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STUDY PROTOCOL

Effects of Transcutaneous Electrical Acustimulation on Patients with Fibromyalgia Syndrome: Study Protocol of a Randomized, Double-Blind, Sham-Controlled Trial

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Background: Fibromyalgia Syndrome (FMS) is a chronic disorder characterized by widespread musculoskeletal pain, fatigue, and localized tenderness. Transcutaneous Electrical Acustimulation (TEA) is a non-invasive therapy that combines Traditional Chinese Medicine with electrical stimulation at specific acupoints. Previous studies have shown that TEA is effective in treating pain-related conditions. This study aims to evaluate the efficacy and mechanisms of TEA treatment for FMS.

Design: This is a prospective, randomized, double-blind, and placebo-controlled trial with two parallel groups, conducted at a single center. Forty participants will be randomly assigned to either the TEA group or the sham-TEA group in a 1:1 ratio. Participants will receive 2 weeks of treatment followed by 2 weeks of follow-up. The primary outcome is the change in VAS pain scores before and after treatment. Secondary outcomes include FMS and pain-related questionnaire scales, infrared thermography (IRT), vibration-controlled transient elastography (VCTE), blood neurobiological markers, cytokines, and metabolomics.

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Keywords: FMS, traditional Chinese medicine, chronic pain, Hegu (LI4), Taichong (LR3)

Introduction

Fibromyalgia Syndrome (FMS) is a chronic and multidimensional condition predominantly characterized by chronic widespread pain (CWP), fatigue, sleep disturbances, and cognitive impairments. It is a relatively common, ranking as the third most prevalent musculoskeletal disease, with global prevalence ranging from 1.78% to 4% of the general population.[1–3] FMS is most frequently observed in women aged 20 to 60, with a female-to-male ratio approximately between 2:1 and 7:1.[1,4,5] The syndrome often presents with multiple comorbidities, which complicating the syndrome and influencing treatment outcomes.[6] As a result, FMS is frequently misdiagnosed, with average diagnostic delays of around 2.3 years.[7] Moreover, the economic burden of FMS is significant, impacting both healthcare systems and patients' quality of life.[8] Studies from Europe and North America indicate that FMS patients face a significant disease burden not only in terms of healthcare costs—which are estimated to be three times higher than for non-FMS individuals—but also in terms of lost productivity and reduced quality of life.[9]

The pathophysiological mechanism remains uncertain and multifactorial, involving factors like central sensitization, abnormal peripheral nociception, autoimmune, inflammatory, and hormonal dysregulation.[10,11] Despite being recognized as a legitimate syndrome by numerous health organizations, there remains significant debate regarding its pathophysiology, diagnosis, and classification. Recent studies have identified small fiber neuropathy in patients with FMS,[12] which, coupled with the observed efficacy of antiepileptic drugs typically used for neuropathic pain, has prompted a re-evaluation of FMS's neuropathic pain characteristics and the exploration of new treatment strategies.[13]

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A 2014 meta-analysis suggested that pharmacologic treatments for FMS, which primarily address pain, show limited effectiveness in managing the condition's multidimensional nature. In contrast, non-pharmacologic approaches offer broader benefits across multiple symptom domains.[14] A 2020 review highlights the necessity of multi-modal treatment approaches, given the complexity of the condition.[1] Consequently, according to the latest EULAR recommendations for FMS, multicomponent therapies are supported (Evidence Ia, Grade A), and nonpharmacological interventions are prioritized as the initial treatment (Evidence IV, Grade D).[15]

Transcutaneous Electrical Acustimulation (TEA) is a promising non-invasive therapy that combines the principles of Traditional Chinese Medicine (TCM) with electrotherapy.[16] Studies have shown that TEA can effectively manage pain, fertility issues, and immune system modulation.[16–20] Basic studies have shown that TEA activates descending inhibitory pathways from the midbrain and brainstem, reducing the excitability of nociceptive neurons in the spinal cord.[21,22] It exerts its effects through molecular pathways, including the release of endogenous opioids.[23] TEA likely achieves analgesia by inhibiting pain-causing substances, promoting opioid peptide production, and disrupting mitogen-activated protein kinase signaling.[20,24]

However, research on TEA has been limited by methodological flaws, including insufficiently rigorous studies, poor replication, and inadequate control groups, making it difficult to conclusively establish its effectiveness for conditions like FMS.[23,25,26] A 2017 Cochrane guideline[27] noted that no strong evidence currently supports or refutes the use of TENS (transcutaneous electrical nerve stimulation, similar to TEA) for FMS pain. Therefore, we conducted this study further to investigate the effect of TEA treatment on FMS.

Our study is based on two hypotheses (Figure 1). First, we hypothesize that TEA alleviates central sensitization by reducing neuroinflammation-related factors.[28] This reduction is proposed to mitigate systemic inflammation[29] through improved microcirculation[30] and metabolic regulation, thereby alleviating the core symptoms of FMS and improving quality of life. Second, we hypothesize that Body Mass Index (BMI), Waist-Hip Ratio (WHR), and TCM syndrome patterns are closely associated with pain severity and treatment response. Specifically, patients with higher BMI and WHR tend to have elevated inflammation levels,[31] more severe pain,[32] and poorer treatment outcomes. TCM syndrome patterns, particularly the Liver Qi Stagnation, may show a better response to TEA treatment.

