Journal of Pain Research Dovepress

Open Access Full Text Article STUDY PROTOCOL

Effect of Acupuncture Intervention on Chronic Musculoskeletal Pain in Hemodialysis-Dependent Kidney Failure Patients: Study Protocol for a Randomized Controlled Clinical Trial

Cuina Yan[1], Hui-Rong Liu[2], Qi Kong[1], Jia-Yi Gan[3], Kun Liu[4], Wei-Guo Yao[4], Xing-Mei Yao[1]

[1]Putuo Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; [2]Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; [3]Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; [4]Jinshan Branch of Shanghai Sixth People's Hospital, Shanghai, People's Republic of China

Correspondence: Xing-Mei Yao, Putuo Hospital, Shanghai University of Traditional Chinese Medicine, No. 164 Lanxi Road, Putuo District, Shanghai, 200062, People's Republic of China, Email yao.xingmei@163.com; Wei-Guo Yao, Jinshan Branch of Shanghai Sixth People's Hospital, No. 147, Jiankang Road, JinShan District, Shanghai, 201599, People's Republic of China, Email saynever2004@163.com

Background: Chronic musculoskeletal pain is prevalent in individuals with hemodialysis-dependent renal failure (HDKF). The current opioid crisis highlights the urgent need for effective non-pharmacological pain management. Acupuncture, identified as a non-pharmacological intervention in clinical settings, holds promise for alleviating chronic musculoskeletal pain in HDKF patients, but well-designed studies assessing its specific effects in this population are lacking. This study aims to comprehensively evaluate the efficacy and safety of acupuncture as a treatment modality for HDKF patients with chronic musculoskeletal pain.

Methods: This trial, conducted at a single center, follows a parallel, three-arm design with randomization and sham control. 90 hDKF patients with chronic musculoskeletal pain will be assigned randomly to three groups (acupuncture, sham acupuncture, and waiting-list control) in a 1:1:1 ratio. The acupuncture and sham acupuncture groups will undergo 24 treatment sessions over eight weeks, while the waiting-list control group will receive no acupuncture. The primary outcome measures changes in the Numeric Rating Scale (NRS) score from baseline at the end of treatment, with secondary outcomes including the Edmonton Symptom Assessment System (revised version) (ESAS-r), Palliative care Outcome Scale (rental) (POS-renal), and hospital anxiety and depression scale (HADS). Adverse events will be recorded throughout the study, and all randomized patients will be included in the intention-to-treat analysis.

Discussion: The outcomes of this research aim to advance the systematic management of chronic musculoskeletal pain in HDKF patients through non-pharmacological interventions. Moreover, it will contribute insights into personalized treatment strategies, integrating individual expectations and genetic biomarkers to provide "precision" acupuncture for HDKF patients experiencing chronic musculoskeletal pain.

Trial Registration: The trial registration number is ChiCTR2400080488. This trial was prospectively registered on 30 January 2024 in the Chinese Clinical Trial Registry.

Keywords: acupuncture, HDKF, pain, clinical trial

Background

Chronic pain is a prevalent issue among those afflicted with HDKF, with an occurrence rate ranging from 33% to 88%, and reports of pain in various regions, such as the head, back, bones, chest, and extremities, are commonplace.[1–3] Within the HDKF demographic contending with prolonged discomfort, musculoskeletal pain takes the forefront, impacting 57% of individuals.[1] Remarkably, a minimum of 50% of these patients contend with chronic pain of moderate to severe intensity, resulting in a burden akin to that experienced by individuals undergoing cancer treatments.[4] Despite regular hemodialysis treatments, the management of pain often proves to be ineffective, with approximately 75% expressing

Received: 10 October 2024
Accepted: 10 December 2024
Published: 14 December 2024

dissatisfaction with the relief provided. Moreover, 35% to 75% experiencing moderate to severe pain, are left without prescribed analgesic medications.[5] The intricate interplay of multiple factors and simultaneous causes of pain, coupled with the altered perception of pain due to associated psychological and social symptoms, poses a formidable challenge in delivering adequate pain management within this patient population.

Acupuncture stands out as a distinctive external treatment modality within Traditional Chinese Medicine (TCM), known for its simplicity, convenience, effectiveness, and cost-efficiency. According to TCM principles, acupuncture addresses diseases primarily by clearing the meridians in the human body and regulating the flow of qi and blood. In the context of HDKF patients, acupuncture demonstrates notable efficacy in alleviating various complications, including pain, skin itching, dialysis-induced hypertension, and insomnia. Recent high-quality clinical studies substantiate acupuncture's effectiveness in pain management.[6,7] Within the realm of analgesia, acupuncture boasts unique advantages in mitigating diverse types of pain and modulating associated emotional imbalances. For instance, its role in treating chronic low back pain is well-documented.[8] Additionally, acupuncture exhibits a significant impact on chronic low back pain stemming from polycystic kidney disease, suggesting its potential to reduce or even replace the use of pain medications like opioids.[9] While these mechanisms could potentially play crucial roles in acupuncture's ability to improve pain and alleviate anxiety and other negative emotions in hemodialysis (HD) patients, further validation is essential.

