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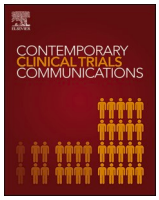

Efficacy and safety of *Tongdutiaoshen* acupuncture on insomnia in maintenance hemodialysis patients: A randomized clinical trial protocol

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ABSTRACT

Background: Patients undergoing maintenance hemodialysis (MHD) experience insomnia frequently. Poor sleep quality impairs the quality of life and adversely affects long-term outcomes. Currently, the treatment of insomnia in patients undergoing MHD is mainly based on medication, although it has severe side effects and poor compliance in patients. Therefore, developing complementary and alternative therapies with higher efficacies is important. This study explores the clinical efficacy and safety of *Tongdutiaoshen* acupuncture in treating insomnia in patients with MHD.

Methods: This randomized controlled trial (RCT) will be performed at Beijing *Luhe* Hospital, affiliated with Capital Medical University in China. We will strictly adhere to the Standards for Reporting Interventions in Clinical Trials of Acupuncture (2010). A total of 110 MHD patients with insomnia will be randomly allocated in a 1:1 ratio to the drug control (DC) or *Tongdutiaoshen* acupuncture (TA) group. Patients in the control group will be administered estazolam tablets (1 mg/day) for four weeks, followed by a 4-week follow-up period. Based on the background therapy provided for the DC group, the TA group will be administered the interventional cohort three times a week for four weeks in a row, followed by a 4-week follow-up period. The primary endpoints will include the Pittsburgh Sleep Quality Index (PSQI), Hamilton Anxiety Scale (HAM-A), TCM Insomnia Syndrome Score, and clinical response rate, which will be evaluated on days 0, 14, 28, and 56. Secondary endpoints will include sleep data monitoring and related laboratory indices, which will be evaluated on days 0, 28, and 56, respectively.

Discussion: This study is designed based on a rigorous methodology to evaluate the efficacy and safety of *Tongdutiaoshen* acupuncture for insomnia in patients undergoing hemodialysis. The findings of this trial will be published in peer-reviewed journals as reliable evidence.

Trial registration: Chinese Clinical Trial Registry ChiCTR2200061967. Registered on July 07, 2022.

1. Background

Chronic kidney disease (CKD) shows an accelerated yearly incidence with its eventual progression to end-stage renal disease (ESRD), for which MHD has become the main method of renal replacement therapy for patients with ESRD. Patients undergoing MHD have multiple acute and chronic complications that deserve attention; notably, sleep disorders are among their most troublesome concomitant symptoms [1]. It has been estimated that sleep disorders exist in 40–85% of patients on hemodialysis worldwide [2], with great diversity in their manifestations and severity. Insomnia is one of the most common conditions, with a prevalence rate as high as 40–84.9% depending on the specific population [3], which is far higher than 15–30% in the general population [4,5]. Imposing a great danger to patients with MHD, prolonged insomnia increases the incidence of cardiovascular events and all-cause mortality, seriously affects their quality of life, and induces anxiety in individuals

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and families. Therefore, treating insomnia in patients undergoing MHD is an urgent issue for medical practitioners.

Until now, the treatment of insomnia in patients has mainly involved medication. Although it forms the basis for the present treatment of insomnia in MHD, medication has been observed to have severe side effects, imposing a burden on the kidney to a certain extent, resulting in poor patient acceptance. Notably, additional therapies are still available, such as cognitive behavior therapy, music biofeedback therapy, and transcranial magnetic therapy, as well as those reported in the literature, including the reduction of dialysate temperature [6], dialysis with high frequency and prolonged duration [7], high-flux hemodialysis [8], kidney transplantation [9], and amelioration of inflammation [10], all of which show certain efficacy in improving insomnia. However, they still have problems, such as poor compliance, self-discipline, and patient cooperation. Therefore, it is important to find a complementary and alternative therapy that is safe and effective for relieving symptoms.

