Preliminary Evidence for Improvement in Symptoms, Cognitive, Vestibular, and Oculomotor Outcomes Following Targeted Intervention with Chronic mTBI Patients

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ABSTRACT Introduction: To determine if targeted, active interventions would improve symptoms and impairment in previously intractable patients with chronic mild traumatic brain injury (mTBI). Materials and Methods: Twenty-six (20 males; 6 females) out of 51 (51%) former military and civilian patients with chronic (1–3 yr) mTBI enrolled in the TEAM traumatic brain injury (TBI) study completed both an initial and 6-mo post-intervention comprehensive mTBI assessment including symptoms (Post-concussion Symptom Scale [PCSS], Dizziness Handicap Inventory [DHI]), cognitive (Immediate Post-concussion Assessment and Cognitive Testing [ImPACT]), vestibular/oculomotor (Vestibular/Ocular Motor Screening [VOMS]), balance (Activities-specific Balance Confidence [ABC] scale, Balance Error Scoring System [BESS]), and cervical (Neck Disability Index [NDI]). Patients were prescribed progressive, targeted interventions and therapies (e.g., behavioral, vestibular, vision, and exertion) that matched their mTBI clinical profile. A series of paired *t*-tests adjusted for multiple corrections were used to compare pre- and post-intervention assessment scores. Results: Patients demonstrated significant improvement from pre- to post-intervention on total symptoms ($t = 2.69$, $p = 0.01$), verbal memory ($t = -1.96$, $p = 0.05$), ABC balance score ($t = -2.05$, $p = 0.05$), smooth pursuits ($t = 2.32$, $p = 0.04$), near-point convergence distance ($t = -3.58$, $p = 0.01$), vestibular ocular reflex ($t = 2.31$, $p = 0.03$), and visual motion sensitivity ($t = 2.43$, $p = 0.03$). Conclusions: Previously recalcitrant patients with chronic complex mTBI demonstrated significant improvement in symptoms, cognitive, vestibular, oculomotor, and balance function following targeted interventions.

INTRODUCTION

Mild traumatic brain injury (mTBI) is a significant public and military health concern, with over 370,000 US Military personnel experiencing mTBI since 2000.[1] Military personnel may experience chronic effects and symptoms from mTBI including physical, cognitive, vestibular, oculomotor, and psychological impairments that can persist for weeks, months, and even years after their injury.[2] These persistent effects contribute to over $60 billion in health care and related costs each year.[3] More importantly, as a result of lingering symptoms and impairment, many current and former military personnel do not fully recover and are left to deal indefinitely with the associated morbidity from mTBI.

Recent research efforts have increased our understanding of mTBI symptoms,[2] impairments,[2,4–6] risk factors,[7,8] and prognosis.[8–10] However, to date, this increase in knowledge has yet to translate into effective, evidence-based conceptual and treatment paradigms for patients with mTBI. Traditionally, traumatic brain injury (TBI) has been categorized as mild, moderate, and severe.[11] This homogeneous approach fails to consider the individual variability of this injury. Consequently, after several decades of research, there are still no FDA-approved treatments and no successful clinical trials for mTBI.[12] Recently, researchers and clinicians have begun to conceptualize mTBI as a heterogeneous disorder with multiple clinical profiles or phenotypes that necessitate a comprehensive assessment and targeted and active interventions.[13,14] With this conceptual framework in mind, our research team developed the Targeted Evaluation, Action and Monitoring of TBI (TEAM-TBI) clinical research project to more effectively treat patients with mTBI.

The objective of the current study is to determine if non-pharmacological, targeted, active interventions from TEAM-TBI would improve symptoms and impairment in previously intractable patients with chronic complex mTBI. We expected that participants would improve in symptoms, cognitive, vestibular/oculomotor, balance, and neck-related domains following a targeted, active intervention period of 6 mo.