The objectives of the study are threefold: First, to evaluate the effect of TEA on the core symptoms of FMS, with a comprehensively evaluate overall clinical efficacy, especially pain relief as measured by VAS scores. Second, to explore the mechanisms of TEA in FMS, focusing on neuroinflammatory factors, microcirculation, metabolomics and VCTE techniques. Third, as an exploratory component of this study, we plan to investigate potential FMS subtypes by

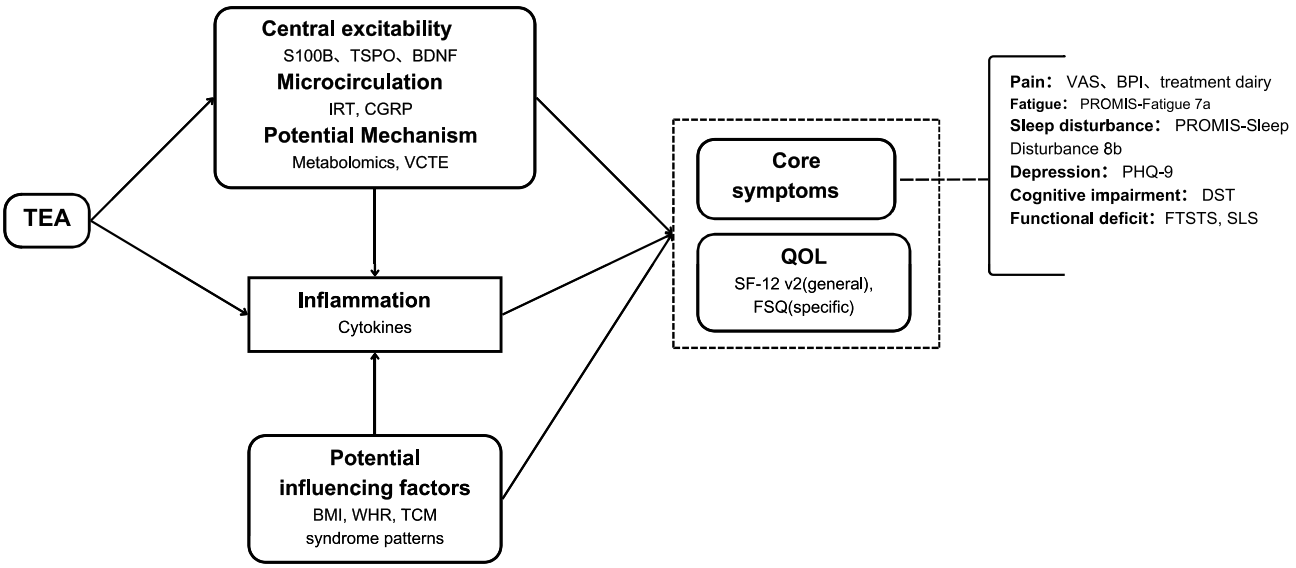

Figure 1 A hypothetical conceptual model of Transcutaneous Electrical Acustimulation (TEA), showing the expected outcomes and the mechanisms by which these outcomes will be assessed.

examining the relationships between BMI, WHR, and TCM syndrome patterns with both the baseline severity of FMS and the therapeutic outcomes of TEA. This analysis aims to provide preliminary insights into how subtype characteristics may influence treatment efficacy.

Materials and Methods

Study Design

The study protocol adhered to the rigorous guidelines set forth by the CONSORT[33] statements. This study is a prospective, randomized, double-blind (patients and researchers), single-center clinical, and placebo-controlled trial with two parallel groups. This trial is scheduled to start on July 1, 2024, and end on June 30, 2025, aiming to recruit 40 patients diagnosed with FMS. Forty participants will be randomly assigned to either the TEA group or the sham-TEA group in a 1:1 randomization ratio. Then they will undertake a 2-week treatment and a 2-week follow-up period. The flow chart is listed in Figure 2. The study schedule is listed in Table 1. The present protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidelines[34,35] and fulfills the SPIRIT checklist (see supplementary material). Any modifications to the protocol must be reported to and approved by the ethics committee.

Sample Size Calculation

The sample size for this study was calculated based on differences in VAS scores observed in pre-experimental results. The mean difference in VAS scores between the experimental and control groups was 1.0, with a standard deviation of 0.32. Using PASS 2023 software, we employed the sample size estimation method proposed by Chow et al, assuming a two-sided significance level (α) of 0.05 and a desired power (1-β) of 0.90.[36] The minimum sample size per group was initially calculated to be 3 participants, with a total of 6 participants required for both groups. To account for potential dropouts, we anticipated a 10% loss, which increased the required sample size to 4 participants per group, resulting in a total of 8 participants. However, considering clinical feasibility and to enhance the robustness and generalizability of the findings, we ultimately recruited 40 participants, with 20 participants in each group. This sample size is deemed sufficient to detect significant differences in VAS scores while ensuring the reliability and external validity of the results.

Setting and Recruitment

The obtain informed consent, intervention and data collection will be independently administered by three research assistants from Beijing University of Chinese Medicine.[37] Unless permission is obtained from the participant, any information that can identify their identity will not be disclosed to anyone outside the research team. Data will be reviewed periodically by a designated investigator. This single-center study is conducted at the China-Japan Friendship Hospital, which also serves as the China National Clinical Research Center for Pain. Participants will be recruited through online platforms, outpatient clinics, and inpatient wards.