Numerous clinical investigations have delved into the impact of physical therapies on pain management for individuals undergoing HD. Modalities such as acupuncture, cryotherapy, infrared treatments, transcutaneous electrical stimulation, massage, aromatherapy, and more have been explored. These interventions demonstrate a degree of effectiveness in alleviating pain symptoms in HD patients.[10] Regrettably, there remains a scarcity of high-quality literature specifically addressing acupuncture's role in addressing chronic musculoskeletal pain among HDKF patients. The existing research programs grapple with certain challenges, including inconsistent criteria for selecting acupuncture points, the use of non-standardized operational techniques, unclear specifications for intervention timing and frequency, and the absence of objective evaluation indicators. To address these gaps, a prospective, parallel, three-arm, randomized, sham-controlled trial is set to unfold. This trial aims to systematically investigate the effectiveness and safety of acupuncture as a treatment for chronic musculoskeletal pain in HDKF patients. The study will compare outcomes with those from sham acupuncture and waiting-list control groups. The anticipation is that the results emerging from this comprehensive study will furnish robust evidence regarding the efficacy of acupuncture in managing chronic musculoskeletal pain, specifically in HDKF patients.

Methods

Study Design

This clinical investigation, based at Putuo Hospital, Shanghai University of Traditional Chinese Medicine, constitutes an innovative and singular endeavor-a single-center, parallel, three-arm, randomized study employing a sham control. Its primary objective is to validate the efficacy of acupuncture as a therapeutic intervention for managing chronic musculoskeletal pain in individuals with HDKF. Delving into the intricacies of this exploration, eligible HDKF patients grappling with persistent musculoskeletal pain will undergo scrupulous selection and be randomly assigned to one of three groups: the acupuncture group, the sham acupuncture group, and the waiting-list group (receiving no treatment), ensuring a 1:1:1 distribution. The comprehensive investigation unfolds across a 13-week timeline, encompassing a foundational 1-week baseline, an intensive 8-week treatment phase, and a contemplative 4-week follow-up period. The visual representation of this research narrative is depicted in Figure 1, while time points are systematically presented in Table 1. Our research protocol is intricately crafted in alignment with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist[11] and its extension dedicated to TCM.[12] The subsequent reporting will rigorously adhere to the guidelines outlined by the Consolidated Standards of Reporting Trials (CONSORT)[13] and its Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) extension.[14] And the trial will comply with the Declaration of Helsinki.

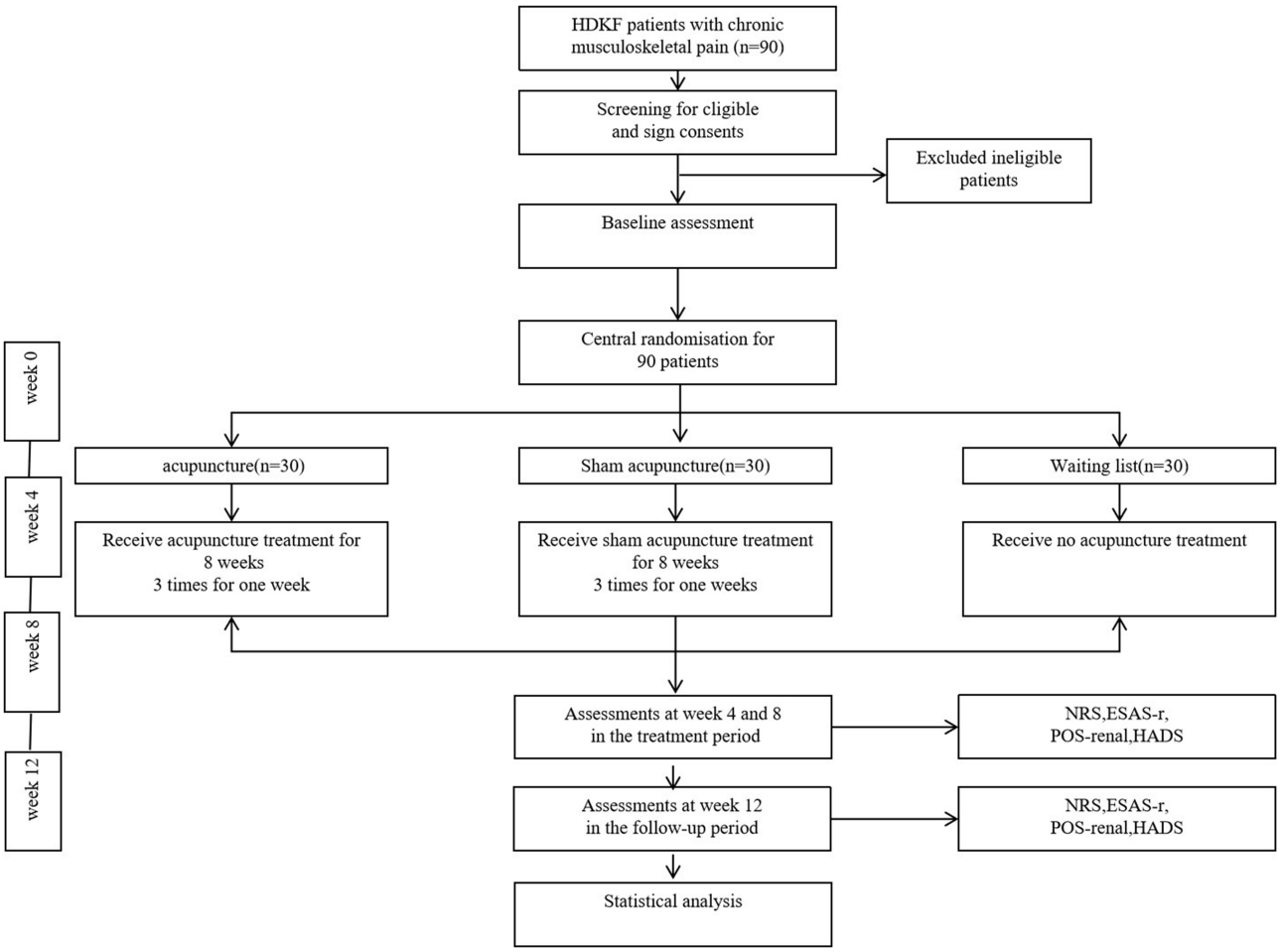

Figure 1 Trial flow chart.