METHODS

Design and Participants

A single-group, pre- to post-intervention design was used for this study. A total of 51 former military and civilian patients with chronic (1–3 yr) mTBI were enrolled in the TEAM-TBI

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study between January 2015 and August 2016. Inclusion criteria for the study included 18–60 yr of age, documented history of diagnosed mTBI with ongoing symptoms, no history of stroke or other neurological disorders, and had complete data for pre- and post-intervention time periods. Participants were excluded if they had active alcohol/drug abuse or dependence, inability or unwillingness to provide informed consent, contraindications to magnetic resonance imaging scanning (such as pacemakers, ferrous metals, body weight above 125 kg, or concerns regarding claustrophobia), non-native English speakers due to majority of neuro-assessments being completed in English. The University of Pittsburgh Institutional Review Board (PRO13070121) approved this study and all participants signed informed consent before undergoing study procedures. The study began in January 2014 and closed to enrollment; however, follow-up visits are still being conducted with participants. ClinicalTrials.gov Identifier: NCT02657135.

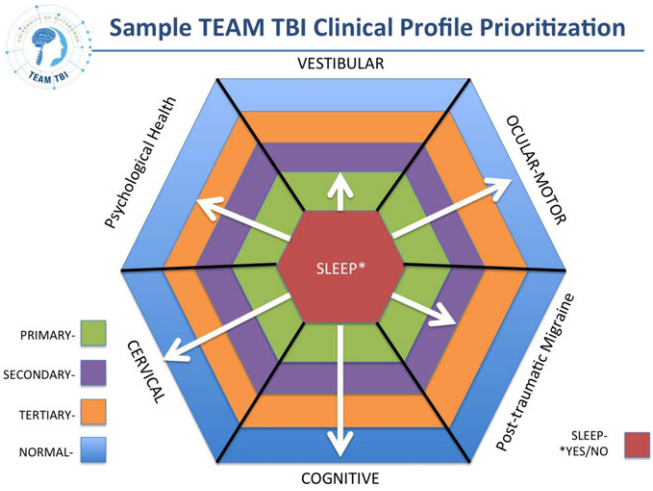

FIGURE 1. Sample clinical profile prioritization model used to characterize and diagnose mTBI patients and inform subsequent targeted, precision interventions.

Chronic mTBI Diagnosis

Mild traumatic brain injury was operationally defined and clinically diagnosed in line with current US Military assessments as including all of the following diagnostic criteria: clear mechanism of injury, normal structural imaging findings, Glasgow Coma Scale = ≥13, and reported or observed signs (i.e., brief [<30 min] loss of consciousness, amnesia [<24 hr], and/or disorientation/confusion) at time of injury. In addition, in the current study, all participants met the following criteria: current reported symptoms (e.g., headache, dizziness, and nausea) and/or impairment (e.g., cognitive, balance, and visual), and at least 6 mo post-injury. Clinical diagnoses were confirmed by a team of neurosurgeons, neuropsychologists, and neurologists with clinical expertise in concussion care, following an initial documented diagnosis in participants' medical records.

Clinical Profiles

Each patient in the current study was further diagnosed with one or more of the following clinical profiles: cognitive, vestibular, ocular motor, anxiety/mood, post-traumatic migraine, and/or sleep. Clinical profiles could co-occur or occur independently. Profiles for each patient were prioritized as primary, secondary, and tertiary based on clinical adjudication (Fig. 1; Procedures section).

Symptom Measures

Post-concussion Symptom Scale (PCSS): The PCSS comprises 22 self-reported symptoms (e.g., dizziness, headache, and difficulty concentrating) rated on a scale from 0 (none) to 6 (severe). A total symptom severity score is calculated by summing the severity rating across all items.

Dizziness Handicap Inventory (DHI): The DHI is a 25-item self-report questionnaire that assesses functional, physical, and emotional impacts of dizziness during the past month. Scores greater than 10 indicate a minimum level of dizziness-related impairment.

Cognitive Measures

Immediate Post-Concussion Assessment Cognitive Test (ImPACT): The ImPACT test was used to assess neurocognitive performance. The test comprised six modules: (1) verbal memory, (2) design memory, (3) X's and O's, (4) symbol matching, (5) color matching, and (6) three-letter memory. These six neurocognitive assessment modules are collapsed into four composite scores for verbal memory (%), visual memory (%), visual motor processing speed (#), and reaction time (RT, sec).

