

The Long-term Effect of Acupuncture for Migraine Prophylaxis

(A Randomized Clinical Trial)

STUDY PROTOCOL

Chengdu University of Traditional Chinese Medicine

Hunan University of Traditional Chinese Medicine

Chongqing Medical University

1. Background

Migraine is a refractory disorder with high socioeconomic impact [1–5]. The prevalence of migraine among adults in the USA is approximately 28.4% [6] and 4.2 to 14.6% in China [7]. It has been listed as one of the most serious, chronic, and dysfunctional disorders that is equal to quadriplegia, mental disorders, and dementia according to the World Health Organization [8]. Several drugs can be used to reduce the frequency of migraine attacks: aspirin, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) [3, 9, 10]. However, the success of treatment is usually modest and tolerability is often suboptimal [11].

Acupuncture is used widely in the prevention and treatment of migraine. Acupuncture is one of the main treatments of traditional Chinese medicine (TCM) and has been used for over 3000 years. According to time course of its curative effect, acupuncture effect can be divided into “instant” and “long-term” effects [12]. In recent years, the instant effect of acupuncture for patients with migraine has been corroborated by numerous studies [13–18]. Most diseases are chronic and tend to recur, so the long-term effect of acupuncture can verify the existence of sustained efficacy or the placebo effect. The main factors affecting long-term effects have been hypothesized to be needling frequency per week and treatment duration [19].

Several randomized controlled trials (RCTs) in China and overseas have paid close attention to how long the effect is maintained after the last acupuncture session. Our previous studies on the effect of acupuncture on migraine showed that

participants in the acupuncture group had fewer days with migraine compared with the control group during weeks 5–8, but that this difference was not significant. However, a significant reduction in the number of days with migraine during weeks 13–16 was noted [20]. In another clinical trial, patients were allocated randomly to receive ≤ 12 acupuncture treatments over 3 months or to a control intervention offering standard care: headache scores at 3 months and 12 months were lower in the acupuncture group than in controls. Those results suggested that acupuncture leads to persistent, clinically relevant benefits for patients with chronic headache (particularly migraine). That study with long-term follow-up concluded that the acupuncture effect for migraine prophylaxis can last 9 months after treatment cessation [21].

2. Study Aims

We conjectured that there would be a long-term curative effect of acupuncture for migraine without aura (MWOA) over a longer follow-up period. We have designed a clinical trial to investigate the effect and safety of acupuncture for the prophylaxis of patients suffering MWOA. In addition, special attention has been paid to a comparison with the placebo effect, accompanied by observation of the intensity and duration of the acupuncture effect.

3. Research Design and Methods

The design of this study is in accordance with the guidelines of the International Headache Society's (IHS) Committee on Clinical Trials in Migraine [22].

3.1 Design

This multicenter randomized, controlled clinical trial comprises three parallel groups. It aims to compare the effectiveness of the individualized acupoint group, non-acupoint control group (in locations not corresponding to acupuncture points), and the waiting-list control group (who receive delayed active acupuncture treatment 24 weeks later) (**Figure 1**).

In all groups, participants will not take any regular medications for migraines, but will be permitted to use necessary analgesics such as the ibuprofen and analgesics during acute attacks of migraine. The type, dose and time of administration of the agent must be recorded in a headache diary.

