FULL STUDY PROTOCOL,

STATISTICAL ANALYSIS PLAN (SAP)

& INFORMED CONSENT FORMS (ICF)

"Effect of Mindfulness Training in Chronic Ankle Instability among Collegiate Athletes"

Ethical approval: FHLS 15/2017

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Table of Contents

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2. Introduction

2.1 Background & Aims

Chronic ankle instability (CAI) is the most common musculoskeletal injury in sports and the rate of CAI accounts for 85% of ankle injuries. It has been estimated that 23,000 ankle sprains occur each day in the United States, representing approximately 1 sprain per 10,000 people per day and nearly one in five ankle injuries result in chronic symptoms. Numerous researchers applied mindfulness for improving the performance of various sports such as table tennis, shooting, cricket, archery, golf, swimming, and cycling. Since many of the players do not possess effective pain coping skills, they are at risk for lifelong impairment of their emotional, social, and physical functioning. Mindfulness-centered interventions may well serve to mitigate pain-related disability. Training in mindfulness meditation improves anxiety, depression, stress, and cognition. Mindfulness-related health benefits are associated with enhancements in cognitive control, emotion regulation, positive mood, and acceptance, each of which have been associated with pain modulation. Since mindfulness has been proven effective in managing various health disorders and in enhancing sports performance, our study aims to apply the mindfulness approach in rehabilitating the most common sports injury, CAI. The improvement in CAI due to the mindfulness approach will be assessed by the improvement in pain response through the Cumberland ankle instability tool, Functional ankle disability index (FADI), Visual analog scale (VAS), Brief Pain Inventory (BPI), Y-balance test, Mindfulness attention awareness score (MAAS), Oxford Happiness Questionnaire (OHQ) quantitative electroencephalography (Q-EEG). This study finding will be useful in assessing the effectiveness of mindfulness in rehabilitating CAI and identify the correlation of CAI pain response with VAS & BPI, quantitative electroencephalography - Q-EEG. In this clinical trial, we wish to use noninvasive methods such as quantitative EEG (electroencephalogram) to find the brainwave patterns during the different stages of

mindfulness intervention (pre and post). The outcome of this study will eventually lead to the identification of a better assessment method to indicate the pain response for the appropriate physiotherapy management. The application of mindfulness technique in CAI management and the usage of Q- EEG to assess the pain response in chronic ankle injury athletes are the novel approaches of this research study.

2.2 Background Literature Review

Chronic ankle pain can affect all age groups, ranging from young athletes to elderly patients with degenerative joint and soft-tissue disorders. As nearly one in five ankle injuries result in chronic symptoms[1]. Approximately 60 percent of the injuries occurred in players younger than 20 years of age. The majority of injuries (91.5 percent) were categorized as mild overuse injury and mostly involved the knee and ankle. The majority of the injuries were diagnosed in younger players and occurred during training/practice sessions[2]. Athletes who sustained an injury are potentially at the risk of developing major depressive and posttraumatic stress disorders. The injured athletes suffer from depression 6 times more in chances as compared to the non-injured athletes[3]. Besides, the injured athletes also exhibit greater anxiety and lower self-esteem. In chronic sports injuries, the athletes are more likely to become depressed than the counterpart. Practicing in elite level sports offers an entirely different set of circumstances, representing a high-pressure career replicate with stressors and constraints that tend to cause injuries to the athletes[4].

In accordance to Putukian, (2016) stress is an important antecedent to injuries and can play a role in the response to, rehabilitation and return to play after injury[5]. The psychological response to injury can trigger and/or unmask mental health issues including depression and suicidal ideation, anxiety, disordered eating, and substance use/abuse. There are barriers to mental health treatment in athletes. They often consider seeking help as a sign of weakness, feeling that they should be able to 'push through' psychological obstacles as they do physical activities. Athletes may not have developed healthy coping behaviors making response to injury. Shivarathre et al., (2014) showed a significant association of anxiety, depression, and neuroticism in patients presenting with chronic foot and ankle pain[6].

Mindfulness meditation has been found to improve a wide spectrum of cognitive and health outcomes. Training in mindfulness meditation improves anxiety, depression, stress, and cognition. Mindfulness-related health benefits are associated with enhancements in cognitive control, emotion regulation, positive mood, and acceptance, each of which have been associated with pain modulation. A pilot study by Schmidt et al., (2015) using 8-week mindfulness-based stress reduction (MBSR) program on a sample of low back pain patients was conducted in order to assess the feasibility and effectiveness of the intervention as well as changes in an EEG pattern called thalamocortical dysrhythmia which is associated with chronic pain[7]. For a full MBSR course, it can take up to eight weeks, with weekly meetings that last for about three hours and daily practice of about an hour[8]. This can be difficult to adhere to especially in the current fast-paced lifestyle of young people[9]. With due consideration with participants' compliance, the mindfulness intervention practice of the present study has been modified to 3- min video assisted mindfulness deep breathing. Furthermore, the follow up of participants' home practices will be monitored with the use of a smartphone app which has the facility to send reminders as text messages to fill in the

practice diaries or online portals to record the frequency of home practice of our intervention. We wish to apply the video assisted mindful deep breathing combined with standard physiotherapy to find the effectiveness of the interventions in attention process to reduce the incidence of reoccurrence of chronic ankle instability.

