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TITLE: Post-Traumatic Headache and Psychological Health: Mindfulness Training for Mild Traumatic Brain Injury

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14. ABSTRACT

Mindfulness training (MT) has proven to be effective for numerous chronic pain syndromes, but it has not been evaluated for chronic post-traumatic headache (PTH). Soldiers with PTH were recruited from Womack Army Medical Center. Ninety-five subjects were randomized to one of the three interventions: Mindfulness training (n=29), headache education (n=33), or usual care (n=33). Both behavioral programs was associated with clinically significant decreases in headache disability, while headache disability following usual care was not significantly affected (HIT-6 change scores: -4.2, -3.8, and -1.4, respectively). Relative to the other groups, the MBSR group had the lowest attrition although the overall drop-out rate across the three groups was high (MBSR, 58%; Head-EP, 75%; UC, 65%). Daily stress was positively associated with headache frequency ($p<.0001$) and those with comorbid PTSD or depression were more susceptible to the effects of stress on headache frequency than those without those psychiatric comorbidities. Limitations of this project include high attrition rates. The preliminary findings suggest that stress negatively impacts headache activity, that two behavioral interventions (stress and education) offer comparable clinical improvement on headache disability, and that soldiers with depression or PTSD are vulnerable to the effects of stress on headache activity.

15. SUBJECT TERMS
Posttraumatic headache, pain rehabilitation, mind/body intervention, mindfulness meditation

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1. **INTRODUCTION**

Posttraumatic headache (PTH) is a cardinal symptom of mild traumatic brain injury (MTBI). PTH is undertreated, associated with high sick calls, missed days, negative psychological/mood states, and impaired quality of life. Comorbid anxiety, depression, PTSD and other psychological, psychosocial, and health stressors portend poorer TBI/headache outcomes, supporting the need for integrative health care. The focus of this research is the evaluation of mindfulness-based stress reduction as one, potentially critical, component of comprehensive rehabilitative efforts for soldiers suffering from PTH, postconcussion symptoms, and psychological health issues.

2. **KEYWORDS**

Post-traumatic headache, traumatic brain injury, concussion, mindfulness meditation, mind/body intervention, stress management, military

3. **ACCOMPLISHMENTS**

3(a). Specific Aims of the project were the following:

Specific Aim 1. To determine the efficacy of MBSR compared to a Headache/TBI-specific Education Program (Head-EP) in the treatment of symptoms in soldiers with posttraumatic headache.

Hypothesis: Compared to soldiers receiving usual headache care plus Head-EP, those receiving usual headache care plus MBSR will demonstrate significant improvement in headache frequency, headache severity, and headache-related quality of life. The improvements in PTH will be specifically related to improved quality of life and reduction in headache-related disability and frequency.

Specific Aim 2. To identify relevant secondary MTBI outcomes associated with standard headache care plus adjunctive MBSR. Secondary endpoints include: balance/dizziness, PTSD symptoms, depression, cognitive functions, stress, sleep disturbances, irritability, blurred vision, sensitivity to light/noise, sick days, health status**,** medication use, substance use, and health care utilization.

Hypothesis: Compared to soldiers receiving usual care plus Head-EP, or usual care alone, those receiving usual care plus MBSR will experience improvement in a broad range of postconcussive symptoms, health and well being.

Specific Aim 3. To identify psychological mechanisms through which MBSR may influence headache in soldiers with TBI. We will examine the influence of pain catastrophizing, rumination, and locus of control on primary endpoints (headache frequency, headache severity and headache-related quality of life). Based on the results of preliminary analyses, sub-analyses testing a mediator model will be conducted.

3(b). **SOW Project Deliverables/Schedule**

Projected Completion: Months 1-6 Actual Completion: Months 1-24

1. Creation of the clinical protocol and submission of application and consent forms to the UNC Institutional Review Board (IRB). Modification of the protocol according to IRB stipulations based on regulatory requirements and review, and resubmission.
    a. Final IRB approved protocol in place by the end of the first 6 months from the start of the funding period.
    b. Manuals describing final testing instruments and their administration.
    c. Manual describing intervention procedures on a week by week basis.
    d. Detailed outline of statistical analytic scheme, including final power calculations, recruitment targets, documented contingencies for drop outs and missing data, agreements for computer support.
    e. Data transfer and entry flow charts with assignments of study personnel for each step in the process of data collection.
    f. Headache diary finalized.
2. Training of study personnel on procedures including administration of informed consent, neuropsychological measures, and balance tests.
3. Training of mindfulness and educational session instructors. Mock session observation by study team of the instructors.
4. Research meeting structure established including timing, locations, participants, minutes and agenda protocol in place.
    a. Start of weekly meetings to review all aspects of the project.
5. Data safety monitoring board (DSMB) agreements finalized with outside reviewers including an expert in mindfulness training, a neurologist with expertise in headache and a member of the medical service at Fort Bragg who are not directly involved in the study.
    a. Meeting timing, frequency and location of the DSMB established.
    b. Data review procedures agreed upon; protocol finalized.
    c. Stopping rules and response to contingencies defined.
    d. Adverse event and unexpected problems forms and procedures developed with IRB approval. Manual developed.
6. Communication. Internet listserv developed for all members of the research team.
7. Computer support and location for data storage and security (CTRC) established.
8. Research case report forms (CFRs) format agreed upon and report forms assembled prior to recruitment. Storage and security at UNC defined.
9. Recruitment fliers, ads and internet messages developed and distributed to key military personnel likely to be recruitment sources.
10. Presentations to military personnel informing them of the study.
11. Telephone screening forms developed and identification of screening personnel.
12. Begin first phases of recruitment.
13. Usual treatment parameters defined in detail and personnel managing subject's headache identified. Schedule of clinical management visits defined. Database developed for recording visits, findings, changes in treatment, medication use and outcomes for entry into research databases as well as the medical record.
14. Randomization protocol finalized.