Acupuncture is an important complementary and alternative medicine treatment with a strong clinical effect on insomnia with minor adverse reactions [11]. It has also been pointed out by the Traditional Chinese Medicine Clinical Guidelines of the Insomnia Research Group that acupuncture can act as one of the recommended methods for treating insomnia [12]. The principle of treating insomnia, as suggested by the review of ancient literature on TCM, lies in the regulation of the mind (*Tiaoshen*), with its key point lying in the dredging *Du* channel (*Tongdu*); therefore, *Tongdutiaoshen* acupuncture is an effective method for treating insomnia [13,14]. Researchers have applied acupuncture-related therapies, such as auricular point pressing and intradermal needles, to treat insomnia in MHD, which shows solid efficacy with good safety [15,16]. However, owing to the small sample size and the fact that no research has applied *Tongdutiaoshen* acupuncture to treat insomnia in MHD, it is necessary to design a more rigorous RCT to verify its clinical efficacy. Therefore, we conducted this prospective RCT to

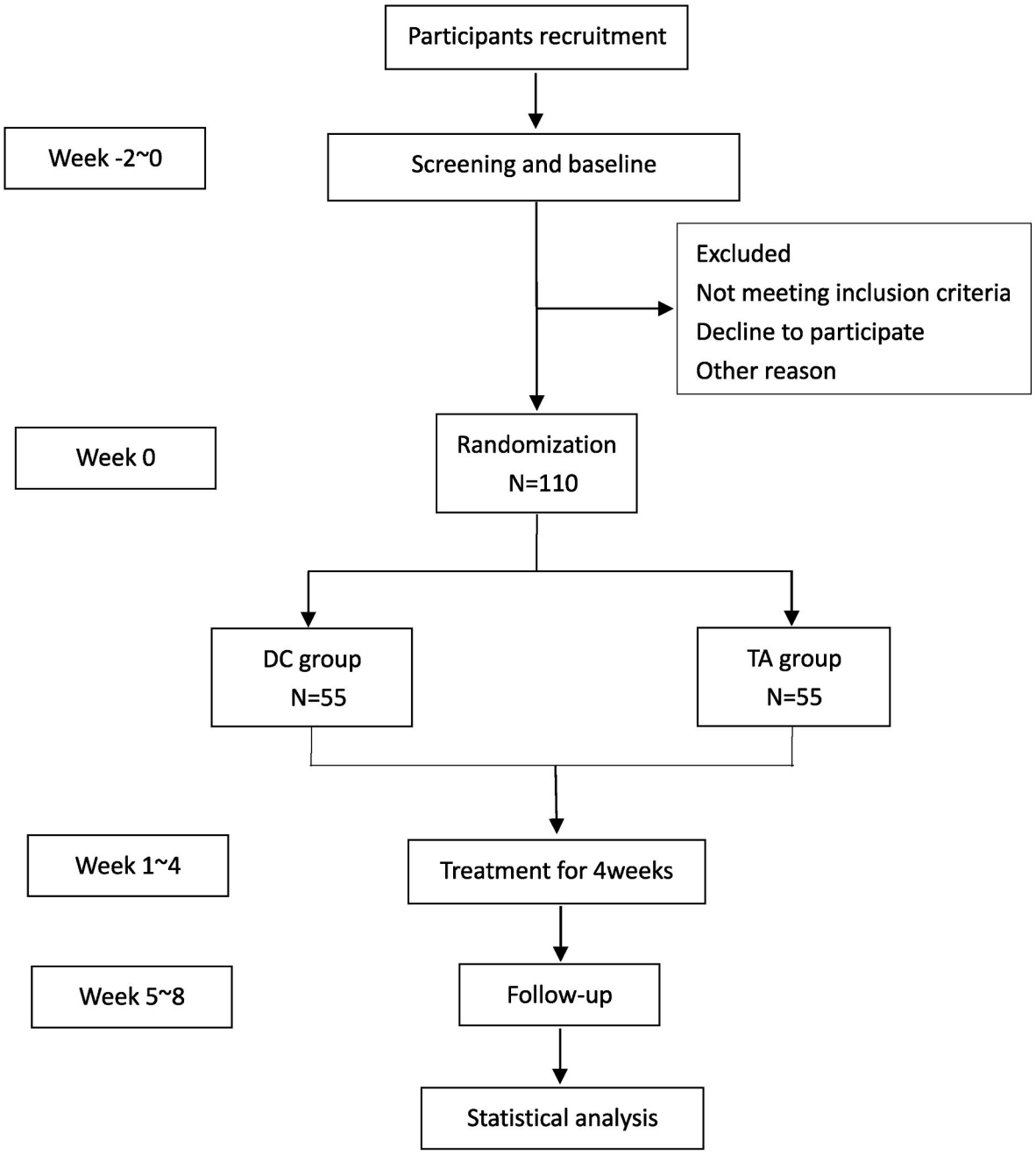

Fig. 1. Flow diagram of study design. Abbreviation: DC, Drug control; TA, *Tongdutiaoshen* acupuncture.

explore the clinical efficacy and safety of *Tongdutiaozhen* acupuncture for treating insomnia in MHD.

2. Objectives

This study aimed to evaluate the efficacy and safety of *Tongdutiaoshen* acupuncture in treating insomnia in patients undergoing MHD. Moreover, the long-term follow-up results of *Tongdutiaoshen* acupuncture for insomnia in patients will be compared. The findings of this trial will provide reliable evidence for *Tongdutiaoshen* acupuncture in the treatment of insomnia in patients undergoing MHD.

3. Methods/design

3.1. Design and setting

This will be a prospective, parallel-arm, randomized clinical trial. 110 MHD patients with insomnia will be allocated into the control group or TA group with an allocation ratio of 1:1. This trial will comprise 1-week baseline (baseline sleep), 4-weeks acupuncture or medicinal treatment, and 4-weeks follow-up periods. Fig. 1 shows the flow diagram of the trial.