Participant Eligibility

Participants must adhere to their ongoing treatment plans and are explicitly instructed not to alter their therapeutic interventions throughout the 4-week trial phase. The use of "as needed" rescue medications will be documented. We will also document factors that may influence treatment in the "treatment diary", such as medication changes, exercise, and emotional status.

The inclusion criteria for participants are as follows: (1) Adults aged 18–80; (2) Diagnosed with FMS based on the 2016 Revisions to the 2010/2011 FMS Diagnostic Criteria. (3) VAS≥3 scores. (4) Volunteer for this clinical study and sign an informed consent form.

Exclusion criteria include: (1) The state of electronic devices such as pacemakers and brain nerve stimulators etc. (2) Serious damage to the heart liver or kidneys or mental disorders or failure to cooperate with examination and treatment. (3) Women in pregnancy. (4) Active malignant tumor. (5) Fragile skin prone to bleeding rupture allergies etc. (6) Used TEA in the last 3 months. (7) Participation in other clinical studies.

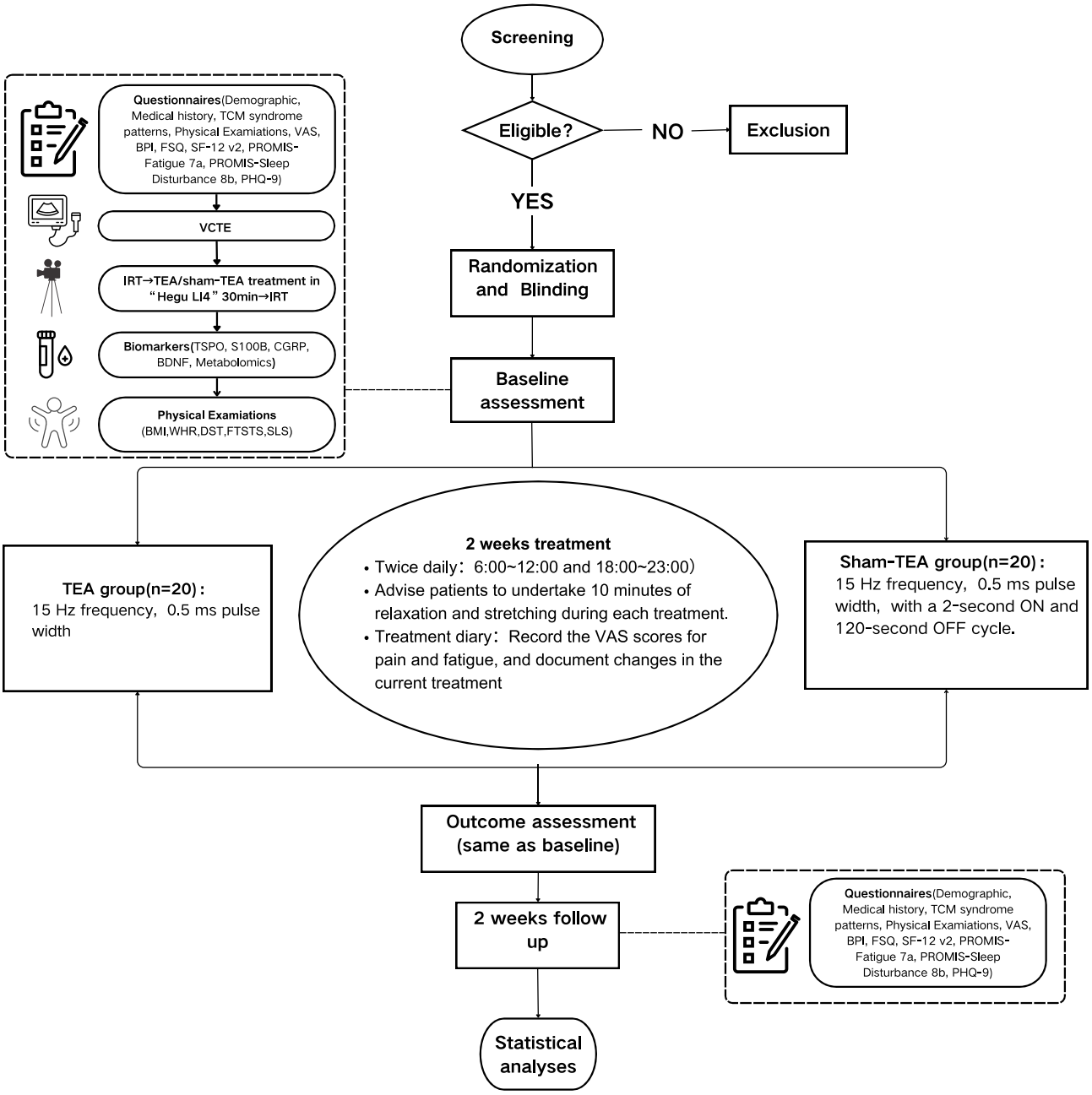

Figure 2 Study flow diagram.

Participants will be withdrawn if they cannot complete the study protocol for any of the following reasons: (1) Withdrawal of informed consent at any stage of the trial. (2) Inability to comply with the study protocol, including missing scheduled visits or not following treatment instructions. (3) Serious adverse events.