Months 6-24. Actual Completion: Months 24-48

1. Screening and recruitment of subjects for baseline, randomization, and intervention phases. Each of the three arms of the study will include 4 groups of ten to twelve subjects each with an anticipated drop out of two per group.
2. Weekly research meetings with agenda and minutes.
3. IRB renewal yearly.
4. DSMB meetings (intervals defined) with reports to the IRB and study leadership.
5. Completion of three groups for each arm of the study including all aspects of the project.
6. Data collection, scoring, and entry.
7. Initiation of 3 month follow-up phase. Measures and interview procedures; data collection.
8. Data security reviewed every six months and as necessary.

Months 24-36 Actual Completion: Months 48-72

1. Completion of follow-up phase. Completion of data analyses and project manuals.
2. Presentation at national/international meetings.
3. Publication of data.

3(c). **Accomplishments/Results**

The primary aim of the present study was to examine the efficacy of MBSR on headache-related disability. While no statistically significant group differences were found, possibly due to inadequate power, the results were in the expected directions. Of the three interventions, MBSR was the only program to produce a clinically significant reduction in headache-related disability although the small sample size should be noted. Due to the lack of statistically significant findings and small sample size, Specific Aims 2 & 3 were not investigated. Rather, we conducted exploratory analyses of the influence of demographic and psychological factors on headache disability which showed notable trends. Those who endorsed being non-white, in a partnership, having an income over 20K, mild/moderate PTSD symptoms (compared to severe PTSD), and high perceived stress (compared to low stress) also endorsed clinically significant improvements in headache-related disability. Please see the attached manuscript draft for detailed description of results, discussion, and conclusions.

3(d). **Training Opportunities/Professional Development**

Nothing to report

3(e). **Dissemination of Results**

Two posters were presented at the 2016 annual Military Health System Research Symposium, "Mindfulness Training for Post-traumatic Headache in Active Duty Soldiers and "The Impact of Daily Stress on Military Post-Traumatic Headache Disability". The presentations offered the opportunity to interact with the military community to disseminate results and develop follow-up project ideas/collaborations. Please see "Products" section for full citations.

4. IMPACT

4(a) Principal Discipline

This project offered significant insights as it relates to the principle discipline. While MBSR continues to offer promise as an intervention for PTH, as shown by clinically significant reductions in headache-related disability, there are numerous institutional, patient-related, and practical challenges to successful implementation of a standard 8-week, in-person program in an active duty military population. Based on the knowledge acquired through this experience, we have collaborated with other institutions to adapt the standard MBSR protocol to an abbreviated, technology-based platform, that employs more military-friendly language and context. Doing so may address some of the barriers to care that adversely impacted participation and engagement in the current project.

4(b) Other Disciplines

Nothing to report

4(c) Technology Transfer

Nothing to report

5. CHANGES/PROBLEMS

5(a). Changes in approach

Nothing to report

5(b). Problems and plans to resolve them

1. Personnel Changes. This project was a collaborative effort between UNC-Chapel Hill (UNC) and Womack Army Medical Center (WAMC). WAMC had multiple personnel changes (2 Directors of the Concussion Care Center, 3 Local PIs) which significantly delayed the project timelines. We were unable to secure an on-site coordinator and were assigned a UNC coordinator who had a 3 hour daily round-trip commute to WAMC, making study coordinator retention a challenge. There were 3 changes in coordinators which created delays due to hiring, training, and WAMC/UNC credentialing. Research centers that offer infrastructure, study personnel, and in-house resources would address many of these issues and streamline the research process.

2. Recruitment/Retention. At the time of SOW timeline development, there were no active concussion studies at WAMC. As concussion research activities grew at WAMC, our project competed with local concussion projects which were shorter and more integrated with their on-site, daytime clinical care

at WAMC. Increasing accessibility through remote delivery of abbreviated MBSR protocols may increase feasibility as well as on-site, daytime options for participation.

5(c). **Changes in that impacted expenditures**

Nothing to report

5(d). **Changes in use/care of human subjects**

Nothing to report

5(a). **Changes in approach**

Nothing to report

6. PRODUCTS

1. Mindfulness training for post-traumatic headache in active duty soldiers. **Ford S**, Gaylord S, Mann JD, Suchindran C, Palsson O, Wang R, O'Garo K, Ballantyne J. MHSRS Abstract 16-1234. *TBI Therapeutics: Treatment and Emerging Care* 2016.

2. Impact of daily stress on military post-traumatic headache disability. Ballantyne J, **Ford S**, Gaylord S, O'Garo K, Mann JD, Suchindran C. MHSRS. Abstract 16-1234. *TBI Therapeutics: Treatment and Emerging Care* 2016.

7. CONCLUSION

In spite of challenges involving retention of study participants, this study points toward the potential for MBSR as an adjunctive intervention to reduction of headache-related disability in an active duty military population. Future studies may benefit from modifications to the protocol to enhance retention through more abbreviated, portable, flexible, and accessible programming to meet the busy schedules of active military with PTH.

ABSTRACT

Objective: Post-traumatic headaches (PTH), the most common symptom of mild traumatic brain injury (mTBI), are reported by more than 33% of returning military troops who have sustained a deployment-related concussion. This pilot study reports the findings of a randomized controlled trial (RCT) investigating the efficacy of mindfulness-based stress reduction (MBSR) program compared to a traumatic brain injury/headache education program (Head-EP) and usual care (UC) for active-duty military suffering from chronic post-traumatic headache (PTH) following a mild traumatic brain injury (mTBI). It was hypothesized that MBSR would be a viable treatment approach and that compared to the other interventions, would elicit significant improvement in headache-related disability.

Materials and Methods: RCT methodology was employed and multivariate regression models were conducted on a pre- and post-intervention headache disability measure (Headache Impact Test-6) for a completer sample.

Results: Results of the completer analyses showed no statistically significant changes in headache-related disability among the three interventions. However, trends analyses showed the MBSR program was the only intervention to achieve a clinically significant reduction in headache-related disability when compared to the education and usual care groups (-4.1, -2.2, and -.8, respectively). Patient flow data revealed challenges with participant engagement and retention over the 12-week study period.

Discussion: This study empirically examined MBSR for the treatment of headache-related disability following PTH in active duty military population. Although the small sample size did not provide power to detect statistically significant changes in headache disability, of the three intervention programs, MBSR was the only one to demonstrate clinically significant improvement in headache disability. Future studies may benefit from modifications to the standard MBSR protocol to enhance retention through more abbreviated, portable, flexible, and accessible programming to meet the busy schedules of active military with PTH.

