International Journal of Women's Health

Dovepress
Taylor & Francis Group

Open Access Full Text Article

STUDY PROTOCOL

The Efficacy and Safety of Electroacupuncture for Prophylaxis of Menstrually Related Migraine: Study Protocol for a Pilot Randomized Controlled Trial

Xinkun Liu[1,*], Ruimin Jiao[2,*], Yaqing Zheng[1,*], Yan Liu[3], Guangxian Yu[1], Jiaxiang Shi[1], Wei Wang[1], Weiming Wang[1]

[1]Department of Acupuncture and Moxibustion, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, 100053, People's Republic of China; [2]Department of Traditional Chinese Medicine, Beijing Friendship Hospital, Capital Medical University, Beijing, 100050, People's Republic of China; [3]Key Laboratory of Chinese Internal Medicine of Ministry of Education, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Weiming Wang, Department of Acupuncture and Moxibustion, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, No. 5 Beixiange St., Xicheng District, Beijing, People's Republic of China, Email wangweiming1a1@163.com

Background: Acupuncture, a well-established non-pharmacological intervention, has displayed promise in migraine management, but high-quality evidence for its effectiveness in menstrually related migraine (MRM) prophylaxis remains scarce. This pilot randomized controlled trial will evaluate the feasibility, efficacy, and safety of electroacupuncture (EA) for MRM prevention and provide evidence-based support for future large-scale trials.

Methods/Design: This single-center, participant- and assessor-blinded, sham-controlled pilot trial will assign 40 eligible patients with MRM in a 1:1 ratio to the EA or sham EA (SEA) group via block randomization. Participants will begin treatment on day −3 of each menstrual cycle (estimated according to the previous cycle), receiving 1–2 sessions during the first week (from day −3 to +4 of menstruation) and 2–3 sessions per week for the following 3 weeks. The intervention period will last 12 weeks and total 30 sessions, followed by 12 weeks of follow-up. The primary outcome is the change from baseline in standardized monthly headache days (SMHDs) at week 12. Secondary outcomes include the MRM cure rate, responder rate for MRM (≥50% reduction in SMHDs), changes in headache severity and medication use, quality of life (Migraine-Specific Quality of Life Questionnaire v2.1), psychological status (Hospital Anxiety and Depression Scale), headache-related disability (Headache Impact Test-6), global impression of change (Patient's Global Impression of Change), and feasibility measures. All analyses will follow the intention-to-treat principle with two-sided $P < 0.05$ considered significant.

Discussion: As the first sham-controlled RCT specifically targeting MRM, this study will apply a menstrual cycle-tailored EA protocol and use uniformly assessed SMHDs as the primary outcome to enhance methodological rigor and novelty. The findings are expected to provide preliminary evidence and inform the design of future large-scale trials.

Trial Registration: The trial protocol has been registered at ClinicalTrials.gov (NCT07023926).

Keywords: menstrually related migraine, electroacupuncture, clinical trial protocol

Introduction

Menstrually related migraine (MRM) is a common subtype of menstrual migraine (MM) in women characterized by headaches occurring predominantly between days −2 and +3 of menstruation, although episodes can also occur at other times,[1,2] with this pattern confirmed in at least two of three consecutive menstrual cycles. According to global epidemiological data, migraine affects approximately 17.0% of women,[3] with MRM occurring for 21–30.5% of all women with migraines.[4–6] Compared with non-MM, MRM is associated with longer episodes, greater pain intensity, lower treatment responsiveness, and greater disability.[2,5,7,8] Furthermore, MRM significantly increases the risk of

Received: 18 June 2025
Accepted: 29 September 2025
Published: 8 October 2025

psychological comorbidities, such as depression and anxiety, negatively affecting patients' quality of life and social functioning.[9,10]

Current treatment strategies for MRM primarily comprise acute analgesic management and preventive therapies.[5,11,12] Although acute-phase analgesics remain the primary modalities for alleviating migraine attacks, they do not reduce the frequency of pain episodes. Their efficacy is frequently compromised by the rapid decline in estrogen levels during menstruation, resulting in substantial inter-individual variability in analgesic effectiveness, increased drug tolerance, and diminished therapeutic response.[13,14] Preventive treatments are typically tailored according to menstrual cycle regularity, employing short-term premenstrual prophylaxis [eg, non-steroidal anti-inflammatory drugs (NSAIDs), triptans, estradiol] or continuous hormonal therapy (eg, oral contraceptives) to stabilize estrogen fluctuations. However, long-term use of these pharmacological agents can induce adverse effects, including gastrointestinal injury and hepatorenal toxicity. Therefore, alternative therapies with superior efficacy and fewer adverse effects are urgently needed for MRM prevention.

Acupuncture, as a primary non-pharmacological intervention in traditional Chinese medicine (TCM), has a longstanding history in headache management, and it is recognized by the World Health Organization as an effective therapy for migraine.[15] Previous studies found that acupuncture effectively reduces both the frequency and duration of migraine attacks.[16–19] It has been reported that EA alleviates migraine through mechanisms involving the modulation of neuroendocrine activity, regulation of pain transmission, and reduction of central sensitization, which provides a biological rationale for its prophylactic application.[20–22] However, its efficacy for MRM, a condition with distinct pathophysiological mechanisms,[4,23] remains insufficiently supported by clinical evidence. The existing research on MRM compared acupuncture and pharmacological treatments,[24] whereas placebo- or sham-controlled trials are lacking. In previous studies on MRM,[24,25] inclusion criteria were often insufficiently defined, resulting in ambiguity in participant selection. In addition, sham acupuncture interventions used similar acupoints and manipulation methods to those used in the true acupuncture groups, potentially causing physiological effects that weakened the placebo control. Furthermore, outcome measures in these studies primarily focused on pain-related symptoms, while broader impacts on patients' social functioning, physical health, and psychological quality of life were frequently overlooked. To address these limitations, we designed a pilot randomized controlled trial (RCT) that employs non-penetrating sham needles at non-acupoints—visually identical to real electroacupuncture needles—along with standardized procedures and credibility assessments to enhance blinding validity and methodological rigor. Furthermore, the study incorporates comprehensive outcomes beyond pain, including social functioning, physical health, and psychological quality of life, to holistically evaluate the intervention's effects on MRM prophylaxis. This pilot study aims to provide preliminary evidence and practical guidance for acupuncture in the treatment of MRM, laying the methodological groundwork for future large-scale, high-quality RCTs and facilitating evidence-based clinical practice.