This study will strictly adhere to the ethical standards as outlined in the revised Helsinki Declaration of 2013. Before the intervention, all participants will be provided with a detailed explanation of the research process and will voluntarily sign a written informed consent form. Participants will be compensated for their time and effort. Upon completion of the study, patients in the sham-TEA group will receive TEA treatment using the same parameters as the experimental group as a form of compensation. If a participant suffers any injury related to the study, they will be entitled to receive free treatment provided by the China-Japan Friendship Hospital and compensation in accordance with relevant Chinese laws.

Table 1 Study Schedule of Enrollment, Intervention, and Assessments

Timepoint	Baseline	Allocation	Treatment	2 weeks Follow Up
	−7 ~ 0 days	0 days	18±4 days	31±4 days
ENROLLMENT				
Informed Consent	√			
Eligibility Check	√			
Demographic	√			
Medical history	√			
Randomization and blinding		√		
INTERVENTION				
TEA Treatment		√	√	
Sham-TEA Treatment		√	√	
ASSESSMENTS				
Primary Outcomes				
VAS*		√	√	√
Secondary Outcomes				
IRT*		√	√	
VCTE		√	√	
TSPO, S100B, CGRP, BDNF, Metabolomics		√	√	
Clinical Outcomes				
BPI		√	√	√
FSQ		√	√	√
SF-12 v2		√	√	√
PROMIS-Fatigue 7a		√	√	√
PROMIS-Sleep Disturbance 8b		√	√	√
PHQ-9		√	√	√
Other Secondary Outcomes				
TCM syndrome patterns		√	√	√
Physical Examinations		√	√	
Satisfaction survey			√	√
Unblinding questionnaire				√
Side effects		√	√	√

Notes: IRT: During the allocation phase, patients will undergo 30min of TEA treatment targeting the Hegu (LI4) acupoints bilaterally. IRT assessments will be conducted before and after the treatment.VAS: VAS scores should be assessed twice during the allocation phase, in conjunction with IRT. Furthermore, VAS scores must be documented before and after each treatment session within a "treatment diary" throughout the treatment period.

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Randomization, Allocation, and Blinding

Randomization was conducted using a table of random numbers. Random numbers from 1 to 100 was performed using SPSS 26.0 software, and the numbers were sorted in ascending order. The first 20 numbers were designated as the TEA group, while the subsequent 20 numbers were assigned to the sham-TEA group. Then the TEA devices from 1 to 40 according to the table of random numbers. The TEA devices and the sham-TEA devices will be visually indistinguishable. An independent statistician expert who is not involved in the trial will complete the aforementioned steps.

After confirming the participants' eligibility based on the inclusion and exclusion criteria, researchers will allocate treatment devices in chronological order of enrollment based on the participants' screening number. Allocation concealment will be maintained using the sealed-envelope method, where the randomization plan is kept in opaque envelopes. These envelopes will be distributed in sequence according to the enrollment order, and unblinding will occur by opening the envelopes to reveal group assignments when necessary.

Intervention

The TEA device is a watch-sized stimulator with two electrodes (SNM-FDC01; Ningbo Maida Medical Device, Ningbo, China), allowing simultaneous stimulation of a single acupoint bilaterally.[38]

The TEA group and sham-TEA group interventions will last for 14 days, with treatments administered twice daily. In the morning (0:00–12:00), participants will receive 30 minutes of stimulation at both sides and the He Gu (LI4) acupoint (depicted in Figure 3), followed by 30 minutes of stimulation at the Tai Chong (LR3) acupoint in the afternoon (12:00–24:00). Participants are instructed to adjust the stimulation intensity (current intensity) to the maximum tolerable level during the treatment period. Additionally, patients are advised to perform 10 minutes of relaxation and stretching exercises during each treatment session.

The parameters will be set to 15 hz, with a pulse width of 0.5 ms. The only difference between the TEA and sham-TEA groups is that the TEA group will receive a stimulation mode of 30 minutes on, while the sham-TEA group will follow a stimulation pattern of 2 seconds on and 120 seconds off.

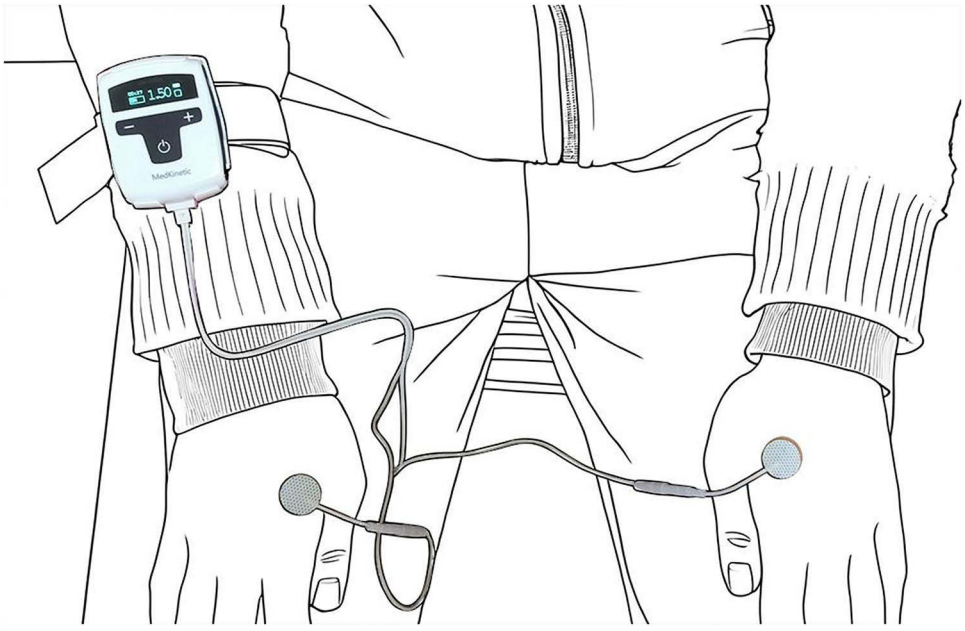

Figure 3 Placement of TEA electrodes at LI4.

