1, df2)	*P*
Time	2.2 (2, 53.7)	0.116
Treatment	0.3 (2, 48.1)	0.752
Blast Exposure	3.5 (1, 44.7)	0.067
PTA	1.7 (1, 45.7)	0.202
LOC	0.7 (1, 44.6)	0.421
PTSD	**8.5 (1, 46.1)**	**0.006**
Injury Elapse	**9.9 (1, 45.0)**	**0.003**
Alcohol Use	1.0 (1, 127)	0.332
Age	2.0 (1, 45.8)	0.163
Previous Head Injury	2.5 (1, 44.4)	0.123
McGill	**5.5 (1, 129)**	**0.020**
WTAR	0.2 (1, 120)	0.647
TOMM	0.7 (1, 43.5)	0.413
Time*Treatment	0.5 (4, 61.2)	0.751

Highlights:

- There are no differences in the profiles of the treatment groups.
- Subjects who had higher pain had lower (*b*=-0.15, SE=0.07, 95%CI: -0.28, -0.02) SWLS scores than subjects who have passed.
- Subjects who did not have PTSD at baseline had higher (*d*=4.40, SE=1.51, 95% CI: 1.35, 7.45) SWLS than subjects who were diagnosed with PTSD at baseline.
- Subjects who had shorter elapse periods since their last blast exposure had higher (*d*=4.54, SE=1.44, 95% CI: 1.63, 7.45) SWLS than those with longer periods since their last blast exposure.

Table A17: CESD (depression)

Predictor	F-ratio(df1, df2)	*p*-value
Time	0.5 (2, 56.3)	0.591
Treatment	0.2 (2, 49.0)	0.823
Blast Exposure	2.2 (1, 48.1)	0.142
PTA	0.0 (1, 48.5)	0.921
LOC	0.0 (1, 47.5)	0.954
PTSD	**6.8 (1, 48.1)**	**0.012**
Injury Elapse	1.3 (1, 47.8)	0.262
Alcohol Use	0.1 (1, 145)	0.767
Age	0.9 (1, 48.6)	0.353
Previous Head Injury	1.5 (1, 47.8)	0.224
McGill	**31.6 (1, 135)**	**<0.001**
WTAR	**4.0 (1, 121)**	**0.047**
TOMM	0.1 (1, 47.0)	0.713
Time*Treatment	0.5 (4, 63.8)	0.767

Highlights:

- There are no differences in the profiles of the treatment groups.
- Subjects who had higher pain had higher (*b*=0.53, SE=0.09, 95%CI: 0.34, 0.71) CESD scores than subjects who have passed.
- Subjects who had higher WTAR had higher (*b*=0.22, SE=0.11, 95%CI: 0.00, 0.45) CESD scores than subjects who have passed.
- Subjects who had PTSD at baseline had lower (*d*=6.04, SE=2.31, 95% CI: 1.38, 10.69) SWLS than those with longer periods since their last blast exposure.