Inclusion and Exclusion Criteria

Inclusion Criteria

To be enrolled, patients must meet all the following criteria:

1. Satisfy the diagnostic criteria for stage 5 chronic kidney disease, also known as end-stage renal disease (ESRD), and meet the general clinical indications for HD as outlined in the "Guidelines for Early Screening, Diagnosis, and Treatment of Chronic Kidney Disease (2022 Edition)" (refer to Supplementary Table 1 for diagnostic criteria).
2. Undergoing routine HD sessions for a duration exceeding three months, three times weekly, each session lasting four hours, and maintaining a stable health status.
3. The patients must have a minimum rating of 4 or above on a numerical rating scale from 0 to 10 for the worst pain intensity experienced in the past week.
4. Individuals aged 20 to 80 years, with no restrictions on gender.

Exclusion Criteria

Patients will be excluded if they meet any of the following aspects:

1. Presently experiencing additional severe chronic issues, including cardiovascular, hepatic, renal, gastrointestinal, hematological, infectious diseases, or malignant tumors.

Table 1 Time Points of Treatment Assessment

	Enrollment	Baseline	Treatment Phase		Follow-up Phase
Time point	Week-1	Week 0	Week 4	Week 8	Week 12
Screening and enrolment					
Clinical interview Eligibility screen Informed consent Randomization	× × ×	 ×	 	 	
Intervention					
Acupuncture Sham acupuncture Waiting-list			24-session treatment 24-session treatment No acupuncture treatment		
Assessments Primary outcome					
NRS		×	×	×	×
Secondary outcomes					
ESAS-r scale POS-renal scale HADS scale		× × ×	× × ×	× × ×	× × ×
Adverse events Blinding assessment Patients' compliance Medicine alliance		 ×	× ×* ×	× × × ×	× ×

Notes: *Assessed after the first session of acupuncture treatment. ×Implementation of the corresponding project at the corresponding point in time.

2. Encountering challenges in articulating their symptoms effectively, such as individuals with significant mental disorders or cognitive impairments.
3. Presenting contraindications to acupuncture, such as a propensity for bleeding or localized infection at the acupuncture points.
4. Individuals who have engaged in or are currently involved in other clinical studies within the month preceding enrollment.

Recruitment Process

This study will be conducted at Putuo Hospital, Shanghai University of Traditional Chinese Medicine and will be jointly designed by physicians from multiple medical institutions. HDKF patients who visit this clinical site can enter the screening process. The main information about the study will be made available to patients through internal promotion within the clinical site, online promotion, brochures, etc.

Written Informed Consent

Within the written informed consent document, each participant will receive detailed information regarding their opportunity for random assignment into one of three groups: acupuncture, sham acupuncture, or the waiting-list control group. This allocation will be carried out with impartiality, offering an unbiased chance to experience the potential benefits and risks associated with each group. Participants are encouraged to willingly endorse the informed consent before engaging in the study, emphasizing their freedom to withdraw at any point throughout the duration of the research.

Randomization, Allocation Concealment, and Blinding

The randomization process will employ the envelope method, utilizing a table of randomly generated numbers. Eligible HDKF patients experiencing chronic musculoskeletal pain will be assigned to one of three groups–the acupuncture group, sham acupuncture group, or waiting-list control group–in an equitable 1:1:1 ratio. A team of independent professional statisticians, uninvolved in trial implementation and statistical analysis, will generate the allocation sequence using SAS 9.4 software. The secrecy of group assignments will be maintained by numbering sealed envelopes from 1 to 90, and these envelopes will be safeguarded by a research assistant not participating in patient recruitment. As eligible patients enroll, the clinical research coordinator overseeing patient enrollment will sequentially open the envelopes, ensuring a transparent and unbiased allocation process.

In this research, a specialized small circular pad equipped with double-sided adhesive functionality and a flat-headed disposable stainless steel needle, both uniquely crafted by the research team, will be employed to introduce a masking element during acupuncture and sham acupuncture sessions among patients belonging to the two acupuncture treatment groups. Each patient will undergo treatment in an individualized room to ensure a distinct therapeutic environment. A blinding assessment will be carried out among patients within the two acupuncture groups. Nevertheless, due to the inherent characteristics of acupuncture, achieving effective masking between the acupuncture groups and the waiting-list control group poses challenges. However, during the execution of this study and the subsequent data analysis, the outcome evaluators and statisticians responsible for statistical evaluations will implement masking procedures concerning group assignments.

Simple Size Estimations

In compliance with the regulations outlined in the Chinese Drug Registration Management Measures, the pilot study necessitates a minimum sample size ranging from 20 to 30 participants per group.[15,16] Taking into account the current financial constraints, an initial proposal outlines a sample size of 30 patients per group, totaling 90 participants for this study. The outcomes derived from this investigation will contribute to the determination of an optimal sample size for subsequent randomized clinical trials.