Outcome Assessment

Primary Outcome

We used Visual Analogue Scale (VAS) to quantify the immediate and long-term pain relief effects of TEA. The VAS is a quantitative tool for assessing pain intensity, represented by a 100-mm horizontal line ranging from "no pain" (0 points) to "worst imaginable pain" (100 points).[39] We calculated the VAS reduction rate pre- and post-treatment for statistical analysis using the formula: $\frac{\text{Pre-treatment VAS score}-\text{Post-treatment VAS score}}{\text{Pre-treatment VAS score}}\times 100\%$. Previous studies have confirmed the construct validity and reliability of this scale.[40,41]

Secondary Outcomes

TCM Syndrome Patterns

We use a symptom questionnaire to determine the Traditional Chinese Medicine (TCM) syndrome patterns of patients, followed by subgroup analysis to preliminarily evaluate which syndrome type responds best to TEA treatment. Each patient was independently evaluated by at least two licensed TCM practitioners using the four diagnostic methods—inspection, auscultation and olfaction, inquiry, and palpation. Diagnoses were made in accordance with the standardized criteria specified in *Traditional Chinese Medicine Diagnostics* (ISBN: 9787117366571). Only cases with consistent diagnoses between the two evaluators were included. Disagreements were resolved through discussion or by consultation with a senior TCM expert. Detailed diagnostic records, including symptom profiles, tongue and pulse characteristics, were documented in case report forms to ensure traceability and support quality assurance.

FMS are diagnosed differentially by Western and Chinese medicine.[42] In TCM, FMS is considered a type of "jinbi" (muscle blockage) with a primary pathomechanism of Liver Qi Stagnation.[43–45] When Liver Qi becomes stagnant, the body's Qi circulation is disrupted, leading to muscle pain, cold intolerance in the limbs, and fatigue. TCM, as a holistic system, views this pathomechanism as potentially triggering a range of symptoms and comorbidities, similar to a "butterfly effect." For example, it can affect the Spleen(In TCM, the spleen is not considered an anatomical organ but rather a functional system responsible for digestion and transformation of food and fluids, which is distinct from the anatomical spleen), leading to symptoms like irritable bowel syndrome (IBS), which is often comorbid with FMS.[1] Additionally, since the Liver governs emotions in TCM, Liver Qi Stagnation can manifest as emotional disturbances, such as depression, which often improves with increased physical activity. This pattern is similar to the symptom characteristics commonly observed in FMS patients.

In summary, TCM believes that the pathogenesis of FMS is related to the liver. From the perspective of epidemiological studies, current research supports a close association between FMS and liver diseases.[4,46] FMS patients exhibit a higher incidence of liver cirrhosis.[47] Furthermore, a cross-sectional study identified significant associations between FMS and Hepatitis C Virus (HCV), Non-Alcoholic Steatohepatitis (NASH)-related cirrhosis, as well as psychiatric symptoms.[48] Moreover, There is growing evidence that chronic inflammatory liver diseases are linked to changes in central neural transmission, contributing to symptoms like fatigue, cognitive dysfunction, mood disorders, and sleep disturbances.[49]

These findings indicate a strong relationship between FMS and liver health. To further explore this, we conducted initial measurements of liver fibrosis/fatty liver in FMS patients using VCTE, a technique capable of detecting early-stage liver abnormalities.

Physical Examinations

The physical examinations need to be done last, because exercise may induce pain to worsen to the extent that the relevant questionnaire is affected.

- Digit Span Test (DST): DST is a neuropsychological assessment that evaluates short-term attention and working memory through two tasks: digit span forward and digit span backward. In the forward task, participants repeat a sequence of digits, while in the backward task, they repeat the same digits in reverse order. Higher DST scores are indicative of better performance. For FMS patients, cognitive symptoms, often called "fibro fog", can impact memory and concentration, making the DST useful for evaluating these cognitive limitations. Studies indicate that

patients with FMS tend to show reduced performance on DST,[50] highlighting attention and working memory deficits which are part of the cognitive challenges faced by individuals with FMS.