INTRODUCTION

Traumatic brain injury (TBI) has been coined the signature injury of the Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF), with mild TBI (mTBI) being the most prevalent (82%) among active US military service members[1]. Post-traumatic headaches (PTH), the most common symptom of mild traumatic brain injury (mTBI), are reported by more than 33% of returning military troops who have sustained a deployment-related concussion [2]. Compared to nontraumatic headaches, PTH have a higher attack frequency, cause more sick call visits, and has been shown to interfere with duty performance in 37% of cases [2].

While PTH is the most common symptom of mTBI, chronic postconcussive symptoms typically offer complex presentations that can include psychiatric (e.g., PTSD, depression), cognitive (e.g., attention, memory) and physical (e.g., pain, sleep) issues. Comorbid psychiatric conditions, namely PTSD and depression, are common to PTH [3-5] and the strong association between these conditions and PTH outcomes suggests that the presence of these psychiatric illnesses may be a critical factor in the PTH onset [6], intensity [4] and chronification [3]. Thus, identification and treatment of mood disturbance may also be an important and potentially modifiable part of PTH care that may reduce PTH-related disability. Despite the recognition of PTH as a common, debilitating pain condition and its complex, interrelated connection to psychiatric issues, there are few investigations of behavioral treatments for PTH.

Mindfulness based stress reduction (MBSR) is a training and practice-based program designed to enhance awareness through intentional, nonjudgmental attention to present-moment experience. Despite the widespread use of MBSR in academic medical centers that has produced research demonstrating its efficacy as an intervention for a broad spectrum of psychiatric, medical, and pain conditions [7-9], our understanding of the efficacy of MBSR for mTBI is limited. Even less understood is whether MBSR can ameliorate PTH, the cardinal symptom of mTBI. In one pilot study of civilians with mTBI who completed an MBSR program, clinically meaningful improvements in quality of life, perceived self-efficacy, and working memory/attention were noted, however PTH was not measured [10]. A pilot study investigating the efficacy of MBSR for headaches in non-TBI civilians established its safety and feasibility; and while significant improvements in headache frequency or severity were not detected presumably due to inadequate power, MBSR showed a beneficial effect on headache duration, disability, self-efficacy, and mindfulness [11]. With respect to psychiatric status, an emerging literature suggests that MBSR improves depression, PTSD, and quality of life in veterans [12-14]. To our knowledge, no prior published research has examined this treatment approach for active duty soldiers with PTH suffering from the persistent symptoms of mTBI.

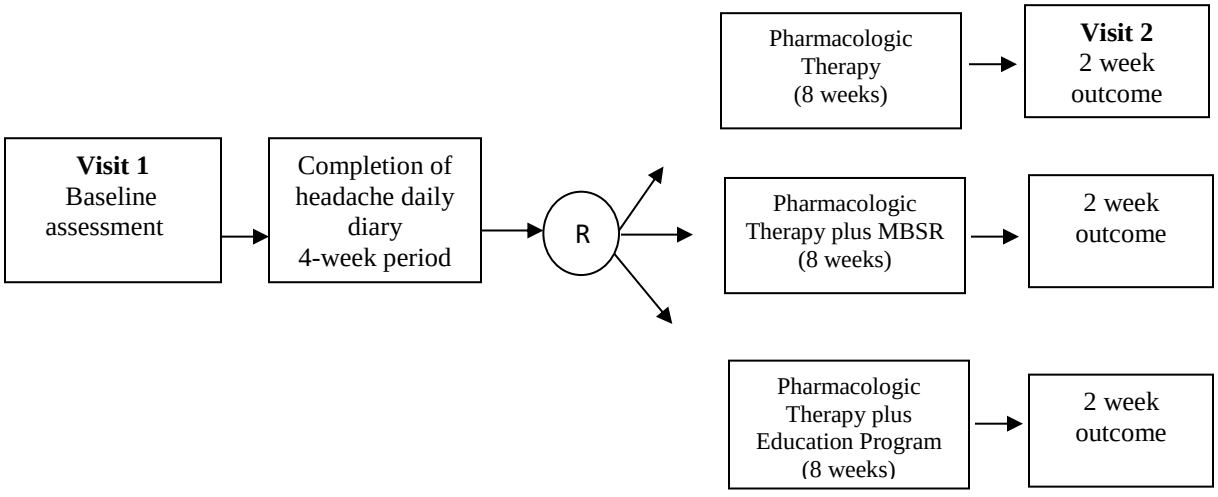
The current study was a randomized, three-arm prospective, behavioral intervention study designed to explore the efficacy of MBSR on the PTH disability and headache activity in active duty soldiers.

MATERIALS AND METHODS

Study Design: This mixed within-between design enabled a pre-post, within-participant comparison of the efficacy of each treatment arm, as well as between-group comparisons. Analyses were conducted using "intention to treat" methods. After an initial 4-week baseline phase of usual headache care only, subjects were randomized to one of three arms: **Arm 1)** Continuation of usual headache care plus participation in an 8-week MBSR program; or **Arm 2)** Continuation of usual headache care plus participation in an 8-week Headache/TBI Educational Program (Head-EP); or **Arm 3)** Continuation of usual headache care only. The design offered reasonably equivalent complementary therapies in terms of time commitment, visit format and intervention procedures for purposes of differentiating between true and perceived placebo effects. See Figure 1 for the Study Flow Diagram. This research was approved by the Institutional Review Boards at the University of North Carolina at Chapel Hill and the Womack Army Medical Center.

Participants and Setting: All participants were recruited from the Concussion Clinic at the Womack Army Medical Center located in Fayetteville, NC. Eligible participants were men and women, 18 years of age and older, with a diagnosis of posttraumatic headache secondary to mTBI, the history extending 3 months or longer with a frequency of 7 or more headache days per month. Participants were excluded if they had 1) a history of or were actively participating in mindfulness training or structured educational interventions; 2) a diagnosis of psychosis or other mental illnesses with psychotic features, 3) history of moderate to severe brain injury, and 4) prior diagnoses that may confound interpretation of test results as determined by the PI. Please see Figure 2 for a CONSORT Flow Diagram.