Vestibular/Ocular Motor Measures

Vestibular/Ocular Motor Screening (VOMS) Tool: The VOMS assesses vestibular and ocular motor impairment via patient-reported symptom provocation following each assessment.[15] The VOMS consists of brief assessments in the following five domains: (1) smooth pursuits, (2) horizontal and vertical saccades, (3) convergence, (4) horizontal and vertical vestibular ocular reflex (VOR), and (5) visual motion sensitivity (VMS). Patients verbally rate changes in headache, dizziness, nausea, and fogginess symptoms compared with their immediate pre-assessment state on a scale of 0 (none) to 10 (severe) following each VOMS assessment to determine if any domain provokes symptoms. Convergence is assessed by both symptom report and objective measurement of the near point of convergence (NPC). NPC values are averaged across three trials, and normal NPC values are within 5 cm.[15]

Activities-specific Balance Confidence (ABC) Scale: The ABC is a self-reported 16-item scale that asks respondents to rank from 0 (no confidence) to 100% (completely confident) their ability to perform daily activities (e.g., walking, reaching, sweeping, and riding an escalator) without losing their balance.[16] A total average balance confidence score is

calculated by totaling the scores across all items, divided by the total number of items.

Balance Error Scoring System (BESS): The BESS measures postural stability and consists of three stances including feet side by side, a tandem stance, and a single-leg stance on the non-dominant leg.[17,18] The three stances are performed for 20 seconds each, three on a firm surface and three on a dynamic (medium density foam) surface. All stances are completed with eyes closed and with hands on the iliac crests. Errors include lifting hands off the iliac crests, opening the eyes, stepping, stumbling, or falling, moving the hip into more than a 30 degree of flexion or abduction, lifting the forefoot or heel, or remaining out of the testing position for more than 5 seconds. Each error equals one point, with higher scores indicating worse performance.

Neck Disability Index (NDI): The NDI is a 10-item questionnaire that assesses the effect of neck pain on several aspects of everyday life including sleep, recreations, driving, and work.[19] The total possible score is 50.

Procedures

Institutional review board approvals were obtained from the University of Pittsburgh (PRO 13080199) and the US Army Medical Research and Material Command, Office of Research Protection, Human Research Protection Office. Following these approvals and written informed consent procedures, all participants completed the initial comprehensive, multimodal clinical assessment including PCSS, DHI; ImPACT; VOMS; ABC, BESS; and NDI. Following a clinical adjudication process involving a multidisciplinary treatment team, patients were prescribed progressive, targeted interventions and therapies (e.g., behavioral, vestibular, vision, and exertion) that matched their mTBI clinical profiles (Fig. 2). "Coaches" from the clinical research team worked individually with patients to facilitate and remotely monitor their prescribed interventions and track changes via phone contact and an iPad-based program. Patients returned to complete the comprehensive assessments again, approximately 6 months following the initial assessment and intervention period.

Data Analysis

Descriptive data were used to describe the sample. We compared the pre- to post-intervention assessment scores for each of the clinical measures described above using a series of paired *t*-tests adjusted for multiple corrections. All statistical analyses were performance using IBM Statistical Package for the Social Sciences version 22, with a statistical significance value set at $p < 0.05$.

RESULTS

Descriptive Data

A total of 26 (20 males; 6 females) out of 51 (51%) former military personnel and civilian patients aged 22–59 (M = 37.0, ±9.6) yr had complete data for the pre- and post-intervention time points. The remaining patients had not yet completed their post-intervention follow-up assessment. Glasgow Coma Scale scores for all participants were 15. Within the sample, 20 (77%) patients were male and 17 (65%) were former military personnel. The injury mechanisms for all participants were as follows: 11 (42%) blast, 11 (42%) blunt, and 4 mixed. As expected, military participants had significantly (chi-square = 7.52, $p = 0.023$) more blast mTBI (9/17, 53%) than civilians (2/9, 22%) and fewer blunt mTBI (2/17, 12%) than civilians (7/9, 78%).

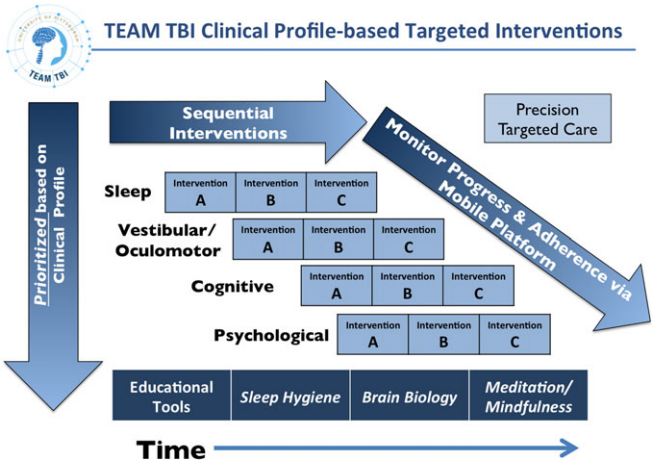

FIGURE 2. Conceptual model for targeted, precision interventions matched to prioritized mTBI clinical profiles for each patient.