Methods

Study Design

This single-center, sham-controlled, participant- and assessor-blinded, two parallel-group pilot RCT will be conducted at Guang'anmen Hospital, China Academy of Chinese Medical Sciences (Beijing, China). Patients with MRM will be enrolled from March 2025 to January 2027. The trial consists of a 12-week treatment period and a 3-month follow-up period. The study flowchart and treatment schedule are presented in Figure 1 and Table 1. This trial will be conducted in accordance with the principles of the Declaration of Helsinki and has been approved by the Institutional Review Board of Guang'anmen Hospital, China Academy of Chinese Medical Sciences on March 11, 2025 (ethical approval No. 2025–031-KY-01). The protocol conformed to the Standard Protocol Items: Recommendations for Interventional Trials checklist and the Standards for Reporting Interventions in Controlled Trials of Acupuncture. In addition, the trial design follows the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement, and the CONSORT checklist is provided in the supplementary materials (Additional file 1). The registration number at www.clinicaltrials.gov is NCT07023926.

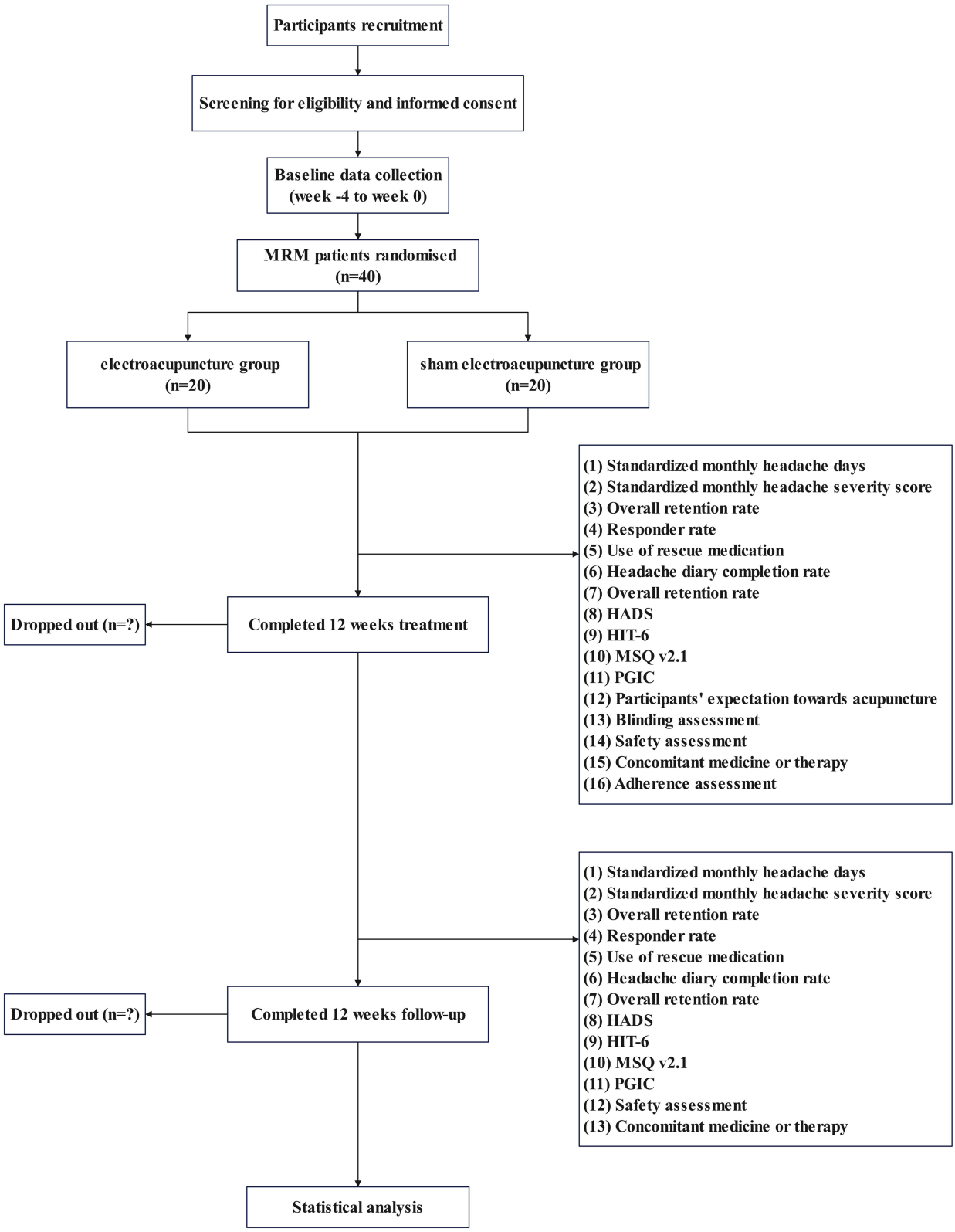

Figure 1 The study flowchart.
Abbreviations: SMHD, standardized monthly headache days; HADS, Hospital Anxiety and Depression Scale; HIT-6, Headache Impact Test-6; MSQ v2.1, Migraine-Specific Quality of Life Questionnaire; PGIC, Patient's Global Impression of Change.

https://doi.org/10.2147/IJWH.S548053

Table 1 The Treatment Schedule

Stage	**Period of Screening and Washout**	**Baseline**	**Period of Regular Treatment (Weeks)**			**Follow-Up Period (Weeks)**		
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
TIME POINT (W, week)	**W −4**	**W 0**	**W 4 ±2d**	**W 8 ±2d**	**W 12 ±2d**	**W 16 ±3d**	**W 20 ±3d**	**W 24 ±3d**
Enrollment:								
Informed consent	√							
Demography information	√							
Disease and treatment history of headache	√							
Inclusion/e√clusion	√							
Record the headache diary daily	√	√	√	√	√	√	√	√
Randomization		√						
Intervention:								
Electroacupuncture group			√	√	√			
Sham electroacupuncture group			√	√	√			
Assessment:								
Standardized monthly headache days		√	√	√	√	√	√	√
Proportion of patients with cured menstrually related migraine					√	√	√	√
Standardized monthly headache severity score		√	√	√	√	√	√	√
Responder rate		√	√	√	√	√	√	√
Use of rescue medication		√	√	√	√	√	√	√
Headache diary completion rate		√	√	√	√	√	√	√
Overall retention rate		√	√	√	√	√	√	√
Hospital An√iety and Depression Scale		√	√	√	√	√	√	√
Headache Impact Test-6		√	√	√	√	√	√	√
Migraine-Specific Quality of Life Questionnaire Version 2.1		√	√	√	√	√	√	√
Patient's Global Impression of Change			√	√	√	√	√	√
Participants' e√pectation towards acupuncture		√						
Blinding assessment					√			
Safety assessment			√	√	√	√	√	√
Concomitant medicine or therapy	√	√	√	√	√	√	√	√
Adherence assessment	√	√	√	√	√			

Note: "√" Indicates items that must be completed.

Randomization and Allocation

Eligible participants will be assigned at a 1:1 ratio to the electroacupuncture (EA) or sham electroacupuncture (SEA) group using a block randomization method. The randomization scheme, which was developed by the Key Laboratory of Dongzhimen Hospital, Beijing University of Chinese Medicine, will be implemented using SAS version 9.4 with a block size of four. Participants will be sequentially numbered from 1 to 40 according to their enrollment order and equally allocated to the EA or SEA group using a pre-generated randomization list. Allocation concealment will be achieved using sealed, opaque envelopes. Each envelope will be labeled externally with a participant number, and the corresponding random code and group assignment (EA or SEA group) will be enclosed. All envelopes will be prepared in advance by personnel not involved in the study. Envelope management and participant allocation will be conducted by independent personnel not involved in treatment or outcome assessment, ensuring the rigor of allocation concealment and blinding throughout the trial.