FIGURE 1: STUDY FLOW DIAGRAM



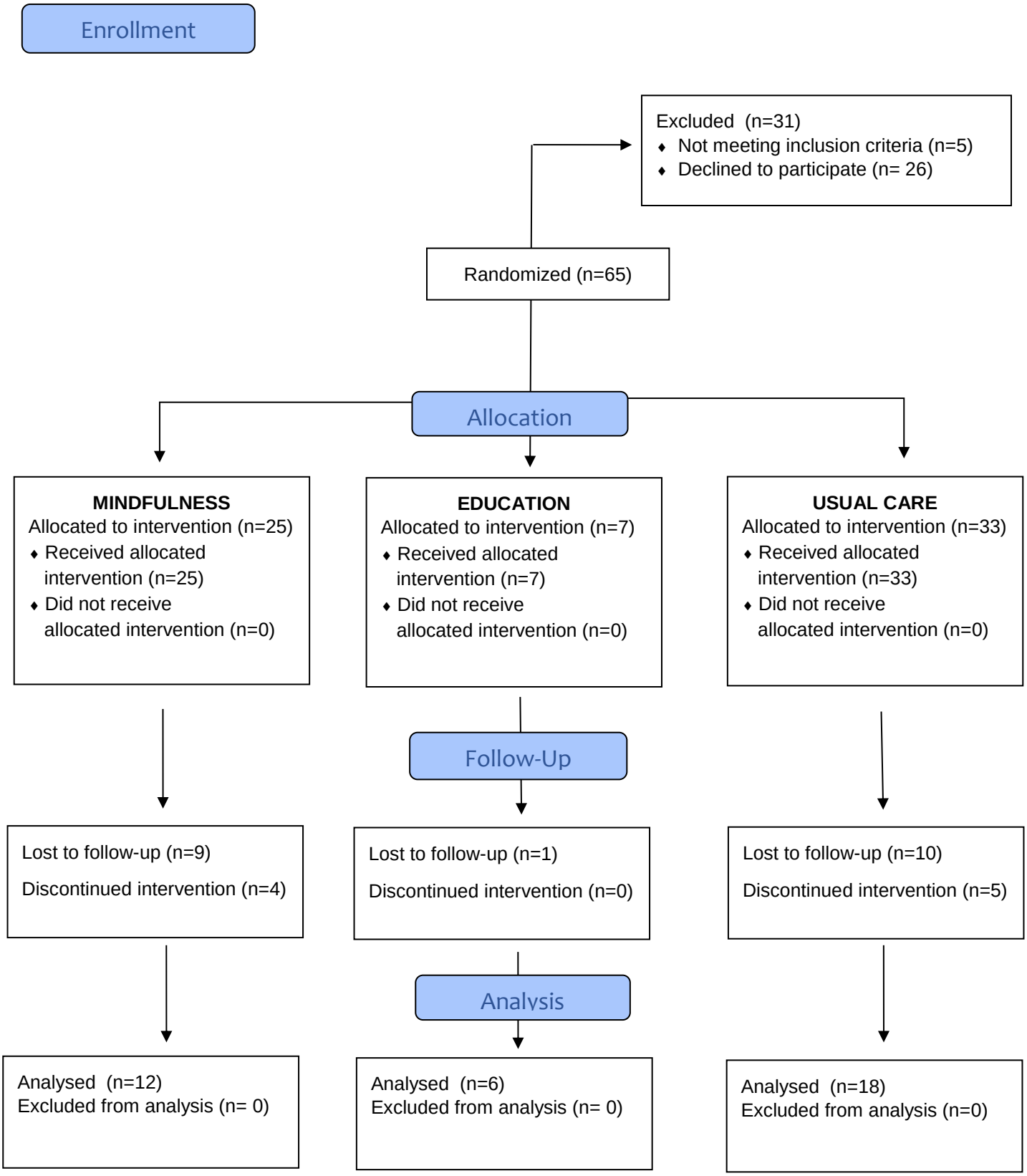
Procedures: All participants expressed willingness to complete baseline self-report inventories, participate in a 4-week baseline period and one of the 8-week interventions, comply with homework assignments, maintain daily documentation of PTH activity, and complete the follow-

up evaluation. After informed consent was obtained, the study neurologist/headache specialist reviewed medical records to confirm that participants met the diagnostic criteria for mTBI and PTH. In addition to a history and physical examination, the baseline assessments included instruments that measure headache characteristics, PTH-related disability, as well as the presence and severity of PTSD, depression, and psychological functions. Baseline data on headache frequency were collected over a 4-week period through web-based, time stamped electronic diaries that captured self-reported headache activity over a 24-hour period.

Participants compliant with baseline data collection were eligible for randomization to one of three treatment arms. Participants continued to complete daily headaches diaries throughout the 8-week intervention period. Measures of headache-related quality of life, PTSD, mood, and psychological attributes were obtained at baseline and upon completion of the 8-week intervention period. The primary endpoint is the reduction of headache-related disability as measured by widely used self-report inventory (HIT-6). Using the electronic headache diary data, headache frequency was calculated as the number of headache hours in a 24-hour period.

Interventions: Throughout the study, all participants received usual headache care by their physician. The MBSR program was facilitated by mindfulness instructors who were trained in the Kabat-Zinn approach for leading mindfulness meditation instruction. The format outlined a version of the Center for Mindfulness MBSR Curriculum Guide was used as the guide for the interventions, which consisted of eight weekly 2-hour sessions plus one 6-hour class held on a Saturday during the second half of the eight-week intervention. HEAD-EP was led by a concussion expert who was not involved in the participants' clinical care. The HEAD-EP intervention was an expansion on the types of educational didactics that occur in the standard care of a mTBI/headache patient and was based on adaptations of educational programs implemented in other TBI/headache group education intervention studies (REF). The HEAD-EP program consisted of 8 sessions. The session durations, face- to-face interactions and homework assignments were designed to parallel the face-to-face time and intervention format used in the MBSR program. This format was selected to control for direct individual subject contact, subject expectations and behavioral involvement, while controlling for the active elements of the mindfulness intervention. Participants who were randomized to UC completed daily diaries and pre-post self-report inventories.