- Five Times Sit to Stand Test(FTSTS): The FTSTS is a validated functional assessment tool used to quantitatively evaluate lower body strength, endurance, and flexibility by measuring the time required for an individual to rise from a seated position to standing and return to sitting five times consecutively.[51] In patients with FMS, who commonly experience compromised muscle endurance and chronic fatigue, FTSTS serves as an objective indicator of functional mobility and physical endurance, both of which are typically reduced in this population. Additionally, diminished performance on the FTSTS in FMS patients has been correlated with an elevated risk of falls, attributable to muscle weakness and balance impairments associated with the condition. Consequently, FTSTS results can provide valuable insights into the physical limitations and fall risks inherent in FMS, aiding in the assessment of therapeutic efficacy and guiding targeted interventions for mobility and stability improvement in these patients.
- Single-Leg Stand Test (SLS): The SLS is a straightforward clinical assessment tool that evaluates balance, lower limb strength, and proprioception. In this test, patients are instructed to maintain stability while standing on one leg for a designated period, allowing for the assessment of neuromuscular control. The SLS is widely utilized in orthopedic and neurological assessments as well as in fall-risk evaluations. This test is particularly relevant in the context of FMS, where impairments in static balance and postural control are common. A small randomized controlled trial (RCT) conducted in 2016 indicated that patients with FMS exhibit poorer bilateral coordination than control subjects,[52] further underscoring the utility of the SLS in evaluating balance deficits and neuromuscular function in this population.

Body Mass Index(BMI) and Waist-Hip Ratio (WHR): Emerging evidence underscores the interrelationship between chronic pain and obesity.[53] In patients with FMS, obesity and increased BMI are commonly associated with greater disease severity and poorer quality of life.[54] Obesity, particularly central obesity, is characterized by the expansion of adipocytes, leading to localized hypoxia which triggers inflammatory responses and stimulates the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[31,55,56] Both BMI and WHR are widely used indicators for assessing obesity.[57] The purpose of measuring BMI and WHR is twofold: First, to verify the association between obesity and the severity of FMS, and analyze the correlation between obesity and the course of FMS. Second, to compare baseline obesity between the TEA and sham-TEA groups, ensuring it does not affect the VCTE results. Waist circumference was measured midway between the lowest rib and the iliac crest during expiration, while hip circumference was assessed at the maximum hip width.[57] The BMI calculation formula is: $\frac{weight\ (kg)}{(\text{height(m)})2}$. The WHR calculation formula is: $\frac{\text{waist circumference(cm)}}{\text{hip circumference(cm)}}$.

Multidimensional Questionnaires

- Brief Pain Inventory (BPI): The BPI can be used to evaluate pain severity, pain interference, average pain, worst pain and its impact on daily functioning. Studies have demonstrated strong reliability of BPI(Cronbach's $\alpha = 0.85$)[58] and BPI-SF (Cronbach's $\alpha = 0.84$).[59]
- Fibromyalgia Survey Questionnaire (FSQ): The FSQ is a valuable tool for assessing the number and intensity of pain sites and tender points in individuals with FMS.[60] The FSQ scale effectively measures the primary symptoms of FMS and provides a reliable assessment of their severity.[61] The FSQ has shown good reliability(Cronbach's $\alpha = 0.814$), convergent and discriminant validity.[61,62] The FSQ consists of two components: the Widespread Pain Index (WPI) and the Somatic Severity Score (SSS).
- Short Form 12 Item (version 2) Health Survey (SF-12 v2): The SF-12 v2 is widely used for assessing health status and is considered a generic health-related quality of life (QoL) instrument. It evaluates eight domains of functioning and well-being, including physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), energy and vitality (VT), social functioning (SF), role limitations due to

emotional problems (RE), and mental health (MH).[63] The eight domains can be summarized into two composite scores: the physical component summary (PCS) and the mental component summary (MCS).[64] The scale ranges from 0 to 100, with lower scores indicating a lower quality of life. Research across multiple domains shown SF-12 had satisfactory reliability (Cronbach's α = 0.7 to 0.910) and validity.[65–74]

- The Patient-Reported Outcomes Measurement Information System® (PROMIS)-Fatigue Short Form 7a (SF-7a) scale (PROMIS-Fatigue 7a) and PROMIS Sleep Disturbance 8b short form(PROMIS-Sleep Disturbance 8b): PROMIS could standardize patient-reported outcomes for chronic conditions through short-form (SF) instruments.[75] The PROMIS-Fatigue 7a consists of seven items, and the PROMIS-Sleep Disturbance 8b comprises eight items. Both utilize a 5-point scale to assess experiences over the past seven days. For FMS, the PROMIS-SF showed moderate test-retest reliability (ICC 0.62 to 0.71) and strong internal consistency (Cronbach's α= 0.89 to 0.92).[76–78]
- Patient Health Questionnaire-9 (PHQ-9): The PHQ-9 consists of nine items, including symptoms such as sleep disturbances, fatigue, and decreased appetite, which are common in FMS. It uses a 4-point rating scale, with the total score reflecting the severity of depressive symptoms. The score ranges from 0 to 27, with higher scores indicating greater depression severity. A systematic review has confirmed PHQ-9 is a validated instrument for identifying and monitoring depression, anxiety, and somatization.[79]

Laboratory Tests and Imaging

- Infrared thermography (IRT)