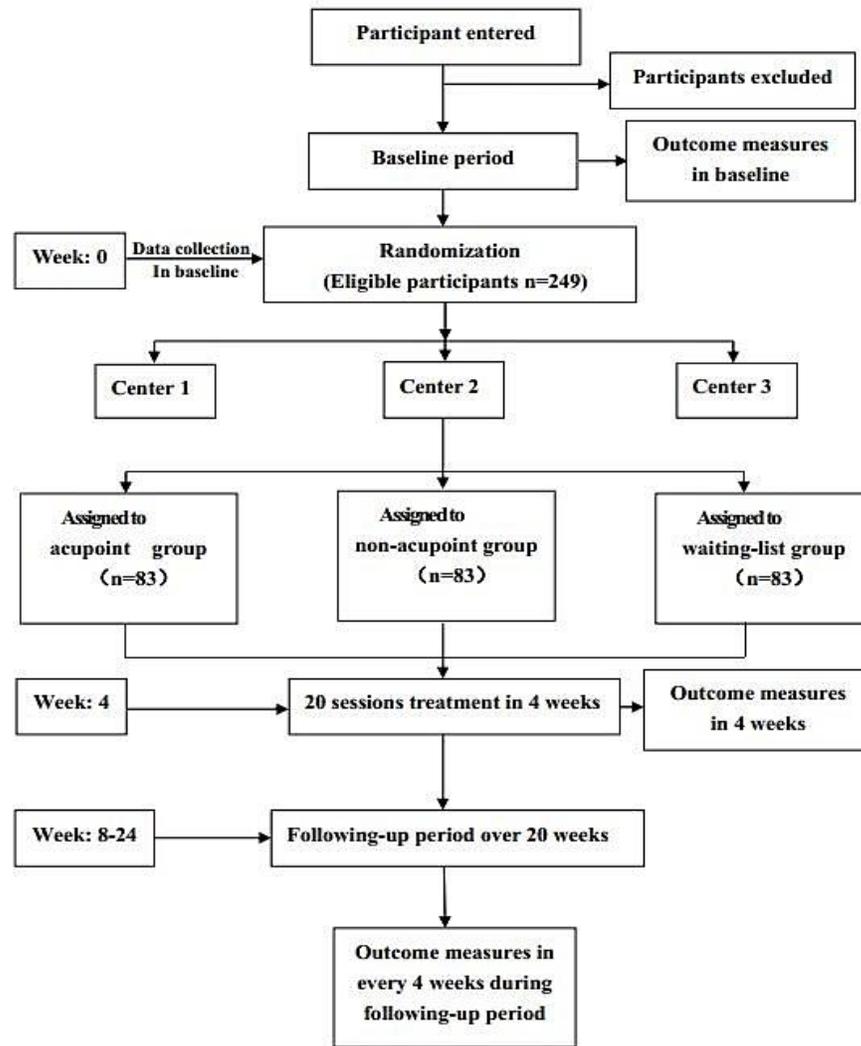


Figure 1 Trial profile

3.2 Randomization

The central randomization will be conducted using the Brightech–Magnasoft Clinical Information Management System (CIMS). Allocation to treatment groups uses a stratified block dynamic randomization method with permuted block, which is

automatically under the control of a central computer system. To guarantee allocation concealment, randomization will be done by an independent researcher. The website and mobile message will be used to send randomization information (including the participants' name in pinyin format, sex and date of birth) to the CIMS center. An independent assessor will interview the participants and carry out the screening. Random numbers and group assignment will be confirmed through e-mail or short message service (SMS) to the independent assessor immediately. This procedure guarantees that randomization concealment is adequate, and not influenced by the acupuncturists or participants. Participants allocated to individualized acupoint or non-acupoint groups will be blinded to their treatment allocation. However, blinding is clearly not possible in the waiting-list control group. All participants will be assessed and the results be analyzed by professionals blinded to the allocations of the different treatments. The duration of the study for every participant will be 28 weeks. Four of them will be before randomization (baseline), followed by 4 weeks of treatment, and lastly 20 weeks of follow-up.

3.3 Ethical Requirements and Registration

The Consolidated Standards of Reporting Trials (CONSORT) statement [23] (<http://www.consort-statement.org/home/>) has been used as a framework for developing the study methodology. The protocol of this study was approved by the Ethics Committee of the Teaching Hospital of Chengdu University of TCM (Chengdu, China) in June 2012 and is in accordance with the Declaration of Helsinki. The trial protocol has permission number 2012KL-007. The trial was registered in

ClinicalTrials.gov with approval number NCT01687660. All participants have provided written informed consent to be included in the trial.

3.4 Setting and participants

A total of 249 participants meeting the diagnostic criteria for MWoA according to the second edition of the IHS' International Classification of Headache Disorders (ICHD-II, IHS 2004) will be recruited at three centers (Chengdu, Hunan and Chongqing) [24]. Participants will be: informed (verbally and through a print-out) of the possible risks associated with the study; instructed to complete the headache diary; told that they can withdraw from the trial at any time without specifying reasons; and told they can provide written informed consent before enrollment voluntarily.