Interventions

Throughout the study duration, participants in the acupuncture, sham acupuncture, and waiting-list control groups underwent standard hemodialysis treatment, routine nursing care, and educational sessions. Subjects were permitted to continue their prescribed medications, encompassing pain relief and sleep aids. It was mandatory for participants to adhere to their treatment plan unless there was a discernible change in their condition. Any medications utilized by the participants were diligently documented, and drugs influencing the primary study outcome were acknowledged as baseline data. Immediate communication with the clinical site investigator was required for any non-urgent modifications to the treatment plan. Each participant received 24 sessions of either acupuncture or sham acupuncture over the course of 8 weeks, with each session lasting 30 minutes and occurring three times per week. Individuals in the waiting-list control group did not undergo any acupuncture treatment during the observation period.

Acupuncture Group

Acupuncture Point Selection Scheme

The acupuncture point selection adopts a semi-fixed standardized scheme.[17] The chosen acupoints include bilateral Hegu (LI-4), Neiguan (PC-6), Zusanli (ST-36), and Sanyinjiao (SP-6), as illustrated in Figure 2. Treatment will adhere to the "WHO standard acupuncture point locations in the Western Pacific region." Simultaneously, points will be selected based on the patient's specific pain sites, with at least four additional corresponding points chosen in other body areas to address other comorbid symptoms. For upper limb pain, additional points such as Jianyu (LI15) and Jianliao (TE14) may be included; for lower limb pain, points like Xuanzhong (GB39) and Yanglingquan (SP9) may be added; for back pain, additional points such as Shenshu (BL23) and Dachangshu (BL25) may be considered.

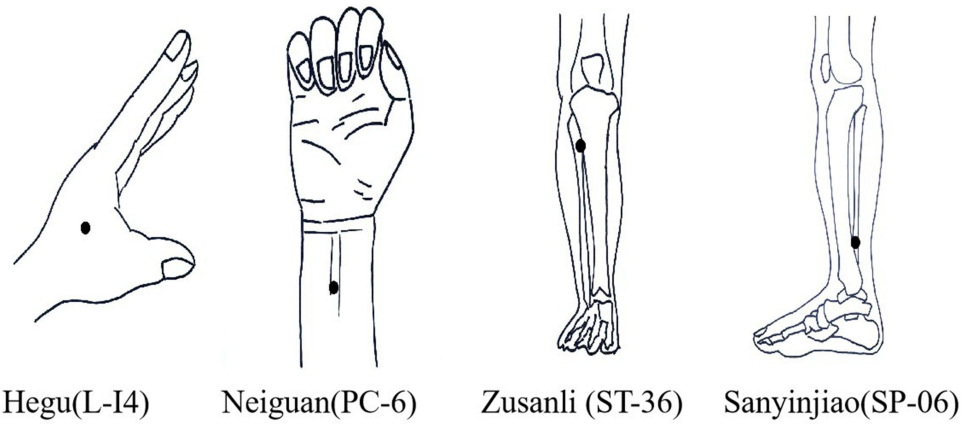

Figure 2 Location of main acupoints: Hegu (L-14), Neiguan (PC-6), Zusanli (ST-36), Sanyinjiao (SP-06).

Needle Insertion Procedure

Subjects undergo acupuncture treatment at the commencement of each hemodialysis session. Based on the patient's pain site, suitable body positions are chosen. A total of 12 to 14 points are selected at the patient's specific pain sites. Following this, both the patient's points and the acupuncturist's hands will undergo regular disinfection using a 75% ethanol solution. Small round adhesive pads with double-sided adhesive foam material (Model: 3M55230, Specifications: 103 mm) are applied to the corresponding acupuncture points on the skin. Subjects are informed that the adhesive pads are used to alleviate the sensation of pain during needle insertion. A disposable stainless steel filiform needle (Acupro Medical Instruments, Suzhou, China. Specifications: 0.2525–40 mm, Batch number: 20210501) is then inserted through the foam pad, penetrating the respective acupuncture point at a depth ranging from 10 to 35 mm. The needle is manipulated using lifting, thrusting, and twisting techniques until the patient experiences a sensation of soreness, numbness, distension, or heaviness. The needle is left in place for 30 minutes, with manipulation performed every 10 minutes throughout this period. Finally, the needle is removed immediately after 30 minutes, and a cotton swab is gently applied for a short time to minimize any potential bleeding.

Conventional Treatment

Standard hemodialysis, nursing education, symptomatic supportive therapy.

Sham Acupuncture Group

Acupuncture Point Selection

Same as the acupuncture group.

Needle Insertion Procedure

Participants receive acupuncture treatment following the initiation of each hemodialysis session. Based on the patient's pain location, appropriate body positions are selected. A total of 12–14 points are selected at the patient's specific pain sites. Following this procedure, both the patient's acupuncture points and the acupuncturist's hands are thoroughly disinfected using a 75% ethanol solution. Small, round adhesive pads made of double-sided adhesive foam material (Model: 3M55230, Specifications: 10*3 mm) are then applied to the corresponding acupuncture points on the skin. Subjects are informed that these adhesive pads are designed to alleviate the sensation of pain during needle insertion. A specially designed flat-tipped, disposable stainless steel filiform needle (Specifications: 0.25*25−40 mm) is then inserted through the foam pad. Once the needle is securely in place in the foam pad without falling, the needle insertion procedure is considered complete, and no further lifting, thrusting, or twisting is performed. Throughout this process, patients sense a slight touch on the skin surface of the acupuncture points, and the acupuncturist perceives a penetrating sensation through the foam pad. The needle remains in place for 30 minutes, with sham manipulation performed every 10 minutes, indicating only a touch without actual lifting, thrusting, or twisting.