Blinding

In this study, participants, outcome assessors, and statisticians will be blinded to group allocation. Because of the inherent nature of acupuncture interventions, acupuncturists cannot be blinded. To enhance blinding credibility in the SEA group, non-penetrating blunt-tip needles will be used to mimic the tactile sensation of real acupuncture. A brief, low-intensity electrical current (≤5 seconds) will be applied at the beginning of each session to simulate the initial sensation of EA, with no current delivered thereafter. Both groups will receive identical environmental cues, instructions, and interaction protocols. Acupuncturists will refrain from discussing treatment details or potential effects with participants. Immediately after the final treatment session, participants will undergo a blinding assessment by being asked to guess their assigned treatment group, thereby evaluating the effectiveness of the blinding. Unblinding will only occur for a serious adverse event requiring treatment assignment disclosure. The principal investigator will access sealed allocation codes as needed, while outcome assessors and statisticians remain blinded. All unblinding instances will be documented.

Recruitment

All participants will be recruited via WeChat, websites, posters, and bulletin boards in Guang'anmen Hospital.

Inclusion and Exclusion Criteria

Participants meeting all of the following criteria will be eligible for enrollment:

1. Meeting the diagnostic criteria for MRM according to the International Classification of Headache Disorders, 3rd edition (ICHD-3),[1] as published by the International Headache Society in 2018, including attacks in a menstruating woman fulfilling the criteria for migraine, with or without aura, headache attacks occurring between days −2 to +3 of menstruation in at least two of three consecutive menstrual cycles, and attacks occurring at other times of the menstrual cycle.
2. A documented history of MRM for at least 12 months with a confirmed diagnosis of migraine by a neurologist.
3. Age of 18–45 years.
4. Regular menstrual cycles (28 ± 7 days) with menstruation lasting 3–7 days;
5. ≥3 headache days during each menstrual cycle (days −2 to +3) and ≥5 total headache days per cycle over the past 3 months and baseline period, with migraines lasting 4–72 h without acute medication or at least 2 h when treated.
6. Completion of a headache diary during the screening period (covering at least one full menstrual cycle), demonstrating good compliance.
7. The headache diary data during screening period must meet the ICHD-3 criteria for MRM and fulfill criteria (4) and (5).
8. Voluntarily sign the informed consent.

Participants meeting any of the following criteria will be excluded:

1. Irregular menstrual cycles, defined as cycle length outside the range of 28 ± 7 days or a menstruation duration of <3 or >7 days.
2. Presence of secondary headache disorders, facial neuralgia, or cranial neuralgia;
3. Presence of serious primary diseases such as cardiovascular, hepatic, renal, gastrointestinal, or hematological disorders that can interfere with the treatment protocol or comorbid neurological conditions such as epilepsy, Parkinson's disease, or other central nervous system disorders.
4. Headache symptoms caused by other conditions, such as moderate-to-severe head or neck trauma, perimenstrual infections, intracranial tumors, intracranial infections, endocrine or metabolic disorders.
5. Receipt of preventive treatment for headache within 1 month prior to the screening visit.
6. Fear of needles or receipt of acupuncture within 3 months before enrollment.
7. Unwillingness to undergo the study intervention.

Withdrawal and Discontinuation Criteria

Participants will be withdrawn from the trial and excluded from further analysis under any of the following circumstances:

1. Incorrect randomization without receiving any study treatment.
2. Protocol violations, including but not limited to, the receipt of acupuncture treatment outside the study protocol, the sue of prohibited concomitant medications, and poor treatment adherence or non-compliance with study procedures.
3. Withdrawal of informed consent, defined as the participant's explicit decision to discontinue participation.
4. Loss to follow-up, defined as failure to attend scheduled visits or respond to contact attempts without formally withdrawing from the study. At least two documented attempts to contact the participant must be made before classification as lost to follow-up.
5. Intolerable acupuncture-related pain or the occurrence of serious AEs.
6. Discontinuation is deemed in the participant's best interest by the investigator because of safety concerns, a lack of therapeutic efficacy, worsening clinical symptoms making continued participation inappropriate, and the emergence of new medical conditions requiring other treatments.
7. Pregnancy during the study period.

Participants who discontinue will not be replaced.

Screening and Washout Period

Before treatment initiation, all preliminarily eligible participants will complete a one-menstrual-cycle screening and washout period after providing written informed consent. Starting from the first day of menstruation, participants will record their headache experiences throughout the entire cycle and complete a headache diary on days on which headaches occur. All headache-related data during this period will be standardized to a 28-day cycle for consistency. During this phase, prophylactic headache medications will not be allowed. Participants must not alter the type or per-administration dosage of any acute rescue medications, although they can adjust the frequency or total usage based on individual need. The use of any other medications or interventions beyond conventional acute analgesics, including, but not limited to, β-blockers (eg, atenolol, propranolol), calcium channel blockers (eg, flunarizine, cinnarizine), antidepressants (eg, amitriptyline, venlafaxine), antiepileptics (eg, topiramate, gabapentin), angiotensin receptor blockers (eg, candesartan, lisinopril), Botulinum toxin, non-invasive neuromodulation (eg, non-invasive vagus nerve stimulation, transcranial magnetic stimulation), dietary supplements, nerve block, infusion therapy, and physical manipulation, will be strictly prohibited.

Interventions

After the baseline assessment and randomization, each patient with MRM will complete a half-day health education session delivered by a neurologist. The health education sessions will be conducted in multiple small-group batches based on participants' enrollment time, rather than in a single large session. This group-matching approach is designed to ensure consistency and personal engagement while maintaining feasibility throughout the recruitment period. Key topics will include the risks of frequent analgesic use; the need for long-term MRM management; cautious use of acute medications; and lifestyle guidance on sleep, smoking cessation, and physical activity.

EA Group Treatment Protocol

All treatments will be performed by a licensed acupuncturist with at least 2 years of clinical experience. Before the study starts, the acupuncturists will be extensively trained on the location, depth, and angle of acupuncture.