This RCT will be performed at the Beijing Luhe Hospital Affiliated to Capital Medical University, China. The hospital has a dialysis center that seats over 400 patients and has a traditional Chinese medicine center which includes 25 acupuncture beds. This study will be conducted in accordance with the Declaration of Helsinki and has been approved by the Ethics Committee of the Beijing Luhe Hospital Affiliated to Capital Medical University (2022-LHKY-035-01) and has been registered in the Chinese Clinical Trial Registry (ChiCTR2200061967). This protocol was compiled in line with the SPIRIT 2013.

3.2. Participants

3.2.1. Sample size

The Study is a parallel designed, randomized and controlled trial, consisting of a control and an acupuncture cohort, with clinical response rate of patients as the primary endpoint. With α taken as 0.05 bilaterally and β as 0.1 unilaterally, according to the response rate of 68.2% in the control and of 90.0% in the acupuncture cohort observed in our preliminary study (an "independent study" with the number of LHYY2021-YJZ33 by Beijing Luhe Hospital Affiliated to Capital Medical University). The sample size was calculated by the following formula:

$$n = \frac{\left[Z_{\alpha/2}\sqrt{2\overline{p}(1-\overline{p})} + Z_{\beta/2}\sqrt{p_1(1-p_1)+p_2(1-p_2)}\right]^2}{(p_1-p_2)}$$

N is calculated to be equaling about 44, i.e. Assuming a rate of lost to follow up is 20%, 55 patients will be included in the control or the acupuncture cohort.

3.2.2. Recruitment

110 MHD patients with insomnia will be recruited from the in-patients in hemodialysis center of Beijing *Luhe* hospital Affiliated to Capital Medical University. Several strategies will be applied in patient recruitment. Bedside education, publicity posters, and door type exhibition stands placed in the hemodialysis center will be adopted. These publicity contents will include the brief introduction of the population that we plan to include, the free examinations and acupuncture treatment, traffic compensation of the patients, and contact information. All patients will be required to sign a written informed consent before participating and will be monetarily compensated. Recruitment was carried out on August 01, 2022, and is supposed to be completed on August 31, 2023.

