Study Protocol and Statistical Analysis Plan

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Title:

Enhancing Chronic Migraine Preventive Therapy: Laser Acupuncture as an Add-On Treatment for Patients with Unsatisfactory Pharmacological Effect, a Pilot Randomized Controlled Trial

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Objective

We aimed to investigate the efficacy and safety of laser acupuncture (LA) as an add-on preventive therapy on chronic migraine (CM).

Methods

A single-blind randomized controlled trial was conducted from January 2022 to November 2023. CM patients with unsatisfactory pharmacological effects were randomly assigned in a 1:1 ratio to receive either LA or sham treatment over a course of 8 sessions spanning 4 weeks. The co-primary outcomes were changes in monthly migraine days (MMD) and acute headache medications usage days per month from baseline. Evaluations were taken at baseline (12 weeks before randomization), at 4^{th} week (treatment completed), 8^{th} week and 12^{th} week from baseline.

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Trial Design and Participants

Our study is a hospital-based (Taichung Veterans General Hospital), single-blind randomized controlled trial. Between January 2022 to September 2023, patients over 20 years old with CM managed pharmacologically with unsatisfactory effect were included. CM was diagnosed by neurologists based on the criteria of International Classification of Headache Disorders, 3rd edition (ICHD-3). Participants were randomly assigned in a 1:1 ratio to receive either LA or sham treatment. Participants were randomized by computer software (Excel 2016 for Windows). All the participants and our collaborative case-manager were blinded to treatment types. Clinical assessments were taken at baseline, with headache defined in diary for 12 weeks before randomization, and other clinical assessments at the time of randomization, at the 4^{th} (treatment completed), 8^{th} and 12^{th} week from baseline. After completing the LA protocol or sham treatment, participants were observed via clinical follow-up examinations and through questionnaires. In addition, participants received anthropometric measurements, including body-mass index (BMI) and blood pressure by case-manager at the time of randomization. Medication histories of patients were recorded, including acute headache medications and preventive medications.

Clinical assessments were as follows: (1) headache diary; (2) headache characteristics and (3) the Migraine Disability Assessment (MIDAS). The headache diary was completed by each participant. Items recorded were headache duration, frequency, location, severity (using Numeric Rating Scale [NRS]), acute headache medications usage, presence of aura or not, menstrual relation, concomitant symptoms. Questionnaires were acquired by a trained and certified case-manager, who was blinded to treatment types.

All participants provided written informed consent prior to enrolment. The study protocol was approved by the ethics committee of the Institutional Review Board at Taichung Veterans General Hospital (approval number: CF22082B).

Trial Inclusion and exclusion criteria

The inclusion criteria included: (1) patients aged >20 years old and had CM managed pharmacologically, including preventive and/or acute migraine medications, and in addition, those who had refused preventive agent despite recommendation of the neurologist; (2) patients who had unsatisfactory effect of current pharmacological treatments, defined as they self-reported[16]; and (3) patients who had a minimum of one-year history of migraine with or without aura.

Exclusion criteria included: (1) patients who had received another LA therapy or traditional acupuncture at baseline; (2) migraine onset after the age of 50; (3) cognitive or psychological impairment interfering with the participant's ability to receive LA protocol and describe symptoms; and (4) patients with missing data at baseline or during the follow-up period.

In our trial, the primary analytical approach utilized is intention-to-treat (ITT) analyses. Simultaneously, we have also performed per-protocol (PP) analyses. The factors listed below was defined as protocol violations which would be excluded from the per-protocol analysis: (1) patients who had records of changing preventive medications during the follow-up period; (2) patients who received another LA therapy or traditional acupuncture during the follow-up period.

Protocol of laser acupuncture and sham control

We selected identical acupoints in both the treatment and sham control groups. Patients in the

LA group sequentially received laser stimulation energy of 4.5 J for 30 seconds at each of the following acupoints: bilateral Cuanzhu (BL2), Fengchi (GB20), Taiyang (EX-HN5), Shuaigu (GB8), Hegu (LI4), Taichong (LR3) and midline Yintang (EX-HN3). Control patients received sham treatment with no laser output. Each treatment course lasted for about 10 minutes. The treatment protocol was conducted over a course of 8 sessions that spanned 4 weeks. During treatment, patients were asked to wear eye goggles and noise-canceling headphones to inhibit visual and auditory perception.

Selected acupoints were localized according to the WHO Standardized Acupuncture Point Location guidelines. The laser application procedures were performed by the same experienced physician who was a well-trained and a licensed Chinese medicine practitioner in Taiwan.

2.4 Trial outcomes

The co-primary efficacy outcomes were (1) changes from baseline in monthly migraine days (MMD), and (2) changes from baseline in acute headache medications usage days per month between baseline and each of the three follow-up time points (4^{th}, 8^{th} and 12^{th} weeks) after randomization.

We classified 4 secondary efficacy outcomes in our study, which were ≥ 30% reduction in migraine days between baseline and each follow-up time point, and changes in the following parameters: (1) headache duration; (2) headache severity (based on NRS) and (3) MIDAS score.

The safety outcome was defined as any adverse event (AE) that had occurred during LA or sham treatment, and during the follow-up period. Serious AEs were defined as those that resulted in patients withdrawing from the trial. We recorded any patient-reported AEs, including but not limited

to nausea, dizziness, local paresthesia, local heat sensation, fatigue, somnolence, and ecchymosis. Trial physicians also inquired patients on the incidence of any AE during treatment and at every follow-up point.

2.5 Treatment Credibility

To evaluate the reliability of treatment blinding and ascertain the credibility of the assigned treatment groups, a credibility questionnaire was administered at each follow-up assessment. Within the questionnaire, patients were queried about their perceptions regarding whether they had undergone laser acupuncture following the principles of traditional Chinese medicine (TCM) or received sham treatment. At the end of the study, participants were surveyed about the treatment logical and their likelihood of recommending the received treatment to others.

2.6 *Statistical Analyses and Sample Size Calculation*

The baseline characteristics and clinical outcomes described are based on the ITT population, which included participants who had completed the LA or Sham treatment protocol. In addition, we also performed another clinical outcome analysis based on the PP population which are available in the supplement.

Descriptive statistics were presented as mean ± standard deviation (SD), and as number and percentage. We used Fisher's exact test and chi-squared test to analyze categorical variables. We used post hoc power analyses based on the primary efficacy, changes from baseline in MMD at 12^{th} weeks, to assess the adequacy of our sample size. All tests were two-sided. Statistical significance

was set at P value less than 0.05 ($p < 0.05$). All analyses were done using the statistical package SAS version 9.4 for Windows.