Acupoints will be selected according to the meridian theory of TCM, prior research, and the consensus of senior doctors. The main acupoints will include Baihui (GV20), bilateral Taiyang (EX-HN5), bilateral Touwei (ST8), bilateral Shuaigu (GB8), bilateral Fengchi (GB20), bilateral Hegu (LI4), bilateral Taichong (LR3), and bilateral Fenglong (ST40). Additional points will be selected according to patients' symptoms as follows: bilateral cervical Jiaji (EX-B2) at the level of C3–C4 for neck discomfort; Yintang (GV29) and bilateral Shenmen (HT7) for emotional disturbances such as anxiety, depression, or sleep disorders; and Zhongwan (CV12), bilateral Tianshu (ST25), and Qihai (CV6) for gastric or abdominal discomfort. All acupoints will be located according to the nomenclature and location of acupuncture points designated by the National Standard of the People's Republic of China (GB/T 12346–2021), as presented in Table 2 and Figure 2A. Before needling, the acupuncturist will disinfect the local skin using 75% alcohol and apply foam pads (Figure 2B). Sterile disposable acupuncture needles (0.3 mm × 25 or 40 mm) will be inserted at the selected points and gently manipulated via lifting, thrusting, and rotating to elicit the Deqi response. Specific needle depths and angles are detailed in Table 2. The EA apparatus (Hwato, SDZ-V, Suzhou Medical Appliance, Suzhou, China) will be connected longitudinally to two pairs of needles on each side at ST25 and ST8, and EA stimulation will use a continuous wave of 10 Hz and current intensity of 0.5–3.5 mA depending on the participant's comfort level. Each treatment session will last 30 min, after which the needles will be gently removed by acupuncturists. Participants will receive treatment starting

Table 2 Details of the Acupoints Location and Insertion in the Electroacupuncture Group

Acupoints	Location	Depth of Insertion
Main		
Baihui (GV20)	On the head, 5 cun directly above the midpoint of the anterior hairline, on the midline of the head.	Oblique insertion, 12.5–25 mm in depth
Taiyang (EX-HN5)	On the head, in the depression approximately one finger-breadth posterior to the midpoint between the lateral end of the eyebrow and the outer canthus.	Perpendicular insertion, 12.5–25 mm in depth
Touwei (ST8)	On the head, 0.5 cun directly above the anterior hairline at the corner of the forehead, 4.5 cun lateral to the midline.	Oblique insertion, 12.5–25 mm in depth
Shuaigu (GB8)	On the head, 1.5 cun superior to the apex of the auricle, within the hairline.	Oblique insertion, 12.5–25 mm in depth
Fengchi (GB20)	In the posterior neck region, in the depression between the upper portion of the sternocleidomastoid muscle and the trapezius muscle, inferior to the occipital bone.	Oblique insertion toward the tip of the nose, 12.5–25 mm in depth
Hegu (LI4)	On the dorsum of the hand, at the midpoint of the radial side of the second metacarpal bone.	Perpendicular insertion, 12.5–25 mm in depth
Taichong (LR3)	On the dorsum of the foot, in the depression anterior to the junction of the first and second metatarsal bones, where a pulsation of the dorsal artery may be felt.	Perpendicular insertion, 12.5–25 mm in depth
Fenglong (ST40)	On the lateral side of the lower leg, 8 cun superior to the prominence of the lateral malleolus, on the lateral border of the tibialis anterior muscle.	Perpendicular insertion, 25 mm in depth

(*Continued*)

Table 2 (Continued).

Acupoints	Location	Depth of Insertion
Additional		
Cervical Jiaji (EX-B2) at the level of C3–C4	Located 0.5 cun lateral to the lower border of the spinous processes of the 3rd and 4th cervical vertebrae.	Perpendicular insertion, 12.5–25 mm in depth
Yintang (GV29)	On the head, in the depression between the medial ends of the two eyebrows.	Oblique downward insertion, 12.5–25 mm in depth,
Shenmen (HT7)	On the anterior wrist, at the ulnar end of the transverse crease of the wrist, on the radial side of the tendon of the flexor carpi ulnaris muscle.	Perpendicular insertion, 7.5–12.5 mm in depth
Zhongwan (CV12)	On the upper abdomen, 4 cun above the umbilicus, on the anterior midline.	Perpendicular insertion, 25 mm in depth
Tianshu (ST25)	On the abdomen, 2 cun lateral to the umbilicus, level with its center.	Perpendicular insertion, 25 mm in depth
Qihai (CV6)	On the lower abdomen, 1.5 cun inferior to the umbilicus, on the anterior midline.	Perpendicular insertion, 25 mm in depth

on day −3 of each menstrual cycle (estimated according to the previous cycle). During the first week (from days −3 to +4 of menstruation), each participant will complete 1–2 sessions, followed by 2–3 sessions per week for the next 3 weeks. This treatment schedule will be repeated for three consecutive menstrual cycles, totaling 12 weeks of treatment and 30 sessions. All treatment sessions will be monitored and recorded using a treatment diary.

SEA Group Treatment Protocol

SEA will be performed using specially designed blunt-tip sham needles (0.3 mm × 25 mm) to closely mimic the sensation of EA and effectively blind participants. To minimize physiological effects, non-acupoint and non-meridian locations differing from those used in the EA group will be selected (Table 3 and Figure 2A). After disinfecting the local skin,