3 Study Protocol

3.1 Research Design Outline

The study aims to perform a randomized control trial on CAI participants in INTI physiotherapy centre and compare with healthy controls as a casual comparative study

Study 1 (Formerly titled "Effect of short duration video assisted mindful deep breathing among collegiate athletes with chronic ankle instability– a Randomised Control Trial") involves participants with chronic ankle instability by using the Cumberland Ankle Instability Tool (CAIT)[10], if the score was ≤27 in the CAIT tool over 30 by fulfilling the inclusion criteria.

Study 2 is a causal comparative study, which involves age matched healthy collegiate athlete from local university and compared them with the baseline parameters of Study 1.

The proposed study designs are all investigator blinded in the randomized control trials (Study 1). Participants only be involved in Study 1 and baseline measurements are compared with Study 2.

3.2 Participants

Study 1 and 2

University students those who involved in collegial sports with chronic ankle instability and without chronic ankle instability/musculoskeletal injuries from INTI International University at Malaysia will be eligible to participate in this study.

Study investigators will not be eligible to participate.

Participants randomized to experimental group in the study 1 will require a personal android support hand phone to the install the VAMDB from the google app store to participate.

3.3Recruitment

Study 1

All participants with chronic ankle instability (CAI) attending the INTI physiotherapy centre will be enrolled in the study at Phase 1. The participation information and consent sheet will be distributed which details including inclusion and exclusion criteria. Interested CAI participants will be invited to undergo baseline assessments (pain – Visual analog score (VAS), Brief pain inventory (BPI); Balance – Cumberland ankle instability tool (CAIT), functional ankle disability index (FADI) and Y-balance test; psychology – mindfulness attention awareness score (MAAS) and oxford happiness questionnaire (OHQ); quantitative EEG) with scheduled appointments.

All participants will have to return a signed consent form to the physiotherapy centre officer to random allocation to a study group.

Study 2

All participants without chronic ankle instability (CAI)/ musculoskeletal injuries will be invited by flyers and sending an invitation to University sports club. The participation information and consent sheet will be distributed which details including inclusion and exclusion criteria. Interested CAI participants will be invited to undergo baseline

assessments (Balance – Cumberland ankle instability tool, functional ankle disability index; psychology – mindfulness attention awareness score and oxford happiness questionnaire; quantitative EEG) with scheduled appointments. All participants will have to return a signed consent form to physiotherapy centre officer for allocation to a study group

3.4 Randomization

Collegiate athletes with CAI who consent to participate will be randomly allocated (within their study) to one of two groups (at a ratio of 1:1): the intervention, the standard physiotherapy, and short duration video assisted mindful deep breathing + standard physiotherapy. Whereas the participants without CAI (healthy age matched control) will be allocated to group 3 as healthy controls.

Computer randomisation (http://www.graphpad.com/quickcalcs/index.cfm) and concealed envelopes will be used for CAI participants.

Participants will be allocated a unique identification number, and this will be recorded against their identification number allocation in an electronic database. This will be done by the INTI physiotherapy centre maintenance officer to ensure the investigators remain blinded.

3.5 Administration

Study 1

Participants allocated to experimental and experimental control group will be given the appropriate access for 12 weeks (instructions provided in the study envelope). Participants will be encouraged to attend the regular appointments for 5 times a week for 6 weeks intervention and follow up (week12) in INTI international university physiotherapy centre. At

the end of week 3, end of week 6 and end of week 12 instructed to participate in post intervention assessments the duration of waiting time and assessment time will be clearly stated under the guidelines.

Study 2

Participants allocated to healthy control group will be given the appropriate access for baseline assessment (instructions provided in the study envelope)

3.6 Assessment & Outcomes Measures

Study 1

Chronic ankle Instability (CAI) participants will be assessed for:

1. Primary outcomes

- Cumberland Ankle Instability Tool (CAIT)
    - Ankle stability will be assessed by validated 9-item Questionnaire, to find the chronic ankle disability score among participants and to recruit in the study if the score was ≤27 in the CAIT tool over 30.