FIGURE 2: CONSORT FLOW DIAGRAM



Materials:

Headache Impact Test (HIT–6). Headache-related disability, the primary outcome variable, was measured using the (HIT–6), the gold standard for quantifying and tracking changes in headache-related functional status. The HIT–6 is a self-administered instrument designed to assess the effect of headache on functional abilities over time based on the frequency and intensity of headache over 30 days [15]. Scores range from 36-84, with a score >60 considered to reflect severe impairment. A difference of 2 points is considered minimally significant and a change of 2.3 points can be considered clinically significant [16].

Headache Frequency. Participants were instructed to maintain a daily record of their headaches using a web-based, time stamped headache diary which could be accessed by cell phone or computer. Headache frequency was determined to be the numbered of headache hours recorded in a 24-hour period.

PTSD Checklist-military version: The PCL-M is a 17-item self-report tool used to screen for PTSD in military populations. Scores range from 17 to 85 and PTSD is indicated by a score of 44 and above. The PCL-M was designed to parallel the diagnostic criteria detailed in "Diagnostic and Statistical Manual of Mental Disorders", 4th edition (DSM-IV)[17].

Beck Depression Inventory-II (BDI-II): The BDI-II is a widely used, 21-item self-report depression screening measure. Each item is rated on a 4-point Likert-type scale ranging from 0 to 3, with higher scores indicating higher levels of depression. Respondents endorsed statements characterizing how they have been feeling over the past 2 weeks. The maximum total score for all 21 items is 63. The BDI-II manual denotes scores of 0 to 13 as minimal depression; scores of 14 to 19 as mild depression; scores of 20 to 28 as moderate depression; and scores of 29 to 63 as severe depression. The psychometric properties are well established across populations.

Perceived Stress Scale (PSS): The PSS is designed to directly measure the degree to which an individual appraises life situations as stressful. This 14-item questionnaire is also widely used in research with healthy individuals as well as subjects with chronic medical, and psychiatric conditions [18-20]. It demonstrated sensitivity to improvements following a six-week behavioral intervention [21].

Statistical Analyses to Test the Primary Hypothesis. The primary hypothesis of the study is that MBSR would improve headache-related disability (as measured by HIT-6) more than educational and usual care interventions. Our preliminary analysis used the complete cases data with the available post randomization HIT-6 data. The intention-to-treat analysis assumption was also invoked because the post randomization HIT-6 was not always measured immediately after completion of the 12-week interventions. Therefore, the analytic approach taken here is to test the hypothesis using the complete case analysis. In addition, we used the multiple imputation (MI) approach which is known to reduce bias and increase efficiency of the parameter estimates compared to procedures compared to the complete case data approach.

We used a cluster randomization. The planned implementation was implemented as follows. It was estimated that we would have 12 cohorts of 10-12 subjects in each cohort. The randomization

procedure prior to the beginning of the study allocated each cohort into one of the three treatment groups. Under the scheme, each cohort was allocated in balance in the sample. However, due to difficulty in recruitment and dropout rates, the project did not get the required balance. At the time of stoppage, the study had recruited and retained very few people in the education group (e.g., failed to do daily headache diaries). Therefore, the analyses presented here are based on the unbalanced data.

RESULTS

Sample Characteristics. Ninety-six participants were consented and enrolled. The first wave of data collection started immediately after receiving the consent. The data collected at this time included demographic factors, clinical factors such as PTSD(PCL-M), stress (PSS-14), and depression (BDI-II). The participants were asked to complete daily electronic headache diaries providing information on number of headache hours per day and number of severe headache hours per day. In order to be eligible to randomized to various treatment groups, subjects were required to complete 80% of diaries over a four-week period, or "baseline period". At the end of the baseline period, all those who have provided all the required data are randomized to the three treatment groups. The study period following randomization is referred as the "post randomization period".

Among 96 participants who provided consent, 31 participants (32.3%) of subjects decided not to participate or failed to keep the required data keeping during the baseline period. Of the 65 participants who were randomized, 36 (55.9%) of the participants completed the study. The three groups did not differ significantly on the sex, race, marital status, education, and income. See Table 1 for the breakdown of demographics by study arms.

Complete case data analysis of HIT-6 scores. We first conducted a preliminary test of equality of the HIT-6 outcome data among the three treatment groups using only complete cases. Complete case data contained with 36 observations with only 6 participants in the education group. The mindfulness group and usual care groups respectively contained 12 and 18 observations.

Table 2 shows the mean and standard deviation of the baseline and outcome HIT-6 values and their differences. First, we conducted a global test of equality of the outcome HIT-6 values among the three treatment groups adjusted for the baseline HIT-6. The corresponding test statistics was not statistically significant [$F(3,33)$, p value = 0.4805)]. Similarly, a second global test of the equality of differences (baseline and outcome HIT-6 among the three groups) was not statistically significant and pairwise tests of group means were therefore not conducted. In the MBSR group, this means that a reduction in HIT-6 scores from 62.4 at baseline to 58.3 outcome (-4.1 points) was not statistically significant compared to the other pairwise differences. However, the MBSR program was the only intervention to achieve a clinically significant reduction in headache-related disability when compared to the education and usual care group (-4.1, -2.2, and -.8, respectively). Figure 3 illustrates the reduction in HIT-6 scores across the three treatment conditions.