Conventional Treatment

Standard hemodialysis, nursing education, symptomatic supportive therapy.

Waiting-List Control Group

The waiting-list control group will receive only routine hemodialysis, nursing education, and symptomatic supportive treatment.

Outcome Measures

Primary Outcome Measurement

Utilizing the difference in NRS scores from baseline at 0, 4, 8, and 12 weeks (follow-up) for each group, expressed as the median difference with a corresponding 95% CI. A mixed-effects model is utilized to assess the primary outcome of the groups.

Secondary Outcome Measurement

1. Additional metrics based on NRS scores:

   (1) Pain relief rate among participants in each group at eight weeks. The relief rate is defined as the proportion of patients showing a decrease of at least 50% in NRS scores compared to baseline, expressed as a rate difference (95% CI).
   (2) Change in NRS scores from baseline to 8 weeks for participants in each group, presented as the median difference (95% CI).

2. Assessment using the chronic kidney disease-related scale: ESAS-r score and POS-renal score.
3. Evaluation of emotional status: HADS scale score.

Blinding Assessment

During the recruitment and screening process for eligible participants, individuals will be notified that they have an equal probability of being assigned to receive acupuncture treatment, sham acupuncture treatment, or no acupuncture treatment. Those allocated to the acupuncture or sham acupuncture groups will be encouraged to speculate on the type of acupuncture they have undergone after the initial and final sessions. This is intended to assess the effectiveness of blinding the patients. The query presented will be, "Which style of acupuncture do you believe you have received?" Participants will have three response options: acupuncture, acupuncture-like stimulation, or uncertainty.

Patients' Compliance Assessment

At the conclusion of the treatment, the adherence of patients will be documented. Instances of participant withdrawal and the underlying reasons will be documented throughout the 12-week observation period.

Use of Medication

Patients are requested to document any self-reported utilization of extra medications or healthcare resources for pain management during the observation period in the provided pain diary.

Safety Assessments

Safety evaluations will encompass routine blood tests and assessments of renal and liver function. These metrics will be gauged during both the screening phase and upon completion of the treatment. Any adverse events (AEs) resulting from acupuncture treatment, such as bleeding, pain, hematoma, fainting, local infections, and the like, will be meticulously recorded. Any serious AEs associated with the interventions will be promptly reported to the principal investigator, documented in the Case Report Form (CRF), and the affected participants will be withdrawn from the study. Swift treatment or rescue measures will be administered as necessary. Throughout the assessment period, researchers will evaluate the potential correlation between AEs and the study, as well as any concurrent medications.

Data Management

Prior to patient recruitment, a data entry form known as the case report form (CRF) will be devised to input and store data. It will be the responsibility of the researchers to record the relevant data pertaining to observed outcomes in the designated sections of the CRF. Upon completion of the trial, the data management team will secure the database, preventing any further modifications by the researchers. Patient-related details, such as names, ID numbers, and phone numbers, will be anonymized for confidentiality. Researchers will undergo training to establish effective communication with patients, ensuring a comprehensive understanding and cooperation with the trial before randomization. In cases where patients deviate from or interrupt the intervention plan, efforts will be made to collect as much trial data as possible through communication, provided the patients are willing to cooperate. All CRFs will be archived for a minimum of 5 years. Patient information data will undergo de-identification and be made public within one year of the research report being disclosed to enhance transparency.

Specialists in acupuncture, nephrology, statistics, and methodology will be organized to assess and enhance the trial plan. Standard operating procedures (SOPs) will be developed for various aspects, including interventions, CRF completion details, result evaluation, and data management. These SOPs will be employed for the training of relevant personnel, and any data modifications will be traceable through the CRF. Additionally, a quality control officer will be designated within the research center to scrutinize and interpret the trial data independently, assessing the progress of the trial. Based on the mid-term analysis results regarding efficacy and safety, the research committee will determine whether to implement adjustments or terminate the study.

Data Analysis and Statistic Methodology

The primary outcome's statistical analysis will be executed within the intention-to-treat (ITT) set, encompassing all pre-grouped patients who will remain in their original groups. Missing data will be addressed using the last observation carried forward method. To assess the analysis results' robustness, the per-protocol set (PPS) will exclude patients not meeting the protocol criteria. All secondary outcome analyses will occur within the PPS. SPSS 26.0 for Windows statistical analysis software will facilitate the data analysis. Frequency (percentage) [n(%)] will express count data, and median (interquartile range) [Median (IQR)] will represent measurement data. Intergroup data presentation will involve the use of corresponding differences (95% CI). For intergroup comparison of single-factor measurement data, the Mann–Whitney *U*-test will be applied, while the mixed effects model will handle statistical inference considering multiple time points. Intragroup comparison of measurement data will utilize the Wilcoxon signed-rank test. Count data intergroup comparison will employ the chi-square test. Survival data will undergo Cox regression with baseline data adjustment, maintaining α=0.05.