- Y-balance test (YBT)
    - The dynamic balance of the participants will be assessed using reliable and validated the Y balance test (YBT) by measuring the distance in anterior, posterolateral, and posteromedial directions.
- Visual analog scale (VAS)
    - CAI participants pain intensity will be record by self-reported pain intensity on a 10 cm line to point out the pain level. The point at 0 cm represents "no pain" and 10 cm represents "worst pain".
- Brief Pain Inventory (BPI)

- Besides VAS, pain intensity and pain interference will be recorded using 4-items (worst pain, least pain, average pain, and pain right now) to measure the pain intensity, and 7 -items (general activity, mood, walking, normal work, relations, sleep, enjoyment of life) to assess the pain interference. The participants will be instructed to report the pain intensity from 0 (no pain) to 10 (as pain bad as you can imagine). Similarly, the pain interference is recorded from 0 (does not interfere) to 10 (completely interferes)

- Mindful Attention Awareness Scale (MAAS)
    - CAI participants will be assessed by 15-item questionnaire to identify the participants' mindfulness level during the ankle instability.
- Oxford Happiness Questionnaire (OHQ)
    - Happiness level of CAI participants will be assessed using the Oxford Happiness Questionnaire (OHQ), which consists of a 29-item questionnaire.
- Functional ankle disability index (FADI)
    - CAI participants will be asked to complete 34-item questionnaire used to check the participant's general daily activity and sports specific functions for physical function and disability.

2. Secondary outcomes

- Non-invasive wireless electroencephalogram (EEG)
    - EEG will be used at 14 positions: AF3, AF4, F3, F4, F7, F8, FC5, FC6, P7, P8, T7, T8, O1, and O2. The EEG recordings of the CAI participants will be collected between 9 and 12 hours in the morning to reduce participants sleeping artifacts and to exclude the EEG from the influence of circadian variables. The EEG recordings will be recorded in eyes closed and eyes

open for 2mins.

The time commitment required of participants for assessment will be approximately 60 mins.

Study 2

Healthy control participants will be assessed for:

1. Primary outcomes

- Cumberland Ankle Instability Tool (CAIT)
    - Ankle stability will be assessed by validated 9-item Questionnaire, among participants and to recruit in the study if the score was >27 in the CAIT tool over 30.

- Functional ankle disability index (FADI)
    - Participants will be asked to complete 34-item questionnaire used to check the participant's general daily activity and sports specific functions for physical function.
- Mindful Attention Awareness Scale (MAAS)
    - Participants will be assessed by 15-item questionnaire to know the mindfulness attention level.
- Oxford Happiness Questionnaire (OHQ)
    - Happiness level of participants will be assessed using the Oxford Happiness Questionnaire (OHQ), which consists of a 29-item questionnaire.

2. Secondary outcomes

- Non-invasive wireless electroencephalogram (EEG)

- EEG will be used at 14 positions: AF3, AF4, F3, F4, F7, F8, FC5, FC6, P7, P8, T7, T8, O1, and O2. The EEG recordings of the participants will be collected between 9 and 12 hours in the morning to reduce participants sleeping artifacts and to exclude the EEG from the influence of circadian variables. The EEG recordings will berecorded in eyes closed and eyes open for 2mins.

The time commitment required of participants for assessment will be approximately 45 mins.

3.7 Sample Size

Study 1

G*power was utilized for sample size calculation with equal group sizes (i.e ratio of groups 1:1). A total of 36 participants with CAI (i.e. 18 in each group) to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.95. The Type I error probability associated with this test of this null hypothesis is 0.05[11].

- Assuming a total drop-out rate of 10%, we will recruit 20 subjects for each group, i.e. 20 experimental and 20 experimental control group.

Study 2

A total of 20 participants without CAI will be recruited and compared with the age matched CAI participants in the study 1.

4. Statistical Analysis Plan (SAP)

All Studies

Descriptive and inferential statistics will be used. Normally distributed data will be presented by mean and standard deviation (SD) and non-normally distributed data will be presented by median and interquartile range. Categorical data will be presented using percentages. SPSS (version 22.0) will be used for all statistical analyses.

4.1 Primary Outcomes

Study 1

The primary analyses will compare: (1) experimental vs experimental control group guidelines on their mean and standard deviation: (i) pain score (VAS & BPI), (ii) balance scores (CAIT &FADI), (iii) mindful attention (MAAS), and (iv) happiness scores (OHQ). Comparisons will be made using an unpaired t-test or a Mann-Whitney test for parametric and non-parametric data, respectively. P-values <0.05 will be considered statistically significant.

2*4-Repeated measures analysis of variance (ANOVA) will be performed to test the significant difference in the intervention effects between the time intervals (baseline, mid-intervention, post-intervention, and follow-up) and also between the two groups (Experimental control group and Experimental Group).