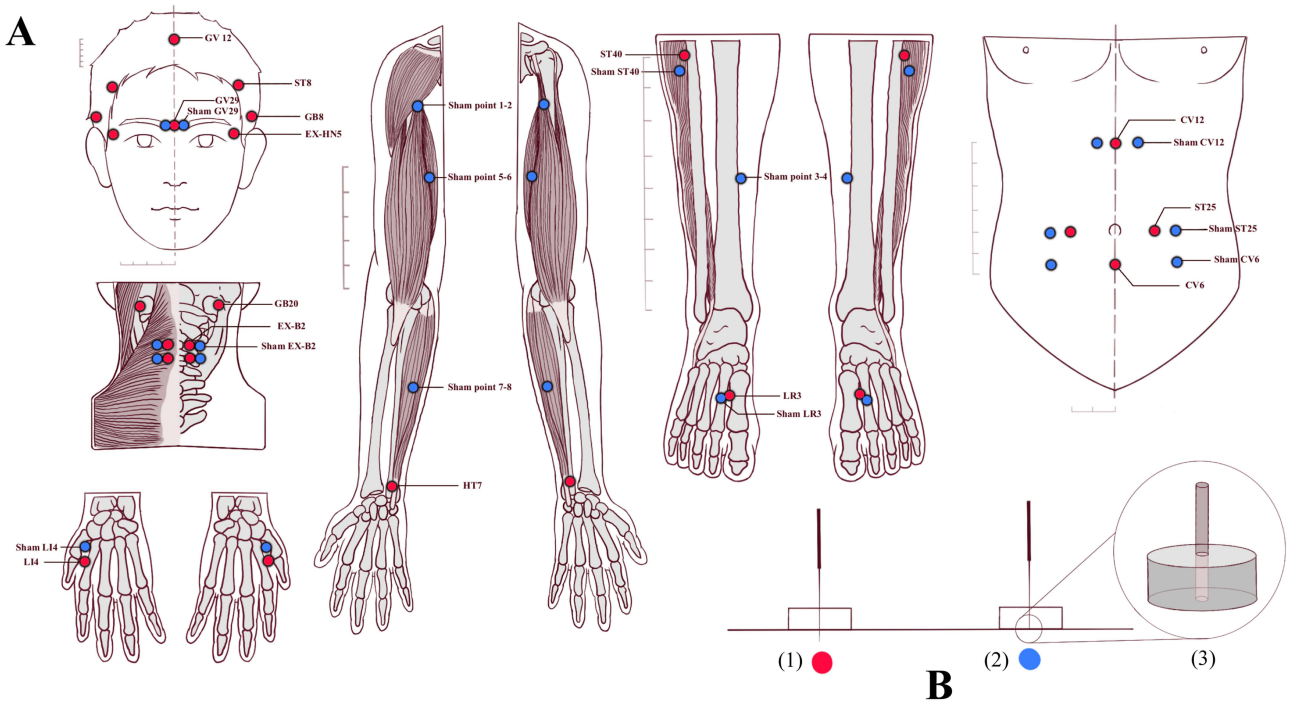

Figure 2 (A) Locations of acupoints: GV20: Baihui; ST8: Touwei; GB8: Shuaigu; EX-HN5: Taiyang; GV29: Yintang; GB20: Fengchi; EX-B2: Cervical Jiaji at C3–C4 level; LI4: Hegu; HT7: Shenmen; ST40: Fenglong; LR3: Taichong; CV12: Zhongwan; ST25: Tianshu; CV6: Qihai. (**B**) Illustration of acupuncture: (1) red point: traditional acupuncture; (2) blue point: sham acupuncture; (3) blunt tip.

Table 3 Locations of Non-Acupuncture Points in the Sham Electroacupuncture Group

Non-Acupoints	Location	Depth of Insertion
Main		
Sham Point 1–2	Bilateral, on the medial upper arm, at the junction of the deltoid and biceps brachii; midpoint between Zhongfu (LU1) and Jianqian (EX-UE); between Spleen and Lung meridians.	Non-penetrating
Sham Point 3–4	Bilateral, 4 cun above the medial malleolus, posterior to the medial tibia; midpoint between Sanyinjiao (SP6) and Ligou (LR5); between Spleen and Liver meridians.	Non-penetrating
Sham Point 5–6	Bilateral, 4.5 cun above the cubital crease, medial upper arm; midpoint between Zhoujian (EX-UE1) and Jiquan (HT1); between Heart and Small Intestine meridians.	Non-penetrating
Sham Point 7–8	Bilateral, 6 cun above the cubital crease, between the ulna and flexor carpi ulnaris; midpoint between Shenmen (HT7) and Shaohai (SI8); between Heart and Small Intestine meridians.	Non-penetrating
Sham LI4	Between bases of 1st and 2nd metacarpals, ulnar side of 1st metacarpal; midpoint between Hegu (LI4) and Taiyuan (LU9); between Large Intestine and Lung meridians.	Non-penetrating
Sham LR3	Midpoint of 2nd metatarsal, between Taichong (LR3) and Neiting (ST44); between Liver and Stomach meridians.	Non-penetrating
Sham ST40	7.5 cun above lateral malleolus, anterior to peroneus longus; midpoint between Fenglong (ST40) and Yangjiao (GB35); between Stomach and Gallbladder meridians.	Non-penetrating
Additional		
Sham cervical EX-B2 at the level of C3–C4	0.5 cun lateral to cervical Jiaji, between Du and Bladder meridians.	Non-penetrating
Sham GV29	Midpoint between Yintang (GV29) and Cuanzhu (BL2); between Du and Bladder meridians.	Non-penetrating
Sham CV12	1 cun lateral to Zhongwan (CV12), midpoint to Liangmen (ST21); between Kidney and Stomach meridians.	Non-penetrating
Sham ST25	1 cun lateral to Tianshu (ST25), midpoint to Daheng (SP15); between Stomach and Spleen meridians.	Non-penetrating
Sham CV6	3 cun lateral to Qihai (CV6), between Ren and Spleen meridians.	Non-penetrating

small foam pads will be taped over the points to conceal the procedure. The acupuncturist will insert the blunt-tip needle through the foam pad, placing it on the skin surface without penetration or manipulation. The sham needles will remain on the skin for 30 min, after which they will be gently removed by the acupuncturist. The EA apparatus will be connected longitudinally to the needles on each side (sham points 1–2 and 3–4). Despite not being switched on, the EA apparatus will present the same working power indicator and sound without actual current output. The treatment frequency and sessions will be identical to those in the EA group, and the treatment diary will also be used in SEA group.

Rescue Medication

Participants will generally be barred from using any analgesic medication during the study period. However, in cases of intolerable pain, we will provide the recommended NSAID for acute migraine attacks, namely oral paracetamol (500 mg per tablet), according to the International Headache Society for the acute pharmacological treatment of migraine.[26] Patients will be limited to one tablet per dose and a maximum of 1000 mg per day. Paracetamol use should not exceed 3 days per menstrual cycle. The dosage and timing of any medication taken will be promptly and accurately documented in the headache diary. To minimize potential bias from the medication's half-life, no rescue medication will be allowed within 48 h prior to any assessment. If medication is taken during this period, the corresponding day will automatically be recorded as a headache day.

Outcomes

Supervised by independent research assistants, patients will complete written headache diaries every menstrual cycle from baseline to week 24.

Primary Outcome

The primary outcome is the change in standardized monthly headache days (SMHDs) at week 12 versus baseline. In addition, changes in SMHDs from baseline to weeks 4, 8, 16, 20, and 24 will also be assessed as secondary outcomes. SMHDs will be calculated by adjusting the actual number of headache days to a standard 28-day menstrual cycle using the following formula: SMHDs = (actual headache days × 28) ÷ individual menstrual cycle length.

Secondary Outcomes

The secondary outcomes are as follows:

(1) The proportion of patients with cured MRM in weeks 12, 16, 20, and 24. Patients no longer meeting the diagnosis criteria for MRM will be defined as cured.

(2) The responder rate for MRM in weeks 4, 8, 12, 16, 20, and 24. The responder rate is defined as at least 50% reduction in SMHDs versus baseline.

(3) Change in standardized monthly headache severity score from baseline to weeks 4, 8, 12, 16, 20, and 24, which will be calculated as follows: standardized monthly headache severity score = (actual monthly severity score × 28) ÷ individual menstrual cycle length.

(4) Change in standardized monthly use of rescue medication from baseline to weeks 4, 8, 12, 16, 20, and 24, which will be calculated as follows: rescue medication taken standardized monthly = (actual doses × 28) ÷ individual menstrual cycle length.

(5) Headache diary completion rate in weeks 4, 8, 12, 16, 20, and 24.

(6) Overall recruitment rate at the end of the recruitment phase. The overall recruitment rate will be defined as the percentage of eligible participants who agreed to participate in the trial and calculated as follows: recruitment rate = (number of enrolled participants ÷ total number of eligible patients) × 100%.