Personnel Preparation and Quality Control Standards

At the study's inception, a research committee was assembled, comprising diverse roles tasked with deliberating on methodological aspects and crafting a comprehensive researcher's manual. The committee members include the research initiator, two clinical acupuncture physicians, one statistician, one nephrologist, one quality control officer, and one recorder tasked with documenting, evaluating, and reporting adverse events. Before project commencement, the team undergoes pertinent training and is furnished with the researcher's manual. The research committee's statistician oversees the management of a semi-independent data monitoring committee and formulates a statistical analysis plan. The research initiator additionally coordinates with the ethics committee. The committee conducts regular assessments of patient enrollment, operational execution quality, and other pertinent details.

Discussion

A systematic review revealed a significant prevalence of pain in individuals undergoing hemodialysis (HD), yet this pain often goes unnoticed and is inadequately addressed.[18] Barriers to effective pain management in end-stage kidney disease patients include limited awareness of the issue, insufficient medical education, concerns about potential drug-related side effects, and widespread misconceptions about the inevitability of pain. Pain management in patients with chronic kidney disease is challenging. Non-opioid analgesia is preferred using acetaminophen, topical analgesics, and gabapentin analogues, but does not provide much pain relief.[19] Acupuncture, compared to medication, holds the potential to emerge as a novel,

straightforward, safe, and cost-effective treatment option for managing chronic pain associated with kidney disease. It can also slow the progression of renal dysfunction and alleviate patients' symptoms.[20] Recent advancements in understanding the analgesic mechanisms of acupuncture have been significant. A previous study has shed light on the mechanisms of acupuncture's action on inflammatory pain, which can be categorized into two levels: peripheral and central. In the peripheral nervous system, the Purinergic pathway, immune cells and neurons, cannabinoid receptors, nociceptive ion channels, and the endogenous opioid peptide system play crucial roles. In the central nervous system, glial cells, TRPV1, glutamate and its receptors, GABAergic interneurons, and signaling molecules are key components.[21] Extensive research has provided evidence supporting the efficacy and safety of acupuncture for pain management across diverse populations. Additionally, the integration of acupuncture and moxibustion within dialysis centers is viewed as a viable and well-received approach by patients, physicians, and nurses involved in HD treatment. Earlier investigations[22] have established the feasibility and safety of acupuncture for symptom management in HD patients, showcasing its potential to enhance their health-related quality of life. Nonetheless, these studies have predominantly addressed non-pain-related aspects, and there is a need for more standardized research and clinical evidence in the realm of pain management in HD patients.

Traditional Chinese medicine believes that pain is mostly caused by disharmony of qi and blood, and stagnation of qi and blood stasis. As the "Yellow Emperor's Classic of Internal Medicine" says, "Passing is not pain, pain is not passing", which reflects a profound understanding of the causes of pain and the principles of treatment in Chinese medicine. Hegu (LI-4) is the original point of the hand Yangming large intestine meridian, and Neiguan (PC-6) is the point of the hand jueyin pericardium meridian, also one of the eight extraordinary points. Zusanli (ST-36) is a point on the stomach meridian and also one of the body's strong points, often used in combination with other points to enhance the effect of pain relief. Sanyinjiao (SP-6) is the meeting point of the three Yin meridians: the Foot Taiyin Spleen Meridian, the Foot Shaoyin Kidney Meridian, and the Foot Jue Yin Liver Meridian. The combination of these four points can dredge the meridians, activate blood circulation, remove blood stasis, and regulate qi and blood, thus achieving the purpose of relieving pain. The semi-standardized acupuncture protocol was developed by referring to previous clinical trials on acupuncture for related diseases such as cancer, knee osteoarthritis, herniated disk, and primary dysmenorrhea.[8,23–25] In these trials, the acupoints including bilateral Hegu (LI-4), Neiguan (PC-6), Zusanli (ST-36), and Sanyinjiao (SP-6) have been demonstrated to relieve pain significantly. Based on the above discussion, the author believes that the selection of acupuncture points in this proposed study is based on comprehensive research, including text mining of premodern Chinese medical literature and a systematic review of contemporary clinical trials.

This study primarily employs the NRS scale, ESAS-r scale, POS-renal scale, and HADS scale to assess the treatment outcomes. The NRS primarily focuses on the quantification of pain intensity, with the advantage of being simple and easy to use, and has been widely applied in the assessment of pain symptoms related to various diseases.[26,27] The ESAS-r scale and the POS-renal scale not only assess pain but also include other dimensions of symptoms and quality of life. For instance, the ESAS-r scale evaluates a range of symptoms including pain, and the version tailored for kidney patients adds three additional symptoms: skin irritation, sleep difficulties, and restless legs. The POS-renal scale is used to evaluate and improve the palliative care outcomes for patients with kidney diseases, including the assessment of symptoms as well as non-symptom issues such as information needs and family anxiety.[28] The HADS scale[29] is specifically designed to assess patients' anxiety and depression, which is closely related to pain assessment, as psychological conditions can significantly affect the perception and management of pain.