Comparison of Clinical Outcomes from Pre- to Post-intervention

The results of the dependent measures *t*-tests supported significant differences from pre- to post-intervention on several of the measures. The results are presented by domain in Table I– symptoms and cognitive; Table II – vestibular/oculomotor, and Table III – dizziness, balance, and neck. Patients demonstrated significant improvement from pre- to post-intervention on total symptoms ($t = 2.69$, $p = 0.01$), verbal memory ($t = -1.96$, $p = 0.05$), smooth pursuits ($t = 2.32$, $p = 0.04$), horizontal vestibular ocular reflex (VOR) ($t = 2.31$, $p = 0.03$), visual motion sensitivity (VMS) ($t = 2.43$, $p = 0.03$), convergence distance ($t = -3.58$, $p = 0.003$), and ABC balance confidence score ($t = -2.05$, $p = 0.05$). For each of these clinical outcome variables, patients improved (i.e., fewer symptoms and less impairment) from pre- to post-intervention. There were no significant differences across time for the other clinical outcomes measured in the study.

DISCUSSION

The current study examines the effectiveness of a targeted, precision medicine approach to treating former military personnel and civilian patients with previously intractable chronic mTBI. The key findings supported our hypothesis and indicated that

TABLE I. Comparison of Pre- and Post-intervention Scores on Symptoms and Cognitive Outcomes ($N = 26$)

	Pre-intervention *M* (SD)	Post-intervention *M* (SD)	*p*
Symptoms	51.3 (21.2)	40.3 (26.5)	0.01
Verbal memory (%)	72.6 (14.5)	77.2 (16.4)	0.05
Visual memory (%)	62.4 (14.5)	63.0 (17.0)	0.78
Visual processing speed (*n*)	30.4 (9.4)	32.3 (8.4)	0.07
Reaction time (s)	0.76 (0.21)	0.73 (0.22)	0.27

TABLE II. Comparison of Pre- and Post-intervention Scores on Vestibular and Oculomotor Outcomes ($N = 26$)

	Pre-intervention *M* (SD)	Post-intervention *M* (SD)	*p*
Smooth pursuits (*n*)	5.4 (5.2)	3.0 (4.0)	0.04
Horizontal saccades (*n*)	5.1 (4.9)	3.3 (4.0)	0.15
Vertical saccades (*n*)	5.9 (5.8)	3.5 (4.3)	0.07
Horizontal vestibular ocular reflex (VOR) (*n*)	7.7 (5.9)	5.2 (4.1)	0.03
Vertical VOR (*n*)	6.4 (5.4)	4.8 (4.6)	0.15
Visual motion sensitivity (VMS) (*n*)	8.5 (4.9)	5.3 (4.8)	0.03
Convergence distance (cm)	21.0 (21.1)	8.4 (8.8)	0.003

TABLE III. Comparison of Pre- and Post-intervention Scores on Dizziness, Balance, and Neck Outcomes ($N = 26$)

	Pre-intervention *M* (SD)	Post-intervention *M* (SD)	*p*
Dizziness Handicap Inventory (DHI) Total (*n*)	13.1 (8.5)	10.0 (7.3)	0.33
Balance Error Scoring System (BESS) (*n*)	24.0 (11.2)	16.1 (9.0)	0.07
Activities-specific Balance Confidence Scale (ABC) (*n*)	76.8 (22.7)	83.7 (14.8)	0.05
Neck Disability Index (NDI) (*n*)	13.9 (9.2)	12.7 (7.2)	0.47

approximately 6 months following the initial comprehensive assessment and subsequent targeted interventions, patients experienced significant improvements across symptom, cognitive, vestibular, and oculomotor domains. Specifically, patients experienced improvements in total symptom burden, verbal memory scores, smooth pursuits, VOR, VMS, convergence distance, and confidence in their balance from pre- to post-intervention. Overall, the current findings support the clinical and research utility of a comprehensive assessment of patients with mTBI, followed by a targeted approach to intervention as advocated by researchers.[13,14,20]