4. Inclusion and Exclusion Criteria

4.1 Inclusion criteria

Eligible participants should match the diagnostic criteria for MWoA set by ICHD-II [24]. They must:

- be male or female, aged between 18 and 65 years, with initial onset of migraines before the age of 50 years;
- have had 2 to 8 migraine attacks, but less than 15 days of attacks per month during the previous 3 months and during baseline measurement;
- suffering from migraine attack for at least 1 year;
- have completed the headache diary and given baseline values within it;
- provided written informed consent by themselves.

4.2 Exclusion criteria

Participants with any of the following conditions will be excluded:

- headache caused by organic disorders such as subarachnoid hemorrhage, cerebral hemorrhage, cerebral embolism, cerebral thrombosis, vascular malformation, arteritis, hypertension or arteriosclerosis;
- the presence of neurological diseases, immunodeficiency, bleeding disorders or allergies;
- those who have used prophylactic drugs in the previous 3 month;
- pregnant women, women in lactation, and those planning to become pregnant in the next 6 months;
- involvement in other RCTs.

5. Interventions

Treatment strategies were developed by consensus with experienced acupuncture practitioners and a neurologist. Based on TCM theory, a systematic review of the literature revealed that acupoints on the Shaoyang meridian were the ones chiefly selected for migraine [19]. There are three groups in this trial: individualized acupoint group, non-acupoint control group, and waiting-list control group. The location and manipulations of individualized acupoints and non-acupoints are shown in **Table 1**.

5.1 Individualized acupoint group

In the individualized acupoint group, the acupoint prescriptions used will be

personalized to each participant and at the discretion of the acupuncturist. Differentiating the location of meridians is an important part of TCM theory, so it was used to select acupoints on the basis of the evolution of the patient's symptoms. Fengchi (GB20) and Shuaigu (GB8), having the highest frequency, were selected as obligatory acupoints. Additional points, which were used in a previous study [25], could be chosen according to syndrome differentiation of meridians: (i) Shaoyang headache (headache only attacks the temporal side): Waiguan (SJ5) and Yanglingquan (GB34); (ii) Taiyang headache (headache involves the occiput): Kunlun (BL 60) and Houxi (SI3); (iii) Yangming headache (headache involves the forehead): Hegu (LI4) and Neiting (ST44); (iv) Jueyin headache (headache involves the vertex): Taichong (LR3) and Qiuxu (GB40).

The acupuncturist responsible for the treatment will insert sterile, single-use filiform acupuncture needles (length, 25–40 mm; diameter, 0.25 mm) and auxiliary acupuncture needles (without manipulating the needles) of length 13 mm and diameter 0.18 mm after first disinfecting the skin with the participant lying down. The needles used are Hwato needles (Suzhou, China). The puncture will be made according to TCM standards to a depth of 0.3–1 cm depending on the points selected. Insertion will be followed by the stimulation methods of lifting and thrusting combined with twirling and rotating the needles to produce a sensation known as *Deqi*. Acupoints on the left and right side are employed alternatively, and punctured by filiform needles unilaterally. Auxiliary needles will be punctured 2 mm lateral to each acupoint to a depth of 2 mm without manual stimulation. This method has been used

successfully in our previous study [20, 26]. Han’s acupoint nerve stimulator (HANS; Model LH 200A; TENS, Nanjing, China) will be connected after needle insertion.

Participants in this group will receive 20 sessions over a 4-week period. Each session will be administered once a day for 5 continuous days followed by a 2-day rest interval, and the participant will be connected to the stimulator for 30 min. All patients should complete ≥ 10 treatment sessions. The stimulation frequency is 2/100 Hz, and intensity varies from 0.1 to 1.0 mA until the participants feel comfortable. Needles will be retained *in situ* for 30 min and then the acupoint holes covered with clean cotton balls to avoid bleeding upon needle withdrawal.