(7) Overall retention rate in weeks 4, 8, 12, 16, 20, and 24. The overall retention rate will be defined as the percentage of enrolled participants who completed the entire treatment and follow-up and calculated as follows: retention rate = (number of participants who completed the study ÷ total enrolled participants) × 100%.

(8) Change in the Hospital Anxiety and Depression Scale (HADS) score[27] from baseline to weeks 4, 8, 12, 16, 20, and 24. HADS is used to assess patients' anxiety and depression over the past week. It consists of 14 items divided into two subscales, namely anxiety and depression, each containing seven items. Each item is scored on a scale from 0 to 3, with subscale scores ranging from 0 to 21. Higher scores indicate more severe symptoms. A score of ≥8 on either subscale is considered indicative of anxiety or depression.

(9) Change in the Headache Impact Test-6 (HIT-6) score[28] from baseline to weeks 4, 8, 12, 16, 20, and 24. HIT-6 is a brief and practical tool used to assess the impact of headaches in both clinical research and routine practice. It covers multiple domains of health-related quality of life, including pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. Each item is rated using a 5-point Likert scale as follows: 6 = never, 8 = rarely, 10 = sometimes, 11 = very often, and 13 = always. The total HIT-6 score is calculated by summing the scores of all six items, giving a possible score range of 36–78. Higher scores indicate a greater impact of headache on daily life.

(10) Change in the Migraine-Specific Quality of Life Questionnaire (MSQ v2.1) score[29] from baseline to weeks 4, 8, 12, 16, 20, and 24. MSQ evaluates migraine-related quality of life across three domains: role function-restrictive, role function-preventive, and emotional function. Each item is rated on a 6-point Likert scale ranging from 1 ("all the time") to 6 ("none of the time"). Scores are calculated for each domain and then converted to a scale ranging from 0 to 100, with higher scores indicating better quality of life. The Chinese version of MSQ v2.1, which has been validated for good reliability and validity,[30] will be used in this study.

(11) Patient's Global Impression of Change (PGIC)[31] at weeks 4, 8, 12, 16, 20, and 24. PGIC will be used to assess participants' subjective perception of overall improvement. The scale consists of seven levels: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. Lower scores indicate greater perceived improvement.

(12) Participants' expectations for acupuncture at baseline. At baseline, the following question will be asked to assess participants' expectations regarding acupuncture for MRM: "What level of improvement do you expect from

acupuncture for your MRM?" Participants may choose one of the following responses: "no improvement", "slight improvement", "moderate improvement", "marked improvement", or "unclear." The relationship between participants' expectations for acupuncture and the primary outcome will be statistically analyzed.

Safety Assessment

Any adverse event (AE), whether related (such as dizziness, palpitations, local hematoma, or infection) or unrelated to acupuncture, will be carefully observed by the acupuncturist and documented in the AE report sheet. Serious AEs (eg, fatal, life-threatening, disabling, requiring hospitalization) must be reported to the Medical Ethics Committee of Guang'anmen Hospital within 24 h. After each treatment session, researchers will record whether any AE has occurred.

Data Management and Quality Control

A designated research assistant will be responsible for completing all outcome assessments throughout the trial, and this researcher will remain blinded to group allocation. The initial data will be filled in printed case report forms (CRFs) by the responsible outcome assessor, who will be the only individual granted access to these data. The investigator will only draw lines for any changes in the CRFs for information, record the modified data, and sign date the forms to prevent the original records from being erased or overwritten. The research team will be responsible for data organization, and two data entry checks will be performed. The personal information of all participants, including name, phone number, ID number, and medical records, will be kept anonymous to prevent information leakage. All participants' paper data will be stored by the researchers in a special cabinet and preserved for at least 5 years after publication. The Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences will periodically review the progress of the trial and oversee the processes of data collection, allocation, and confidentiality. Any modifications to the trail protocol or termination of the trial will be decided by the Ethics Committee. The data monitoring committee is independent of the study sponsor, and it has no conflicts of interest.

Acupuncture will be delivered by licensed practitioners with at least 2 years of clinical experience. Because both EA and SEA are considered safe in this study, the intervention protocols will remain unchanged throughout the trial. Management of AEs will follow the same procedures in both groups, and the trial will be paused immediately if any serious AE occurs. Unblinding will occur only in the event of a serious adverse event requiring knowledge of treatment assignment, as specified above. Participants in the SEA group who wish to receive further treatment after the study will be eligible for 12 additional EA sessions. All cases of withdrawal or dropout will be carefully recorded.

Sample Size

This trial is designed to evaluate the feasibility and efficacy of EA for MRM prevention, with the change in SMHDs from baseline as the primary outcome. As a feasibility-oriented pilot study, no formal power calculation was performed. Instead, the sample size was determined with reference to previous research on acupuncture for migraine[19,24] and the methodological recommendation that at least 12 participants per group[32] are sufficient to estimate feasibility parameters such as recruitment, retention, variability, and effect size for planning a future definitive trial. Therefore, a total of 40 participants (20 per group) was planned, which ensures that the 95% confidence interval width for a target retention rate of approximately 80% would not exceed ±10% under the normal approximation. This sample size is considered sufficient to achieve the practical aim of our study.

Statistical Analysis

Continuous variables will be expressed as the mean ± standard deviation or median with interquartile range, as appropriate. For data following a normal distribution, between-group differences from baseline will be analyzed using the independent-samples *t*-test. Non-normally distributed data will be assessed using non-parametric tests. Categorical variables will be summarized as counts and percentages and compared using the chi-squared test or Fisher's exact test. The primary outcome will be assessed by employing a mixed-effects model for repeated measures (MMRM). The dependent variable will be the observed change from baseline scores at each scheduled post-baseline visit. This approach will also be utilized for analyzing other continuous outcomes, such as changes from baseline in headache severity scores

and alterations in the number of days with headache. All analyses will be conducted on an intention-to-treat basis, including all participants as originally assigned, regardless of their adherence to the intervention protocol. A safety set including all participants who received at least one safety evaluation after treatment will also be analyzed in this study. Further details are described in the statistical analysis plan. Statistical analyses will be performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA), with two-sided $P < 0.05$ denoting statistical significance.

Discussion

Currently, acupuncture, physiotherapy, and manual trigger point treatment are widely applied as non-pharmacological interventions for migraine.[33,34] However, high-quality sham-controlled RCTs specifically for MRM remain scarce. To address this gap, we conducted the first randomized, two-arm, parallel-group pilot RCT. Although acupuncture has been investigated for preventing MM,[35–37] evidence specifically targeting MRM remains limited and inconclusive. To date, only one RCT has reported the efficacy of manual acupuncture combined with placebo compared with naproxen plus placebo. No placebo- or sham-controlled RCTs of EA for MRM have been reported. Therefore, this trial is designed to evaluate the feasibility, efficacy, and safety of EA in preventing MRM by comparing EA and SEA over a 12-week treatment period followed by 12 weeks of follow-up.