3.2.3. Patient screening

Prior to the trial, potential subjects will undergo screening at hemodialysis center of Beijing *Luhe* hospital accordance with the criteria to determine whether they are eligible for the study. At first, doctors will introduce the study to him/her in as much detail as possible, and carefully answer the doubts of subjects and their families. It is critical that the patients comprehend the purpose, procedure and duration of the study, as well as the benefits, risks and discomfort that may appear in the course of the research. After potential patients voluntarily consent to the study, they will be screened using predetermined inclusion/exclusion criteria at the first visit. Written informed consent will be obtained from all the patients by the principal investigator or sub-investigators prior to enrollment.

3.2.4. Diagnose criteria

Based on *Nephrology* [17] edited by Hai-yan Wang, the diagnosis of maintenance hemodialysis is defined as: 1) a glomerular filtration rate (GFR) during the uremic stage of chronic renal failure lesser than 15 ml/min/1.73 m^2, which may be complicated by a series of syndromes, such as disorders in water, electrolyte, and acid-base balance, as well as retention of metabolic wastes and systemic involvement; and 2) exposure to replacement therapy using regular hemodialysis for no less than 3 months.

According to the Guidelines for Diagnosis and Treatment of Insomnia in Chinese Adults (2019 Edition), insomnia is defined as follows: 1) difficulty in falling asleep (sleep latency >30 min); 2) sleep maintenance disorder (number of times of awakening during one night ≥2); 3) early awakening and reduced sleep quality and total sleep time (less than 6 h); and 4) complications of any daytime dysfunction, including fatigue, low mood or irritation, and physical discomfort). A diagnosis was made if the patient experienced one of these symptoms in the past month.

3.2.5. Inclusion criteria

(1). Males and females aged 18–80 years.
(2). No exposure to any drug influencing sleep, such as γ-Aminobutyric acid A agonist, antianxietic and antidepressant, or had the drug withdrawal more than 2 weeks ago.
(3). PSQI score >7.
(4). Patients who are able and willing to sign written informed consent and complete the study

3.2.6. Exclusion criteria

(1). Patients with any acute severe primary disease of heart, brain, liver or hemopoietic system.
(2). Patients with any neurological or psychiatric disorder, or unable to cooperate.
(3). Patients with insomnia induced by any other factor (such as environmental, physiological and medicinal factors, prolonged excessive exposure to alcohol, cafe or strong tea, pain, infection, surgery or any other systemic disease).
(4). Patients with moderate to severe depression, defined as a standard score ≥63 based on Self-Rating Depression Scale (SDS).
(5). Patients with progressive malignant tumor or any other severe consumptive disease, and vulnerable to infection.
(6). Patients with severe coagulation disorder.
(7). Patients with severe dermal infection at acupoint selected, or acupuncture phobia.
(8). Patients with severe metal allergy.

3.3. Randomization

Randomization will be done by statistical professionals who belong to the third party and will not participate in the study. Random number tables will be generated by SPSS24.0 software(SPSS Inc., Chicago, IL).

Randomization will be performed by a person who will not be engaged in the study in order to blind the identity of the participants. Once patients are recruited in the study, they will be randomly allocated into two groups of drug control group and *Tongdutiaoshen* acupuncture group.

The randomized regimen generated will be blinded with an opaque envelope and submitted to a third party to be managed. After the completion of filling in enrollment data of patients, the investigational assistant will call the administrator of randomization scheme to inform him/her of the enrollment sequential number and name of the patient, and the administrator of randomization scheme will inform the investigational assistant of the randomization number and information about the randomized treatment, according to the randomization scheme. Only the investigational assistant will be allowed to contact the administrator of randomization scheme, so as to guarantee the blinding of the randomization scheme.

3.4. Blinding

Blinding methods will be applied to data statisticians and outcome evaluators throughout the trial. They will not be able to obtain information regarding the grouping and treatment of patients. Acupuncturists will not be masked due to the nature of acupuncture. However, acupuncturists will not participate in the data collection, statistics, and final outcome evaluation. For the intervention, different patients will be assigned to independent beds so as to avoid contact among patients. Personnel in charge of random grouping, acupuncture treatment, data processing, and outcome evaluation will be completely separated so as to ensure the authenticity of the outcome of the trial to the greatest possible extent.