TABLE 1: STUDY ARMS BY DEMOGRAPHICS

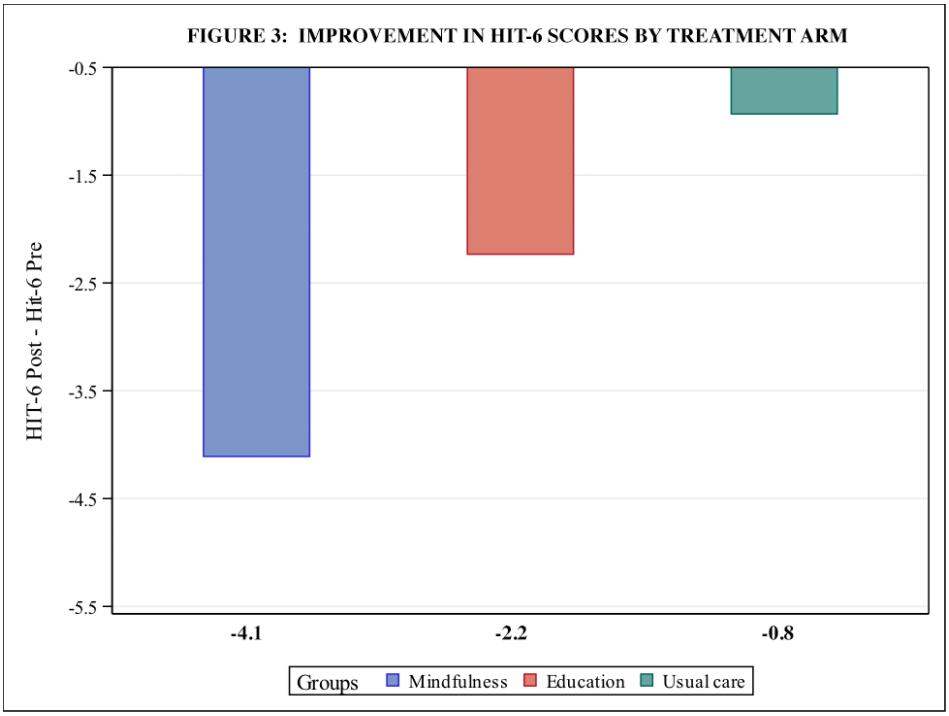
		Study arm	N	Total (%)
Sex	Male	1	23	56 (86.15)
		2	6	
		3	27	
	Female	1	2	9 (13.85)
		2	1	
		3	6	
Race	White	1	18	36 (55.38)
		2	4	
		3	14	
	Non White	1	7	29 (44.62)
		2	3	
		3	19	
Marital Status	Partnered	1	15	47 (72.31)
		2	6	
		3	26	
	Non P	1	10	18 (27.69)
		2	1	
		3	7	
Education	Less than Col. Degree	1	18	47 (72.31)
		2	5	
		3	24	
	At least Col. Degree	1	7	18 (27.69)
		2	2	
		3	9	
Income	<= 20k	1	9	24 (36.92)
		2	3	
		3	12	
	21-40k	1	8	22 (33.85)
		2	3	
		3	11	
	>=41 k	1	6	13 (20.00)
		2	1	
		3	6	

TABLE 2: BASELINE HIT-6, OUTCOME HIT-6, AND MEAN DIFFERENCES BY TREATMENT GROUP (COMPLETE CASE DATA)

Variable	Mindfulness(1)		Education (2)		Usual care (3)	
	Sample size	Mean (Sd)	Sample Size	Mean(sd)	Sample size	Mean (sd)
Hit6(Baseline)	12	62.41(5.7)	6	65.83(4.4)	18	62.55((5.5)
Hit6 (Outcome)	12	58.33(8.57)	6	63.67(10.4)	18	61.78(4.96)
Difference	12	-4.08(9.6)	6	-2.17(10.9)	18	-0.78(4.9)

** Comparing the group difference in outcome HIT 6 adjusting for baseline HIT 6 gives a test statistic with F value of 0.75 with degrees freedom (2. 33). P value 0.4805 (NS)

*** Comparing the pre-post difference among the three treatment arms gives a test statistic value of F 0.64 with degrees of freedom (2,33) with P value 0.5367(NS)



We extended the analysis to include a number of control variables in a multivariable linear regression model adding a number of control variables. Because the education arm group had six observations, for the multivariable regression model the treatment group was treated as binary: mindfulness and other (i.e., education and usual care groups combined). We examined age, sex, race (white vs. non-white), marital status (partnered or non-partnered), and education (high school vs. at least some college). The regression analysis also accounted for clusters of waves to which each participant was recruited. The results showed that, after controlling for selected demographic characteristics, the outcome HIT-6 differed between the two treatment groups (mindfulness vs.

others). The regression coefficient -5.9 shows the tendency to further reduce headache-related disability in the mindfulness group. Table 3 shows the results from the complete case analysis.

TABLE 3: REGRESSION ANALYSIS OF OUTCOME HIT-6 (COMPLETE CASE DATA)

Parameter	Estimate	Std. Error	95% confidence Interval
Intercept	35.12	17.01	1.78, 68.47
HIT6-Pre	0.47	0.31	-0.14, 1.09
Mindfulness Vs Other	-5.92	3.85	-13.48, 1.63
White Vs Non-White	1.63	3.06	-4.36, 7.62
Partnered Vs Non-Partnered	-6.05	3.63	-13.16, 1.06
Some college Vs Less than college	-2.38	4.08	-10.37, 5.61
Male Vs Female	0.74	6.11	-11.23, 12.71
Age	0.05	0.20	-0.34, 0.44

Multiple Imputation approach to analyze the HIT-6 data. Under the assumption that the dropouts during the study follow a missing at random pattern, we conducted multiple imputations using the MICE (Multiple imputation by Chained Equations) approach to analyze the data. We created 20 data sets where missing values for age and HIT-6 post intervention were imputed using a regression with predictive mean matching method. The following covariates without missingness were included in the imputation model: treatment arms, HIT-6 pre-intervention, age, race, marital status, sex, education and all two-way interactions between treatment arms and demographics. We obtained parameter estimates and standard errors were obtained. Table 4 shows the results obtained after combining estimates from the 20 imputed data sets. Compared to complete case data analysis, the imputed data analysis showed a smaller treatment affect. (-5.92 for complete case vs. -3.81 for imputed data). In both cases the parameter estimates did not reach statistical significance.