Although the precise mechanisms remain unclear, we hypothesize that EA exerts its effects on MRM through multiple potential pathways. Estrogen withdrawal is linked to migraine attacks via CGRP release, vascular dysregulation, and central sensitization.[38] EA may prevent attacks by stabilizing estrogen fluctuations through hypothalamic–pituitary–gonadal (HPG) axis modulation, thus mitigating neuronal hyperexcitability and neuroinflammation. This proposed mechanism provides a strong rationale for EA's use in MRM prophylaxis and merits further investigation.

This trial has several methodological strengths. First, it is the first to systematically assess EA for MRM prevention. The intervention is aligned with menstrual phases: 2–3 sessions of preventive EA in the intermenstrual period and 1–2 sessions of stabilizing EA during menstruation. Second, the use of SMHDs as the primary outcome enhances the study's methodological rigor. By normalizing headache frequency to a standard 28-day cycle, the study reduces variability from differing menstrual lengths and improves data consistency and comparability. This approach also provides a foundation for outcome standardization in future large-scale trials. Third, the study includes a broad set of secondary outcomes covering quality of life, psychological state, medication use, and patient-reported improvement. This multidimensional evaluation supports a more comprehensive understanding of treatment mechanisms and helps identify optimal primary outcomes for future studies. Fourth, feasibility indicators such as headache diary completion, recruitment rate, and retention rate are incorporated to assess patient adherence and identify potential compliance barriers. Participants will maintain detailed headache diaries, thereby improving outcome accuracy.

Regarding the sham control design, previous migraine trials[16–18] commonly used superficial needling at non-acupoints. However, this method can generate larger placebo effects than pharmacological placebos because of the physical act of needling.[39–41] By contrast, blunt-tip sham needles, which do not penetrate the skin, have been demonstrated to elicit fewer physiological responses,[42] and they are methodologically superior.[43] This trial therefore employs non-penetrating superficial stimulation at non-acupoints as the sham control to minimize placebo effects and better isolate the specific effects of EA.

This trial has several limitations. First, as a pilot study, the relatively small sample size limits the statistical power to draw definitive conclusions on efficacy, and the findings should therefore be interpreted with caution. Second, it is not feasible to blind acupuncturists, potentially introducing bias. Third, the 12-week follow-up period might be insufficient to assess long-term effects, and the study will not evaluate individualized acupuncture protocols. Fourth, although sex hormones such as estradiol and progesterone are believed to play critical roles in the pathophysiology of MRM, hormonal profiling including estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone, prolactin, and testosterone will not be performed because of budgetary constraints. These limitations should be addressed in future large-scale trials.

This pilot study aims to optimize the EA treatment frequency based on menstrual patterns while minimizing patient burden. The findings will inform the design of future definitive RCTs and contribute to evidence-based, cycle-specific

non-pharmacological management for MRM, with positive outcomes potentially leading to refined acupuncture protocols tailored to the menstrual cycle for direct clinical application.

Data Sharing Statement

The study protocol and the statistical analysis plan will be available from the corresponding author upon reasonable request after publication for up to 3 years. Requests should be directed to Weiming Wang, MD, PhD, Department of Acupuncture and Moxibustion, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, No. 5 Beixiange St., Xicheng District, Beijing, China, Email: wangweiming1a1@163.com.

Ethics Approval and Consent to Participate

The study has been approved by the Institutional Review Boards of Guang'anmen Hospital in China (approval No. 2025-031-KY-01, Tel +8610-88001552), and all investigators have complied with the Declaration of Helsinki. Participants have the right to withdraw their consent at any time, and we guarantee the confidentiality of all participants.

Acknowledgment

The authors appreciate the support and efforts of the patients involved in this study. We thank Medjaden Inc. for scientific editing/proofreading of this manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study is supported by the Programme for Cultivation of Outstanding Young Scientific and Technological Talents (Innovation Category) under the Basic Scientific Research Fund of China Academy of Chinese Medical Sciences (grant no. ZZ13-YQ-019), Scientific and Technological Innovation Project of China Academy of Chinese Medical Sciences (grant no. CI2021A03517), National High Level Traditional Chinese Medicine Hospital Clinical Research and Achievement Transformation Capacity Enhancement Project - Pilot and Continuing Project Backbone Talent Cultivation Project (grant no. CZ40906), and the High Level Chinese Medical Hospital Promotion Project (grant no. HLCMHPP2023089), National Natural Science Foundation of China (grant no. 82405192) and the project of "Friendship Seed Plan" Talent Project of Beijing Friendship Hospital, Capital Medical University (grant no. YYZZ202333).

Disclosure

The authors declare that they have no competing interest in this work.

References

1. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1–211. doi:10.1177/0333102417738202
2. Burch R. Epidemiology and treatment of menstrual migraine and migraine during pregnancy and lactation: a narrative review. *Headache*. 2020;60 (1):200–216. doi:10.1111/head.13665
3. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. *J Headache Pain*. 2022;23(1):34. doi:10.1186/s10194-022-01402-2
4. Brandes JL. The influence of estrogen on migraine: a systematic review. *JAMA*. 2006;295(15):1824–1830. doi:10.1001/jama.295.15.1824
5. Ansari T, Lagman-Bartolome AM, Monsour D, Lay C. Management of menstrual migraine. *Curr Neurol Neurosci Rep*. 2020;20(10):45. doi:10.1007/s11910-020-01067-x
6. Martin VT. Menstrual migraine: a review of prophylactic therapies. *Curr Pain Headache Rep*. 2004;8(3):229–237. doi:10.1007/s11916-004-0057-1