Our study aims to deliver timely insights in the era of the opioid epidemic, guiding evidence-based acupuncture interventions for HDKF patients experiencing pain. This is a prospective, randomized, controlled, and single-blinded pilot clinical trial. The primary objective of this study is to assess the clinical impact of acupuncture on alleviating chronic musculoskeletal pain in patients with HDKF through rigorous, standardized, and scientific clinical trials. The research aligns with the HOPE Alliance's new direction in pain management for HDKF patients, emphasizing the prevalence of pain in individuals undergoing hemodialysis and investigating the effectiveness of combined behavioral and medical interventions within multimodal strategies to reduce long-term opioid use in this patient population. The study advocates a return to a holistic, "people-centered" pain management model, prioritizing non-pharmacological approaches like acupuncture. It encourages the involvement of multidisciplinary medical teams, including acupuncture specialists, nephrologists, and nurses, to transition from a uniform pain management model to a personalized and diversified approach for chronic musculoskeletal

pain in HDKF patients. The outcomes of this research aim to advance the systematic management of chronic musculoskeletal pain in HDKF patients through non-pharmacological interventions. Moreover, it will contribute insights into personalized treatment strategies, integrating individual expectations and genetic biomarkers to provide "precision" acupuncture for HDKF patients experiencing chronic musculoskeletal pain.

Trial Status

Tistrial was registered at the Chinese Clinical Trial Registry (http://www.chictr.org.cn) on 30 January 2024 (registered number: ChiCTR2400080488, the protocol version number: V2.0). This study is currently in the recruitment stage. The first patient was enrolled on 15 March 2024. Recruitment will be approximately completed before 30 November 2024, and the trial is estimated to end in May 2025.

Conclusion

We hope that this clinical trial will become a high standard and high-quality study to evaluate the effect of acupuncture on chronic musculoskeletal pain treatment outcomes in HDKF patients.

Abbreviations

HDKF, hemodialysis-dependent kidney failure; NRS, Numeric Rating Scale; ESAS-r, Edmonton Symptom Assessment System (revised version); POS-rental, Palliative care Outcome Scale (rental); HADS, Hospital Anxiety and Depression Scale; TCM, traditional Chinese medicine; HD, hemodialysis; SPIRIT, Recommendations for Interventional Trials; CONSORT, Consolidated Standards of Reporting Trials; STRICTA, Standards for Reporting Interventions in Clinical Trials of Acupuncture; ESRD, end-stage renal disease; AEs, any adverse events; CRF, Case Report Form; SOPs, Standard operating procedures; ITT, intention-to-treat; PPS, per-protocol set.

Data Sharing Statement

The data can be obtained by contacting the corresponding author of this study after this study has been completed.

Ethics Approval and Consent to Participate

The study protocol for this research has obtained approval from Putuo Hospital, Shanghai University of Traditional Chinese Medicine medical ethics committee (Approval ID: PTEC-A-2023-41-1). The trial registration number is ChiCTR2400080488. This trial was prospectively registered. Each participant will receive comprehensive information regarding the study's objectives, potential risks, and benefits. The recruiting physician will discuss the written informed consent with the patient, who must sign it before entering the study.

Consent for Publication

All named authors adhere to the authorship guidelines of Trials. All authors have agreed to publication.

Acknowledgments

The authors would like to acknowledge the contributions of all the medical staff and HDKF patients at the Putuo Hospital, Shanghai University of Traditional Chinese Medicine. Special thanks are given to the following professor for his guidance in this study: Prof. Peihao Yin from Putuo Hospital, Shanghai University of Traditional Chinese Medicine.

Author Contributions

All authors made a significant contribution to the work reported, whether that is 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 14th Five-Year Plan Chinese Medicine Specialty Project (ZYTSZK2-8), the Shanghai Famous Chinese Medicine Academic Experience Research Studio Construction Project (SHGZS-202237), the Shanghai Jinshan District 7th Cycle Key Medical Specialty Construction Project (JSZK2023H04) and the Shanghai Putuo District Health System Clinical Specialty Construction Plan (2021tszk02).

Disclosure

The authors have no relevant financial or non-financial interests to disclose. This paper has been uploaded to ResearchSquare as a preprint: https://www.researchsquare.com/article/rs-4475842/v1.

