

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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29 **Objective**

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

32 **Methods**

33 A single-blind randomized controlled trial was conducted from January 2022 to November 2023.

34 CM patients with unsatisfactory pharmacological effects were randomly assigned in a 1:1 ratio to
35 receive either LA or sham treatment over a course of 8 sessions spanning 4 weeks. The co-primary
36 outcomes were changes in monthly migraine days (MMD) and acute headache medications usage
37 days per month from baseline. Evaluations were taken at baseline (12 weeks before randomization),
38 at 4th week (treatment completed), 8th week and 12th week from baseline.

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51 **Study Protocol and Statistical Analysis Plan**

52 *Trial Design and Participants*

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

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

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

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77 *Trial Inclusion and exclusion criteria*

78 The inclusion criteria included: (1) patients aged >20 years old and had CM managed
79 pharmacologically, including preventive and/or acute migraine medications, and in addition, those
80 who had refused preventive agent despite recommendation of the neurologist; (2) patients who had
81 unsatisfactory effect of current pharmacological treatments, defined as they self-reported¹⁶; and (3)
82 patients who had a minimum of one-year history of migraine with or without aura.

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

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

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93 *Protocol of laser acupuncture and sham control*

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

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

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

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106 *2.4 Trial outcomes*

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

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

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

117 to nausea, dizziness, local paresthesia, local heat sensation, fatigue, somnolence, and ecchymosis.
118 Trial physicians also inquired patients on the incidence of any AE during treatment and at every
119 follow-up point.
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121 *2.5 Treatment Credibility*

122 To evaluate the reliability of treatment blinding and ascertain the credibility of the assigned
123 treatment groups, a credibility questionnaire was administered at each follow-up assessment. Within
124 the questionnaire, patients were queried about their perceptions regarding whether they had
125 undergone laser acupuncture following the principles of traditional Chinese medicine (TCM) or
126 received sham treatment. At the end of the study, participants were surveyed about the treatment
127 logical and their likelihood of recommending the received treatment to others.
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129 *2.6 Statistical Analyses and Sample Size Calculation*

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

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

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

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