The post–hoc analysis will be conducted to investigate significant effect within the time intervals. Condition on if the sphericity violated (p-value < 0.05), the Greenhouse- Geisser estimated correction will be applied.

Effect sizes for will be calculated using Cohen's d (*d*) with 95% confidence intervals (95%CI) using the 'effsize' package[12]. Effect sizes will be considered small if $0.2 \leq d < 0.5$, medium if $0.5 \leq d < 0.8$, and large if $d \geq 0.8$.

Study 2

The primary analyses will compare: (1) CAI participants vs healthy control group guidelines on their mean and standard deviation: (i) balance scores (CAIT &FADI) (ii), mindful attention (MAAS) and (iii) happiness scores (OHQ). Comparisons will be made using an unpaired t-test or a Mann-Whitney test for parametric and non-parametric data, respectively. P-values <0.05 will be considered statistically significant.

Effect sizes for will be calculated using Cohen's d (*d*) with 95% confidence intervals (95%CI) using the 'effsize' package[12]. Effect sizes will be considered small if $0.2 \leq d < 0.5$, medium if $0.5 \leq d < 0.8$, and large if $d \geq 0.8$.

4.2. Secondary Outcomes

Study 1

The primary analyses will compare: (1) experimental vs experimental control guidelines on their mean and standard deviation of brain waves (alpha, beta, theta, gamma and delta). Comparisons will be made using an unpaired t-test or a Mann-Whitney test for parametric and non-parametric data, respectively. P-values <0.05 will be considered statistically significant.

2×4-Repeated measures analysis of variance (ANOVA) will be performed to test the significant difference in the intervention effects between the time intervals (baseline, mid-intervention, post-intervention, and follow-up) and also between the two groups (Experimental control group and Experimental Group).

The post–hoc analysis will be conducted to investigate significant effect within the time intervals. Condition on if the sphericity violated (p-value < 0.05), the Greenhouse- Geisser estimated correction will be applied.

Effect sizes for will be calculated using Cohen's d (*d*) with 95% confidence intervals (95%CI) using the 'effsize' package. Effect sizes will be considered small if $0.2 \leq d < 0.5$, medium if $0.5 \leq d < 0.8$, and large if $d \geq 0.8$.

Study 2

The primary analyses will compare: (1) CAI participants vs healthy control group guidelines on their mean and standard deviation brain waves (alpha, beta, theta, gamma and delta). Comparisons will be made using an unpaired t-test or a Mann-Whitney test for parametric and non-parametric data, respectively. P-values <0.05 will be considered statistically

significant.

Effect sizes for will be calculated using Cohen's d (*d*) with 95% confidence intervals (95%CI) using the 'effsize' package. Effect sizes will be considered small if $0.2 \leq d < 0.5$, medium if $0.5 \leq d < 0.8$, and large if $d \geq 0.8$.

Pearson's correlation or a spearman's correlation for parametric and non-parametric data, respectively will be used to report the association of EEG with the primary outcomes pain intensity (VAS &BPI) and pain interference (BPI).

4.3 Missing Data

Forparticipants who are randomized and do not attend for assessment, a mean imputation of the assessment scores from their allocation group will used.

5. Informed Consent Forms (ICF)

Study 1

Written consent will be gained from the study participants with CAI using the consent forms attached tothe application.

Study 2

Written consent will be gained from the study participants without CAI using the consent forms attached to the application.

5.1 Rights and Risks to participants

Rights

The participants may decide to stop being a part of this research study at any time without explanation. The participants have the right to omit or refuse to answer or respond to any question that is asked. In addition, they have the right to ask any questions about the procedures practiced (unless answering these questions would interfere with the study outcome). If they having any questions on this information sheet/test/training, they may ask the investigator or research in-charge person before the study begins or during the course of assessment and interventions. Participation in this study is voluntary and it does not carry any remuneration or reimbursement.

Risks

Researcher does not anticipate any risk from this research study. However, researchers have to touch at the head, injured ankle joint and neighboring muscles during the primary, secondary outcomes and during the intervention procedures. Also will have to fix the surface electrodes of 14-channel EEG headset to record the brain waves. The intervention

may reduce the occurrence of pain and provide an insight about the risk factors associate with injuries among collegiate athletes.

5.2 Privacy and Confidentiality

All study participants will be de-identified and given a unique ID number at the time of enrolment; this will be recorded by the front desk officer in the physiotherapy centre (INTI international university) and emailed or WhatsApp to the participant. The key linking study participants to their unique ID number will only be accessed by the front desk officer and will be stored in the password protected folder on the secure physiotherapy centre (INTI international university) hard drive. This will be destroyed after the 7-year retention period. Participants will not be able to be identified from any results published.

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