We use IRT to detect the highest, lowest, and average temperatures of a patient's hands and face, and the facial image can also generate a TCM Pattern Identification Report. IRT can capture the body's infrared emissions to generate "IR thermograms", reflecting skin surface temperature variations that indicate underlying physiological conditions.[80,81] IRT has demonstrated a sensitivity of 90% and a specificity of 86%.[81] Previous studies have revealed the presence of microcirculatory abnormalities in patients with FMS, which may be associated with dysfunction of the autonomic nervous system (ANS)[82,83] and pain modulation.[84] FMS often exhibits exacerbation upon cold exposure and alleviation with heat, suggesting that improved blood circulation through TEA may be one of its therapeutic mechanisms.[85] We will record IR thermograms before and after TEA treatment, including the facial region and the palmar and dorsal aspects of both hands. In our study using the D-LU384 model IRT camera produced by Xi'an Zhongke Lead IR-Tech Co., Ltd, China. This device employs a non-cooled focal plane infrared detector (polysilicon), with a working wavelength range of 8-14μm, a frame rate of ≥25Hz, thermal sensitivity of <60mK, temperature measurement range of 28-42°C, and effective pixels of ≥384×288. The imaging distance is 0.5 to 3m, with temperature measurement accuracy of ≤0.4°C, temperature consistency of ≤0.2°C, operating within an ambient temperature range of 10 °C to 30 °C. Results were analyzed using the Xi'an Taihao Infrared Management System V1.0 software, which generates reports on maximum, minimum, and average temperatures. Additionally, the software produces an extra report on TCM constitution identification. All IR thermograms were collected in compliance with the standards of the International Academy of Clinical Thermology. (IACT)

- Vibration controlled transient elastography (VCTE)

VCTE, provided by the FibroScan box device from Echosens in Paris, France, is a state-of-the-art, non-invasive method for assessing liver fibrosis/fatty liver.[86] This device enables the real-time, non-invasive acquisition of both Liver Stiffness Measurement (LSM) and Controlled Attenuation Parameter (CAP), where LSM evaluates liver fibrosis and CAP assesses steatosis.

LSM, which is calculated from shear wave velocity measurements and converted via Hooke's law, offers a quantitative assessment of hepatic fibrosis in kilopascals (kPa).[87] Fibrosis stages are categorized as follows: F0 for 0–5.9 kPa, F1 for 6.0–6.9 kPa, F2 for 7.0–9.0 kPa, F3 for 9.1–10.3 kPa, and F4 for values ≥10.4 kPa. LSM values below 8 kPa effectively rule out advanced fibrosis, while values above 12–15 kPa are indicative of its presence, thereby facilitating the diagnosis and staging of liver fibrosis.[88]

The CAP, utilizing ultrasonic attenuation, is specifically designed to stage hepatic steatosis by quantifying liver fat content.[87] Elevated CAP values suggest more severe steatosis, rendering it a valuable tool for investigating and monitoring liver diseases associated with fatty liver conditions. Patients were classified into three steatosis categories based on CAP values: low (<250 dB/m), intermediate (250–300 dB/m), and high (>300 dB/m). A CAP value >275 dB/m diagnoses significant steatosis.[88]

The FibroScan is performed by specially trained physicians. Before the examination, patients should fast for at least 3 hours and refrain from alcohol consumption for 24 hours.[89] Measurements are taken with patients lying supine, their right arm placed above the head and the right leg crossed over the left, creating a "C" shape to enhance intercostal access for measuring the right liver lobe.[90]

- Biomarker Testing:

To better understand the mechanisms of tea treatment, we conducted blood biomarker assessments before and after the intervention. Venous blood samples were collected on days −7 to 0 and at 18 ± 4 days, with each collection yielding 4–6 mL (divided into two tubes) using EDTA anticoagulant tubes. One tube was sent immediately to China-Japan Friendship Hospital Laboratory for cytokine analysis(IL-1β, IL-2, IL-4, IL-6, IL-5, IL-10, IL-12p70, IL-17, TNF-α, IFN-α, IFN-γ, IL-8), while the other tube was processed for centrifugation within 30 minutes at 2–8°C, at 1000×g for 15 minutes. After centrifugation, the supernatant was aliquoted into four 200 μL samples and stored in a −80°C freezer within 5 minutes. One for measuring TSPO, S100B, BDNF, and CGRP, another for metabolomics analysis, and the remaining two as backups. The assays for TSPO, S100B, CGRP, and BDNF were conducted every four months using the same batch of ELISA plates. To minimize inter-group variability, metabolomics samples will be sent for analysis after the completion of the trial.Translocator Protein (TSPO),[91] S100 calcium-binding protein B (S100B),[92] Brain-Derived Neurotrophic Factor (BDNF),[93] and Calcitonin Gene-Related Peptide (CGRP)[94,95] were detected using commercial enzyme-linked immunosorbent assay (ELISA) kits from FineTest (Wuhan, China) with the following catalog numbers: EH4447 for TSPO, EH0543 for S100B, EH0043 for BDNF, and EH2808 for CGRP. We analyzed the metabolites extracted from a 200 μL plasma sample using liquid chromatography-mass spectrometry (LC-MS), followed by peak extraction and alignment of the resulting mass spectrometry data.[96,97]

Covariables

- Demographic and Medical history: The demographic information including date of birth, age, sex, ethnicity, marital status, occupation, and education level. Medical history including past medical history, concurrent medications, personal history (smoking, alcohol consumption), allergy history, menstrual history (for female participants), and family medical history.
- Rescue medications.

Quality Control

All researchers must undergo training and pass a training assessment before performing trial procedures. All distributed TEA devices can connect via Bluetooth, allowing researchers to monitor TEA operating time on their terminals. Researchers will check device performance daily at 10 AM and 8 PM to identify participants who have not completed their treatment and provide reminders. This feature facilitates the supervision of participants and enables the assessment of treatment adherence post-therapy. We have also designed a "treatment diary", which must be completed before and after each day's treatment. Sample collection will strictly follow the "Sample Handling Manual." Our electronic "treatment diary" questionnaire will prompt participants daily at 9 AM and 6 PM to engage in their treatment.