In contrast to expectations, patients did not improve significantly across the intervention time period in balance and neck-related outcomes, as well as several individual components within the cognitive and vestibular/oculomotor domains. Statistical differences from enrollment to 6 months post-intervention were not supported for certain subdomains of cognitive function including visual memory, visual processing speed, reaction time, and oculomotor function including saccades. Moreover, there were no significant differences in DHI scores, clinical balance performance on the BESS, or neck-related outcomes as measured by the NDI. There are several explanations for the lack of improvement in these areas including that patients' impairment in these areas was of low magnitude or was unrelated to their mTBI. In addition, these outcomes may not have fully improved during the study period. With regard to the neck and lack of improvement in NDI scores, it is relevant to acknowledge that the TEAM-TBI intervention did not include cervical rehabilitation, which may have limited any positive effect on the cervical or neck-related outcomes. The measures employed in the current study, which were focused on assessing multiple domains, may in some cases lack sensitivity to the subtler improvements experienced by patients with chronic mTBI. In addition, statistical group differences were analyzed in this article, and the analyses controlled for multiple comparisons in a relatively small sample, which likely increased the chance of type II error, or false negative findings. It is also important to note that in each of the preceding domains where negative findings were reported – with the exception of the neck – non-significant but potentially clinically relevant improvements occurred. Moving forward, researchers should assess clinical outcomes over a longer period of time and include targeted interventions for the neck in patients with mTBI.

Strengths and Limitations

The sample in the current study was small and only represented just over half of the patients currently enrolled in the trial. As such, we frame our findings as preliminary and strongly encourage additional research with larger samples to more appropriate power statistical analyses. However, it is important to point out that the primary objective of the TEAM-TBI project is to promote improvement in individual patients, rather than demonstrate group statistical differences across patients. In the

current study, we did not employ a randomized controlled design or include a control group or intervention, which limits our ability to attribute the reported improvements to the targeted treatment approach of the TEAM-TBI intervention *per se*. However, given that the patients in the current study had not experienced improvement – and in many cases had worsened – since their initial treatment before being enrolled in the study, it is unlikely that the improvement reported was a product of time or maturation effects. We also did not control for all possible confounding factors during the interim period between the initial assessment and 6-month follow-up period. Patients may have experienced confounding events or factors such as changes in personal and family circumstances, improvements in overall health, occupational changes, and other changes that were not adequately controlled for in the analyses. We did monitor patients during the interim period via phone and mobile health technology contact with the coaches. In doing so, we were able to monitor changes and ensure that patients were compliant with their prescribed treatment interventions. Finally, we did not measure the clinical outcomes in between the approximately 6-month time span between the two assessments nor did we measure outcomes beyond the 6-month time period of the study. Consequently, we do not know if the changes reported represent a linear progression toward recovery. We also do not know if recovery in some of the other (i.e., non-significant) clinical outcomes did not continue beyond the time period of the current study.

CONCLUSION

Previously recalcitrant patients with chronic complex mTBI demonstrated significant improvement in cognitive, vestibular, oculomotor, and balance impairment and symptoms following the TEAM-TBI targeted intervention. The TEAM-TBI approach utilizes a comprehensive, multimodal assessment to inform targeted, active interventions that can be adapted to active duty and veteran population to improve outcomes in patients with chronic complex mTBI. We recognize that the current results are preliminary and do not consider several confounding factors. As, such we cannot rule out the effects of time (in this case, approximately 6 months), as well as personal contact with the patients on the finding reported with this sample. We acknowledge that these and other factors may have played a role in the reported outcomes. However, the patients in this study had experienced little or no improvement in their mTBI-related symptoms and impairments for months and even years following their initial diagnosis. Therefore, the current findings suggest that the targeted interventions from the TEAM-TBI project were successful in improving patient outcomes. Additional research using RCT designs is warranted to determine the comparative effectiveness of the current targeted intervention approach that emphasizes an expose–recover model to current standard of care approaches that focus on prescribed rest and symptom-guided return to activity.

PRESENTATION

Presented as a poster at the 2016 Military Health System Research Symposium, Kissimmee, FL (abstract number: MHSRS-16-1461).

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