5.2 Non-acupoint control acupuncture

Participants assigned randomly to this group will be given non-acupoint acupuncture, i.e., insertion of acupuncture needles at four bilateral non-points. The protocol of non-acupoints was developed in our latest acupuncture clinical trial [27]. The method will not differ from that used for the individualized acupoint group except for that an attempt will not be made to yield the *Deqi* sensation.

Table 1 Details of the acupoint and non-acupoint groups

Group	Acupoint	Manipulation
Individualized acupoint	(i) Fengchi (GB20)	(i) is punctured obliquely 0.8–1.2 cm toward to apex nasi
	(ii) Shuaigu (GB8)	(ii) is punctured horizontally 0.5–0.8 cm
	(iii) Waiguan (SJ5)	(iii) is punctured perpendicularly 0.5–1 cm
	(iv) Yanglingquan (GB34)	(iv) is punctured perpendicularly 1–1.5 cm
	(v) Kunlun (BL 60)	(v) is punctured perpendicularly 0.5–0.8 cm
	(vi) Houxi (SI3)	(vi) is punctured perpendicularly 0.5–0.8 cm
	(vii) Hegu (LI4)	(vii) is punctured perpendicularly 0.5–1

		(viii) Neiting (ST44)	cm (viii) is punctured perpendicularly 0.5–1 cm
		(ix) Taichong (LR3)	cm (ix) is punctured perpendicularly 0.5–1 cm
		(x) Qiuxu (GB40)	(x) is punctured perpendicularly 0.5–0.8 cm
Non-acupoint acupuncture	control	(i) At the medial arm on the anterior border of the insertion of the deltoid muscle at the junction of deltoid and biceps muscles	(i) is punctured perpendicularly 0.5–1 cm
		(ii) Half way between the tip of the elbow and axillae	(ii) is punctured perpendicularly 0.5–1 cm
		(iii) Ulnar side, half way between the epicodylus medialis of the humerus and ulnar side of the wrist	(iii) is punctured perpendicularly 0.5–1 cm
		(iv) Edge of the tibia 1–2 cm lateral to the Zusanli (ST36) horizontally	(iv) is punctured perpendicularly 0.5–1 cm

5.3 Waiting-list control group

No intervention will be used in the waiting-list group. The participants will be informed that they are scheduled to receive 20 acupuncture treatments for free after a waiting period of 24 weeks.

6. Outcome Measurement

The efficacy of acupuncture for migraine is assessed by the primary outcome measure: change in the frequency of migraine attacks during the 16th week after randomization.

The secondary outcome measures are:

- frequency of migraine attacks;
- number of days with migraine;

- visual analogue scale (VAS) score and grade of headache intensity (0–3);
- medication intake;
- number of participants with adverse events (AEs) and serious adverse events (SAEs);
- summary scales of the Migraine-Specific Quality-of-Life Questionnaire (MSQ) [20];
- Zung Self-Rating Anxiety Scale (SAS) [28] and Zung Self-rating Depression Scale (SDS) [28];
- acupuncture expectation value.

The outcome measures shown above will be measured before randomization, the week of the last acupuncture session, and 8, 12, 16, 20 and 24 weeks after randomization, except that the acupuncture expectation value is assessed before randomization, and MSQ, SAS and SDS are assessed only at 4 weeks after treatment.

Detailed time points of outcome assessments are provided in **Table 2**.

Table 2 Timetable of treatment and outcome collection

Period	Baseline	Treatment phase			Follow-up phase			
Visit	1	2	3	4	5	6	7	
Week	–4	1–4	8	12	16	20	24	
Informed consent	×							
Demographic characteristics	×							
Medical history	×							
Laboratory test, electrocardiography, pregnancy test	×							
Inclusion/exclusion criteria	×							
Vital signs	×	×	×	×	×	×	×	

Change of medical history	×	×	×	×	×	×	×
Random allocation	×						
Acupuncture		⊗					
Headache diary	×	×	×	×	×	×	×
Visual analogue scale	×	×	×	×	×	×	×
MSQ	×	×					
SAS	×	×					
SDS	×	×					
Acupuncture Expectancy Questionnaire	×						
Safety Assessment							×

×, All groups; ⊗, treatment groups.