References

1. Kitala-Tanska K, Kania-Zimnicka E, Tanski D, Kwella N, Stompor T, Stompor M. Prevalence and management of chronic pain, including neuropathic pain, in dialysis patients with end-stage renal disease. *Med Sci Monit*. 2024;30:e943808. doi:10.12659/MSM.943808
2. Dos SP, Mendonca CR, Hernandes JC, et al. Pain in patients with chronic kidney disease undergoing hemodialysis: a systematic review. *Pain Manag Nurs*. 2021;22(5):605–615. doi:10.1016/j.pmn.2021.05.009
3. MacRae C, Mercer SW, Guthrie B, Henderson D. Comorbidity in chronic kidney disease: a large cross-sectional study of prevalence in Scottish primary care. *Br J Gen Pract*. 2021;71(704):e243–e249. doi:10.3399/bjgp20X714125
4. Tobin DG, Lockwood MB, Kimmel PL, et al. Opioids for chronic pain management in patients with dialysis-dependent kidney failure. *Nat Rev Nephrol*. 2022;18(2):113–128. doi:10.1038/s41581-021-00484-6
5. Weisbord SD. Patient-centered dialysis care: depression, pain, and quality of life. *Semin Dial*. 2016;29(2):158–164. doi:10.1111/sdi.12464
6. Hershman DL, Unger JM, Greenlee H, et al. Comparison of acupuncture vs sham acupuncture or waiting list control in the treatment of aromatase inhibitor-related joint pain: a randomized clinical trial. *JAMA Netw Open*. 2022;5(11):e2241720. doi:10.1001/jamanetworkopen.2022.41720
7. Liao HY, Satyanarayanan SK, Lin YW, Su KP. Clinical efficacy and immune effects of acupuncture in patients with comorbid chronic pain and major depression disorder: a double-blinded, randomized controlled crossover study. *Brain Behav Immun*. 2023;110:339–347. doi:10.1016/j.bbi.2023.03.016
8. Tu JF, Shi GX, Yan SY, et al. Acupuncture vs sham acupuncture for chronic sciatica from herniated disk: a randomized clinical trial. *JAMA Intern Med*. 2024;184:1417. doi:10.1001/jamainternmed.2024.5463
9. Chen L, Michalsen A. Management of chronic pain using complementary and integrative medicine. *BMJ*. 2017;357:j1284. doi:10.1136/bmj.j1284
10. Sahin S, Tokgoz B, Demir G. Effect of lavender aromatherapy on arteriovenous fistula puncture pain and the level of state and trait anxiety in hemodialysis patients: a randomized controlled trial. *Pain Manag Nurs*. 2021;22(4):509–515. doi:10.1016/j.pmn.2021.01.009
11. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586. doi:10.1136/bmj.e7586
12. Dai L, Cheng CW, Tian R, et al. Standard protocol items for clinical trials with traditional Chinese medicine 2018: recommendations, explanation and elaboration (SPIRIT-TCM extension 2018). *Chin J Integr Med*. 2019;25(1):71–79. doi:10.1007/s11655-018-2999-x
13. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c869. doi:10.1136/bmj.c869
14. MacPherson H, Altman DG, Hammerschlag R, et al. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *PLoS Med*. 2010;7(6):e1000261. doi:10.1371/journal.pmed.1000261
15. Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: a confidence interval approach. *J Clin Epidemiol*. 2013;66(2):197–201. doi:10.1016/j.jclinepi.2012.09.002
16. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Stat Methods Med Res*. 2016;25(3):1057–1073. doi:10.1177/0962280215588241
17. Mao JJ, Liou KT, Baser RE, et al. Effectiveness of electroacupuncture or auricular acupuncture vs usual care for chronic musculoskeletal pain among cancer survivors: the PEACE randomized clinical trial. *JAMA Oncol*. 2021;7(5):720–727. doi:10.1001/jamaoncol.2021.0310
18. Brkovic T, Burilovic E, Puljak L. Prevalence and severity of pain in adult end-stage renal disease patients on chronic intermittent hemodialysis: a systematic review. *Patient Prefer Adherence*. 2016;10:1131–1150. doi:10.2147/PPA.S103927
19. Roy PJ, Weltman M, Dember LM, Liebschutz J, Jhamb M. Pain management in patients with chronic kidney disease and end-stage kidney disease. *Curr Opin Nephrol Hypertens*. 2020;29(6):671–680. doi:10.1097/MNH.0000000000000646
20. Liu X, Wang X, Ma H, Zhang W. Mechanisms underlying acupuncture therapy in chronic kidney disease: a narrative overview of preclinical studies and clinical trials. *Front Nephrol*. 2022;2:1006506. doi:10.3389/fneph.2022.1006506
21. Zhang Q, Zhou M, Huo M, et al. Mechanisms of acupuncture-electroacupuncture on inflammatory pain. *Mol Pain*. 2023;19:814404162. doi:10.1177/17448069231202882
22. Correia DCM, Nunes DAJ, Azevedo P, Pires C, Machado JP, Laranjeira M. Effectiveness of acupuncture on health-related quality of life in patients receiving maintenance hemodialysis. *Healthcare*. 2023;11(9):1355.
23. He Y, May BH, Zhang AL, et al. Acupuncture for cancer pain: protocol for a pilot pragmatic randomised controlled trial. *BMJ Open*. 2019;9(7):e25564. doi:10.1136/bmjopen-2018-025564
24. Yeung WF, Chen SC, Cheung D, et al. Self-administered acupressure for probable knee osteoarthritis in middle-aged and older adults: a randomized clinical trial. *JAMA Netw Open*. 2024;7(4):e245830. doi:10.1001/jamanetworkopen.2024.5830
25. Ravi P, Boopalan D, Vijayakumar V, et al. Effect of Sanyinjiao (Spleen-6) acupoint for pain management in primary dysmenorrhea: an updated systematic review and meta-analysis. *Med Acupunct*. 2024;36(4):178–188. doi:10.1089/acu.2023.0100

26. Boas FW, Politti F, Blanco CR, et al. Effect of osteopathic visceral manipulation for individuals with functional constipation and chronic nonspecific low back pain: randomized controlled trial. *J Bodyw Mov Ther*. 2023;34:96–103. doi:10.1016/j.jbmt.2023.04.006
27. Droog W, Coert JH, Walbeehm ET, Stolker RJ, Galvin EM. Incidence of chronic postsurgical pain after upper extremity surgery and its correlation with preoperative pain. *Plast Reconstr Surg Glob Open*. 2023;11(4):e4922. doi:10.1097/GOX.0000000000004922
28. Wen J, Jin X, Al SF, et al. Mapping the Edmonton Symptom Assessment System-revised: renal to the EQ-5D-5L in patients with chronic kidney disease. *Qual Life Res*. 2022;31(2):567–577. doi:10.1007/s11136-021-02948-5
29. Garaiman A, Mihai C, Dobrota R, et al. The hospital anxiety and depression scale in patients with systemic sclerosis: a psychometric and factor analysis in a monocentric cohort. *Clin Exp Rheumatol*. 2021;39(Suppl 131):34–42. doi:10.55563/clinexprheumatol/qo1ehz