7. Vetvik KG, MacGregor EA. Menstrual migraine: a distinct disorder needing greater recognition. *Lancet Neurol*. 2021;20(4):304–315. doi:10.1016/S1474-4422(20)30482-8
8. Lichten EM. Menstrual migraine and treatment options: review. *Headache*. 2018;58(1):145–146. doi:10.1111/head.13203
9. Yalınay Dikmen P, Onur Aysevener E, Kosak S, Ilgaz Aydınlar E, Sağduyu Kocaman A. Relationship between MIDAS, depression, anxiety and alexithymia in migraine patients. *Acta Neurol Belg*. 2020;120(4):837–844. doi:10.1007/s13760-017-0856-x
10. Ferini-Strambi L, Galbiati A, Combi R. Sleep disorder-related headaches. *Neurol Sci*. 2019;40(Suppl 1):107–113. doi:10.1007/s10072-019-03837-z
11. Maasumi K, Tepper SJ, Kriegler JS. Menstrual migraine and treatment options: review. *Headache*. 2017;57(2):194–208. doi:10.1111/head.12978
12. MacGregor EA. Prevention and treatment of menstrual migraine. *Drugs*. 2010;70(14):1799–1818. doi:10.2165/11538090-000000000-00000
13. Khoo CCW, Liu CC, Lu M, Huang YC, Weng HY. Acute and preventive treatment of menstrual migraine: a meta-analysis. *J Headache Pain*. 2024;25(1):143. doi:10.1186/s10194-024-01848-6
14. Ornello R, De Matteis E, Di Felice C, Caponnetto V, Pistoia F, Sacco S. Acute and preventive management of migraine during menstruation and menopause. *J Clin Med*. 2021;10(11):2263. doi:10.3390/jcm10112263
15. Organization WH. Guidelines on basic training and safety in acupuncture. Available from: https://iris.who.int/handle/10665/66007. Accessed June 3, 2025
16. Zhao L, Chen J, Li Y, et al. The long-term effect of acupuncture for migraine prophylaxis: a randomized clinical trial. *JAMA Intern Med*. 2017;177(4):508–515. doi:10.1001/jamainternmed.2016.9378
17. Li Y, Zheng H, Witt CM, et al. Acupuncture for migraine prophylaxis: a randomized controlled trial. *CMAJ*. 2012;184(4):401–410. doi:10.1503/cmaj.110551
18. Liu L, Chen Q, Zhao L, et al. Acupuncture plus topiramate placebo versus topiramate plus sham acupuncture for the preventive treatment of chronic migraine: a single-blind, double-dummy, randomized controlled trial. *Cephalalgia*. 2024;44(6):3331024241261080. doi:10.1177/03331024241261080
19. Xu S, Yu L, Luo X, et al. Manual acupuncture versus sham acupuncture and usual care for prophylaxis of episodic migraine without aura: multicentre, randomised clinical trial. *BMJ*. 2020:368:m697. doi:10.1136/bmj.m697
20. Yu JS, Zeng BY, Hsieh CL. Acupuncture stimulation and neuroendocrine regulation. *Int Rev Neurobiol*. 2013;111:125–140. doi:10.1016/B978-0-12-411545-3.00006-7
21. Zhou M, Pang F, Liao D, et al. Electroacupuncture improves allodynia and central sensitization via modulation of microglial activation associated P2X4R and inflammation in a rat model of migraine. *Mol Pain*. 2024;20:17448069241258113. doi:10.1177/17448069241258113
22. An Y, Zhang J, Ren Q, Liu J, Liu Z, Cao K. The mechanism of acupuncture therapy for migraine: a systematic review of animal studies on rats. *JPR*. 2025;18:473–487. doi:10.2147/JPR.S504892
23. Krause DN, Warfvinge K, Haanes KA, Edvinsson L. Hormonal influences in migraine - interactions of oestrogen, oxytocin and CGRP. *Nat Rev Neurol*. 2021;17(10):621–633. doi:10.1038/s41582-021-00544-2
24. Liu L, Zhang CS, Liu HL, et al. Acupuncture for menstruation-related migraine prophylaxis: a multicenter randomized controlled trial. *Front Neurosci*. 2022;16:992577. doi:10.3389/fnins.2022.992577
25. Linde M, Fjell A, Carlsson J, Dahlöf C. Role of the needling per se in acupuncture as prophylaxis for menstrually related migraine: a randomized placebo-controlled study. *Cephalalgia*. 2005;25(1):41–47. doi:10.1111/j.1468-2982.2004.00803.x
26. Puledda F, Sacco S, Diener HC, et al. International headache society global practice recommendations for the acute pharmacological treatment of migraine. *Cephalalgia*. 2024;44(8):3331024241252666. doi:10.1177/03331024241252666
27. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;67(6):361–370. doi:10.1111/j.1600-0447.1983.tb09716.x
28. Rendas-Baum R, Yang M, Varon SF, Bloudek LM, DeGryse RE, Kosinski M. Validation of the Headache Impact Test (HIT-6) in patients with chronic migraine. *Health Qual Life Outcomes*. 2014;12(1):117. doi:10.1186/s12955-014-0117-0
29. Cole JC, Lin P, Rupnow MFT. Validation of the migraine-specific quality of life questionnaire version 2.1 (MSQ v. 2.1) for patients undergoing prophylactic migraine treatment. *Qual Life Res*. 2007;16(7):1231–1237. doi:10.1007/s11136-007-9217-1
30. Chang HY, Jensen MP, Yang CC, Lai YH. Migraine-specific quality of life questionnaire chinese version 2.1 (MSQv2.1-C): psychometric evaluation in patients with migraine. *Health Qual Life Outcomes*. 2019;17(1):108. doi:10.1186/s12955-019-1169-y
31. Dodick DW, Silberstein S, Saper J, et al. The impact of topiramate on health-related quality of life indicators in chronic migraine. *Headache*. 2007;47(10):1398–1408. doi:10.1111/j.1526-4610.2007.00950.x
32. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharm Stat*. 2005;4(4):287–291. doi:10.1002/pst.185
33. Tedeschi R, Pillastrini P, Pierangeli G, Favoni V, Cortelli P, Cevoli S. Is physiotherapy in migraines known to sufferers? A cross-sectional study. *Neurol Sci*. 2024;45(4):1669–1674. doi:10.1007/s10072-023-07195-9
34. Tedeschi R. Manual trigger point treatment in migraine management: a scope review. *Confinia Cephalalgica*. 2024;34(2). doi:10.4081/cc.2024.15777
35. Yang M, Du T, Long H, Sun M, Liang F, Lao L. Acupuncture for menstrual migraine: a systematic review. *BMJ Support Palliat Care*. 2022;12(e6):e882–e892. doi:10.1136/bmjspcare-2019-002024
36. Yu X, Salmoni A. Comparison of the prophylactic effect between acupuncture and acupressure on menstrual migraine: results of a pilot study. *J Acupunct Meridian Stud*. 2018;11(5):303–314. doi:10.1016/j.jams.2018.04.003
37. Zhang Y, Wang Z, Du J, et al. Regulatory effects of acupuncture on emotional disorders in patients with menstrual migraine without aura: a resting-state fMRI study. *Front Neurosci*. 2021;15:726505. doi:10.3389/fnins.2021.726505
38. Delaruelle Z, Ivanova TA, Khan S, et al. Male and female sex hormones in primary headaches. *J Headache Pain*. 2018;19(1):117. doi:10.1186/s10194-018-0922-7
39. Lundeberg T, Lund I, Näslund J, Thomas M. The Emperors sham - wrong assumption that sham needling is sham. *Acupunct Med*. 2008;26(4):239–242. doi:10.1136/aim.26.4.239
40. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev*. 2010;2010(1):CD003974. doi:10.1002/14651858.CD003974.pub3
41. Linde K, Niemann K, Meissner K. Are sham acupuncture interventions more effective than (other) placebos? A re-analysis of data from the Cochrane review on placebo effects. *Forsch Komplementmed*. 2010;17(5):259–264. doi:10.1159/000320374

42. Lim SM, Go E. A systematic review of sham acupuncture validation studies. *BMC Complement Med Ther*. 2024;24(1):215. doi:10.1186/s12906-024-04506-1
43. Goddard G, Shen Y, Steele B, Springer N. A controlled trial of placebo versus real acupuncture. *J Pain*. 2005;6(4):237–242. doi:10.1016/j.jpain.2004.12.009