TABLE 4: REGRESSION ANALYSIS OF OUTCOME HIT-6 (IMPUTED DATA)

Parameter	Estimate	Std. Error	95% confidence Interval
Intercept	27.47	11.37	5.18,49.77
HIT6-Pre	0.56	0.18	0.21, 0.90
Mindfulness Vs Other	-3.81	2.76	-9.22, 1.60
White Vs Non-White	1.87	1.91	-1.87, 5.61
Partnered Vs Non-Partnered	-2.74	2.48	-7.60, 2.12
Some college Vs Less than college	-1.85	3.21	-8.15, 4.44
Male Vs Female	0.38	5.03	-9.47, 10.23
Age	0.02	0.14	-0.25, 0.28

Influence of Demographic and Psychological Factors on Headache Disability. We conducted exploratory analyses of the effect of demographic and psychological factors on improvement in HIT-6 outcomes. While not statistically significant, participants who were Non-White, married,

earned over 20K annual income, endorsed low/moderate PTSD, and high stress showed clinically significant improvement in headache disability. Comparison of changes in HIT-6 scores between participants with mild/moderate depression and those with severe depression was not possible because none of the 12 severely depressed participants completed the study. Table 5 for shows the pre-post differences by treatment arms, demographics and psychological factors. The enrolled participants recorded 3145 diary hours. Analyses of headache frequency showed no statistically or clinically significant changes by intervention, demographic, or psychological factors

TABLE 5: PRE-POST DIFFERENCES IN HIT-6 SCORES BY DEMOGRAPHICS AND PSYCHOLOGICAL STATUS

	HIT-6 pre-			HIT-6 post-			Difference
	N	Mean	Std	N	Mean	Std	(post–pre)
Mindfulness	25	63.52	5.97	12	58.33	8.57	-5.19
Education	7	65.57	4.12	6	63.67	10.37	-1.9
Usual care	33	63.64	5.97	18	61.78	7.29	-1.86
Male	77	62.95	5.83	31	60.48	6.68	-2.47
Female	11	66.09	5.26	5	63.80	15.82	-2.29
White	50	63.12	5.56	24	61.21	8.52	-1.91
Non White	38	63.66	6.20	12	60.42	8.05	-3.24
Partnered	64	63.08	6.13	26	59.73	9.16	-3.35
Non Partnered	24	64.08	4.93	10	64.10	4.12	0.02
At least College	25	64.32	6.00	12	61.00	7.16	-3.32
Less than College	63	62.97	5.75	24	60.92	8.90	-2.05
Less than 20 K	33	63.33	5.38	13	62.08	9.65	-1.25
20-40 K	29	63.86	5.81	13	60.77	9.49	-3.09
More than 40 K	18	63.06	4.32	9	59.44	4.36	-3.62
PCL-M Low/Mod	28	61.71	5.62	10	59.00	7.35	-2.71
PCL-M High	26	65.50	5.45	7	64.14	5.49	-1.36
Rumination Low	23	62.17	5.04	10	60.00	7.57	-2.17
Rumination High	55	62.58	5.80	25	60.88	8.52	-1.7
BDI-II Mild/Mod	69	62.67	5.68	21	60.14	6.68	-2.53
BDI-II Severe	12	67.75	3.98	0	--	--	--
PSS Low/Mod	13	61.69	7.23	3	60.00	3.46	-1.69
PSS High	67	63.55	5.43	19	60.42	7.03	-3.13

Summary of headache disability (HIT-6). A complete case analysis of HIT-6 data showed no significant effect among the three treatment groups. A comparison of post HIT-6 values adjusted for pre HIT-6 values did not show any statistical significance among the three treatment groups (mindfulness, education and usual care). Further comparisons of the mindfulness group with the education group also did not show any statistically significant difference. The analysis was further extended to test the difference in the post HIT-6 among the two treatments (mindfulness vs. others) using imputed data. This analysis did not show any statistical difference in the treatment effects when controlled for a number of demographic factors.

Analyses of Dropout Rates: Often clinical trials with multiple scheduled visits face patient dropouts, which usually results in incomplete data for those who dropped out. Incomplete data pose a big challenge in data analysis. The presence of dropouts can result in biased effect size estimates as well as producing inefficient estimation of effect size. We examined the dropout rates in the present study and briefly report the approach we took in adjusting for dropouts in the effect size estimation. We first examined the overall dropout rates. Special attention was given to the timing of dropouts followed by examining the association of dropout rates and selected known factors that influence patient dropouts. These impact factors include demographic factors such as age, sex, race, marital status, education and income. In addition to the demographic factors, we also looked at the association of dropout rate with clinical variables such as depression, stress, and PTSD. In addition, we conducted a post-hoc analysis of the dropout rates by the treatment groups. We used a multiple imputation (MI) approach in analyzing the data, making a key assumption that the data are missing at random. This assumption states that the missingness may depend on a set of observed covariates, but does not depend on the outcomes in the study.

The results from dropout analysis are presented in Tables 6-9. A detailed analysis of the dropout rates by demographic factors (age, sex, race, marital status, education, and income) showed no statistically significant differences in dropout rate across the three periods (baseline, post-randomization to completion and completion), however noteworthy trends were evident. For example, that average age of those who completed study was 33.0, whereas those who dropped out after randomization was 31 suggesting younger age of dropouts in the post randomization period. Proportion completed the study was higher for females than males (45.4 % vs. 39.2 %), Whites than non-whites (47% vs. 43%), and participants with post-high school education compared to high school education (46.2 % vs. 38.0%). Participants who responded to follow-up inquiry regarding reasons for dropout stated they were too busy (44%), had conflicting personal obligations (24%), or were deploying/relocating (42%).

TABLE 6: DROPOUT RATES DURING THE STUDY (N=96)

	N(%)
Baseline to randomization	31 (32.29)
Randomization to Post	29 (30.21)
Completed	36 (37.50)

The analysis of headache and psychiatric factors also showed no statistical significance among dropouts and completers. However, several trends were apparent. The baseline PTSD score for completers was lower compared to post randomization dropouts (44.3 vs. 47.2). Depression scores were lower for completers compared to post randomization dropouts (15.8 vs. 18.2). Stress ratings did not exhibit any significant statistical difference between completers and post randomization dropouts. A post hoc analysis also showed that the dropout rates among the three study groups did not statistically differ.