7. Adverse Events and Safety

Any AE and SAE, and how they are dealt with, will be recorded during the 4 treatment weeks and 20 follow-up weeks. AEs include bleeding, hematoma, fainting, severe pain, and local infection. Any SAE (including life-threatening SAEs) can lead to hospitalization or prolongation of existing hospitalization, and persistent or significant disability/incapacity. Therefore, intervention to prevent permanent impairment is required. Physicians should assess the causal-effect relationship of the intervention with AEs/SAEs and collect details related to the last treatment session. If participants suffer AEs or SAEs, all details will be documented. Moreover, if SAEs occur in participants, physicians should immediately provide the appropriate care to ensure their safety. Additionally, physicians will report the SAEs and treatment to the principal investigator in each clinical center and the Ethics Committee within 24 hours.

8. Drop-outs

Patients who withdraw from the trial for any reason will be considered a drop-out. The common reasons for dropping out including AEs, poor compliance with the protocol, unsatisfied efficacy, withdraw and quit, and others. Investigators should complete the case report form (CRF) and record the reason for dropping out. All the information from participants who have dropped out will be used for intention-to treat (ITT) analysis.

9. Data Management

All CRFs for each patient should be filled in by study staff in each clinical center timely. All data, including the time of migraine onset, duration, severity and rescue medication use based on headache diary, questionnaires, assessment scales, physical examinations, treatment compliance and screening details will be filed accurately in CRFs. Medical histories, original documents and CRFs will be stored in the clinical study office. Researcher staff will double-entered all data in electronic CRFs which produced by the Brightech–Magnasoft CIMS. The CRFs and electronic CRFs are identical. When the data entry is complete, the database will perform consistency check automatically. Whenever inconsistencies are found, the data will be rechecked and corrected in according to the CRFs and original documents.

10. Training for Study Physicians

All physicians who enroll participants and assessors who collect data must attend training classes to ensure all practices at each hospital are identical. The training classes comprise theoretical and practical lessons. Physicians must pass the training test to understand the purpose and content of the trial, treatment strategies and quality control. Additionally, to maintain quality control, quality monitoring will be carried out by Brightech–Magnasoft CIMS, and specially trained physicians will check all trial processes.

11. Calculation of Sample Size and Statistical Analyses

11.1 Calculation of sample size

Sample size will be estimated by n-Query Advisor ver4.0 (Statistical Solutions, Boston, MA, USA). For this trial, it has been determined prospectively that $\alpha=0.05$ and $1-\beta=0.90$, and that the standard deviation will be 1.81 according to the three group subsets. According to a previous study [20], we anticipated that a mean frequency of migraine attack in the non-acupoint group is 3.7 whereas, in the individualized acupoint group, it is 2.7. Hence, a minimum difference of clinical effect is 1.0. Thus, at least 70 participants are required for each group. To compensate for a prevalence of withdrawal of 15%, we plan to enroll 249 participants in the three groups, with 83 patients for each group.

11.2 Statistical analyses

For the final outcome analysis, we will make all pair-wise comparisons using a general linear model adjusted for baseline value, age, sex, clinical center, and disease course. The comparison between the individualized acupoint group and non-acupoint group is the primary interest in this study. In general, the summarization of difference is in accordance with CONSORT expectations, which will be addressed using effect size estimates and the associated confidence intervals.

All data in this trial will be assessed by Brightech–Magnasoft CIMS, with SPSS ver13.0 (SPSS, Chicago, IL, USA) and SAS ver9.1.3 (SAS, Cary, NC, USA). All analyses will be done on the ITT population (i.e., any participant randomized regardless of whether he/she receives any treatment). Missing data will be replaced according to the principle of the last observation carried forward method. In addition, the per-protocol (PP) population will be analyzed. The results of ITT and PP analyses will be compared to ascertain if the results are consistent. Moreover, analysis of variance (ANOVA) for repeated measures will be used for numerical variables. The Chi-square test will be used for categorical variables. $p < 0.05$ will be considered significant.

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