Statistical Analyses

We will perform an Intention-To-Treat (ITT) analysis and will analyze the study data using SPSS 26.0. Missing data will be addressed using multiple imputation. Descriptive statistics summarize participants' baseline and outcome characteristics.

Normally distributed continuous data are expressed as mean ± standard error of the mean (SEM), while non-normally distributed data are presented as median (P25, P75). Categorical variables are reported as numbers and percentages (n, %). Parametric and non-parametric tests will be used to compare baseline differences between the two groups. To assess the magnitude of changes in primary and secondary outcomes across time and between the two groups for continuous variables, linear mixed models for repeated measures were employed, with baseline severity included as a covariate.[98] The categorical variables were analyzed using McNemar's test or Cochran's Q test. Bonferroni correction was applied for the primary outcome analyses to account for multiple comparisons. Hypothesis testing was performed using two-tailed tests with a significance level of $\alpha = 0.05$. The fixed effects include group, visit time and covariates (eg gender, sex).

Discussion

This study, grounded in TCM theory, explores the therapeutic efficacy of TEA in treating FMS. FMS's multisystem involvement and complex symptomatology pose significant challenges for treatment. While pharmacological treatments offer some benefits, their single-target mechanisms often provide limited relief. Non-pharmacological approaches, by contrast, address a broader range of FMS symptoms, including pain, sleep disturbances, mood changes, and cognitive impairments, offering a more comprehensive management strategy.

Our approach seeks to overcome the drawbacks of traditional therapies, which are often prolonged and time-consuming. Evidence suggests that combining TEA with exercise significantly enhances therapeutic outcomes compared to TEA alone.[27] In this study, we implemented a daily 1-hour treatment protocol, consisting of 10 minutes of simple stretching and relaxation exercises in the morning and afternoon. This regimen, known as "Dongqi Therapy" in TCM (mobilizing the affected area during acupuncture-related treatments), aims to amplify therapeutic effects without disrupting patients' daily routines.

Emotional stress is closely linked to the severity of FMS,[99] and TCM attributes its primary pathogenesis to Liver Qi Stagnation. Guided by the principle of soothing the liver and regulating Qi, we selected acupoints such as Hegu (LI4) and Taichong (LR3), integrating these with "Dongqi Therapy" to facilitate Qi flow to affected areas.[100] Moreover, since previous research suggests that FMS patients experience microcirculatory insufficiency,[101] we employed infrared thermography to measure surface temperature, exploring TEA's mechanisms of action.

We also hypothesize that FMS-related fatigue may be linked to liver dysfunction. Patients with chronic liver diseases, such as inflammatory liver conditions or non-alcoholic fatty liver disease (NAFLD), often exhibit cognitive, emotional, and behavioral disturbances due to liver-brain axis alterations,[102] which resemble FMS symptoms. Therefore, our study included VCTE assessments to preliminarily explore whether FMS-related fatigue has a liver-related pathological basis.

Despite certain limitations, including the absence of a healthy control group and only a single-centre, our findings provide preliminary evidence supporting TEA as a viable treatment for FMS. Future studies should expand sample sizes, include subgroup analyses, and investigate precision treatments tailored to patient-specific factors such as age, gender, body weight, TCM syndrome types, and non-depressive FMS.[103] These analyses will deepen our understanding of FMS heterogeneity and enable the development of more personalized and effective treatment plans.

Abbreviations

FMS, Fibromyalgia Syndrome; TEA, Transcutaneous Electrical Acustimulation; IRT, infrared thermography; VCTE, vibration-controlled transient elastography; CWP, chronic widespread pain; TCM, Traditional Chinese Medicine; BMI, Body Mass Index; WHR, Waist-Hip Ratio; S100B, S100 calcium-binding protein B; TSPO, Translocator Protein; BDNF, Brain-Derived Neurotrophic Factor; CGRP, Calcitonin Gene-Related Peptide; QOL, Quality of Life; SF-12 v2, Short Form 12 Item (version 2) Health Survey; FSQ, Fibromyalgia Survey Questionnaire; VAS, Visual Analogue Scale; BPI, Brief Pain Inventory; PROMIS-Fatigue 7a, The Patient-Reported Outcomes Measurement Information System® (PROMIS)-Fatigue Short Form 7a (SF-7a) scale; PROMIS-Sleep Disturbance 8b, PROMIS Sleep Disturbance 8b short form; PHQ-9, Patient Health Questionnaire-9; DST, Digit Span Test; FTSTS, Five Times Sit to Stand Test; SLS, Single-Leg Stand Test; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; LI4, Hegu; LR3, Taichong; LSM, Liver Stiffness Measurement; CAP, Controlled Attenuation Parameter; kPa, Kilopascals; ELISA,

Enzyme-Linked Immunosorbent Assay; LC-MS, Liquid Chromatography-Mass Spectrometry; ITT, Intention-To-Treat; SEM, Error of the Mean; NAFLD, Non-Alcoholic Fatty Liver Disease.

Ethics

The study has been approved by the China-Japan Friendship Hospital Ethics Committee (approval number: 2024-KY-278-1).

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Disclosure

The authors report no conflicts of interest in this work.

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