TABLE 7: DROPOUTS BY STUDY ARMS

Missingness	Study Arms			Total	P
	1	2	3		
Missing	13	1	15	29	0.68
Non Missing	12	6	18	36	
Total	25	7	33	65	

TABLE 8: DROPOUTS BY AGE BASELINE HIT-6, PCL-M, PSS-14 and BDI-II
(N is the number of participants with available data)

	Dropouts	N	Mean(Std)	K-W Chi-Sq	P
Age	Baseline to randomization	20	33.53 (8.30)	1.18	0.55
	Randomization to Post	21	31.03 (7.44)		
	Completed	31	32.96 (9.50)		
Hit6-Pre	Baseline to randomization	24	62.04 (5.81)	1.36	0.51
	Randomization to Post	29	64.72 (6.09)		
	Completed	36	63.06 (5.45)		
PCL-M(PTSD)	Baseline to randomization	19	40.79 (13.77)	1.21	0.55
	Randomization to Post	18	47.17 (16.72)		
	Completed	17	44.29 (13.19)		
PSS-14 (Stress)	Baseline to randomization	19	29.84 (3.62)	0.83	0.66
	Randomization to Post	26	30.50 (4.81)		
	Completed	35	30.74 (4.18)		
BDI-II (Depression)	Baseline to randomization	18	16.17 (10.14)	1.36	0.51
	Randomization to Post	28	18.25 (9.87)		
	Completed	35	15.83 (9.57)		

TABLE 9: RETENTION RATES BY TIMING OF DROPOUTS AND DEMOGRAPHICS

	N	Baseline period	Post randomization	Completion	P
Male	79	29.1	31.6	39.2	0.53
Female	11	18.2	36.4	45.5	
White	51	29.4	23.5	47.1	
Non- White	38	23.7	44.7	31.6	0.1
Partnered	64	26.6	32.8	40.6	
Non Partnered	25	28.0	32.0	40.0	0.9
At least College	26	30.8	23.1	46.2	
Less than College	63	25.4	36.5	38.1	0.3
<=20k	33	27.3	33.3	39.4	
21-40k	29	24.1	31.0	44.8	0.69
>=41k	18	27.8	22.2	50.0	

DISCUSSION

This study empirically examined the efficacy of an MBSR program for the treatment of headache-related disability following mTBI. Clinically, this research question has important implications since a standard 8-week MBSR program has shown efficacy for headaches, headache-related psychological health, and psychiatric conditions [12, 14, 22-25] and thus holds promise as a behavioral intervention for soldiers who experience headache-related disability following a mTBI.

The primary aim of the present study was to examine the efficacy of MBSR on PTH disability, using the gold standard measure of headache disability, the HIT-6. While no statistically significant group differences were found, possibly due to inadequate power, the results were in the expected directions. Despite the limitations, the data offered important information about participants engaged in a standardized MBSR program. Of the three interventions, MBSR was the only program to produce a clinically significant reduction in headache-related disability although the small sample size and variance should be noted. Exploratory analyses of the influence of demographic and psychological factors on headache disability showed notable trends. Those who endorsed being non-white, in a partnership, having an income over 20K, mild/moderate PTSD symptoms, and high perceived stress also had clinically significant improvements in headache-related disability.

The drop-out rate found in the current study is similar to other investigations of a standard, in-person, 8-week MBSR program in military populations [26, 27]. In a small feasibility study of MBSR for active duty females with chronic pelvic pain, none of the 11 participants completed all training sessions although 4 women (36%) attended most sessions, regular home practice, and

diary completion of at least 4 days a week [26]. Reasons for withdrawal included deployment, family care problems, and work issues. While most participants in the current study were lost to follow-up, the challenges reported by those who dropped out were lack of time, conflicting evening obligations, family responsibilities, and relocation/deployment. Other challenges to participation included institutional requirements that all interventions be offered during off-duty hours (evening/weekends) and off-campus.

That the dropout rate for all participants was comparable for pre- and post-randomization periods suggests that factors not associated with treatment may have influenced participation. Further supporting this notion is the modest increase in attrition in MBSR program compared to the usual care program (52% vs. 45%) suggesting that the additional demands of a weekly 2-hour class and daily homework assignments did not appear to have a large impact on dropout rates. In comparison, the educational program had an 86% completion rate; however the small and unbalanced sample precludes speculation regarding reasons for the difference in retention rate.

Exploratory analyses showed that compared to non-completers, study completers trended toward being female, older, Caucasian, higher income bracket, and have completed at least some post high school education. In addition, completers endorsed lower baseline headache-related disability, depression, and PTSD. Taken together, these trends may indicate that mood, headache, and some demographic factors often associated with higher functional status were important to successful participation and completion of the interventions, regardless of the program type. Future research may target vulnerable populations for additional program support, such as increased coordinator contact, to maximize their chances of successful program participation and completion. Compared to pharmacological approaches, the salutary effects of behavioral interventions require a more significant investment of effort over a longer period of time. That none of the severely depressed participants remained in the study was notable, underscoring the possible benefits for supportive psychoeducational counseling, encouragement, and expectation setting to improve retention for participants struggling with more severe psychiatric symptoms.

The results of this study must be interpreted with caution due to several limitations. First, due to the small sample size it is possible that lack of statistically significant change is due to lack of power rather than lack of treatment efficacy. Second, different instructors were used for the MBSR and educational programs, raising the possibility that instructor-related variables, such as likability or perceived competency, influenced outcomes. In addition, implementation of the standard 8-week in-person MBSR intervention; rigorous study protocol (e.g., daily diaries, homework); and evening/weekend programming that has been successfully utilized in civilian and veteran populations may not be practical in an active duty military population. The high dropout rates suggest that the intervention should be better adapted to the specific needs of these soldiers. Considerable options for a better adaptation are: employing telehealth technology to increase accessibility from different locations and at different times; developing more abbreviated weekly sessions; and incorporating individualized support/psychoeducation to support those at risk for drop-out (i.e., male, minority, lack of post-high school education, and severe depression/PTSD).

CONCLUSION

In spite of challenges involving retention of study participants, this study points toward the potential for MBSR as an adjunctive intervention to reduction of headache-related disability in an active duty military population. Future studies may benefit from modifications to the protocol to enhance retention through more abbreviated, portable, flexible, and accessible programming to meet the busy schedules of active military with PTH.

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