3.5. Withdrawal criteria and management

Patients will be allowed to leave the study at any time for any reason if they wish to, without any consequences. This study will be prematurely ended in case of any adverse events or procedural-related complications or if the independent specialist in acupuncture and moxibustion advises its termination. The criteria for study termination will also include any serious adverse event (SAE).

3.6. Intervention

Interventions will be based on records in ancient books and the research results of modern papers on treating diseases related to sleep disorders with acupuncture in China or the West. The project team has created SOPs for clinical research to ensure that treatment is followed throughout the clinical research. Patients will be randomly allocated to the DC or the TA group.

3.7. Drug control (DC) group

The patient will be treated with estazolam tablets (Beijing Yimin Pharmaceutical Co., Ltd., Beijing, China; product batch number: 20220302, specification: 1 mg/tablet), 1 mg q. d., p.o. before sleeping, with the regimen of the same category of drugs remaining unchanged within one month.

3.8. Tongdutiaoshen acupuncture (TA) group

The patients will be treated with *Tongdutiaoshen* acupuncture and estazolam tablets, with the latter being identical to the control group. The manipulation of *Tongdutiaoshen* acupuncture is as follows: The acupoints to be used in the TAE group are *Baihui* (GV-20), *Shenting* (GV24), *Yintang* (EX-HN3), *Shenmen* (HT-7), and *Sanyinjiao* (SP-6), which are the recommended points for the treatment of diseases related to sleep disorders [18]. All acupoints have been localized according to their names and locations (GB/T 12346–2021), as shown in Table 1 and Fig. 2.

Specific operation of acupuncture: The patient will be kept in the supine position with the local skin at the acupoints routinely disinfected using 75% alcohol. A Ø0.25 mm × 25 mm disposable sterile acupuncture needle (Yunlong Medical Instrument Co., Ltd., Wujiang, China) will be used for acupuncture, penetrating promptly 5–10 mm under the cap aponeurosis along the direction of *Du* Meridian in a 15° needling angle with the skin at the acupoints of GV-20, GV-24, and EX-HN3, and penetrating 5–10 mm hypodermically in a vertical needling angle at the acupoints of HT-7 and SP-6. The mild reinforcing and attenuating method will be implemented after the insertion of the needle for each acupoint until *Deqi* is obtained (The *Deqi* of compositional sensations, including soreness, numbness, distention, or heaviness, known as *deqi*, is indicative of effective needling). The needle will be withdrawn after 30-min needle retaining. Acupuncture will be performed three times a week for four weeks successively, with a 4-week subsequent follow period.

4. Procedures for MHD

All patients enrolled will receive routine hemodialysis, with a detailed regimen formulated according to the Guideline on Clinical Practice of Hemodialysis Adequacy in China [19]: 1) the mode and the frequency of dialysis will be modified, prescribing regular dialysis three times per week (consisting of two times of low-flux dialysis and one hemodiafiltration) with a duration of 4 h for each dialysis; 2) symptomatic treatment will be carried out to correct actively metabolic acidosis, control blood pressure, achieving a pre-dialysis systolic blood pressure lower than 160 mmHg under drug administration; use erythropoietin and chalybeates to correct anemia with the target hemoglobin range of 110–130 g/L; and regulate calcium and phosphorus metabolism, using reasonably calcium agent, phosphorus binding agent, active vitamin D and its analogues, with the target ranges of 1.13–1.78 mmol/L, 2.1–2.75 mmol/L, and 150–300 ng/L, respectively for blood phosphorus, corrected blood calcium, and parathyroid hormone prior to dialysis. 3) Primary diseases and other underlying diseases will be actively treated, and 4) dietary guidelines for patients on hemodialysis will be strictly followed.

5. Outcome measurements

5.1. Primary outcome

(1) PSQI (see Attachment 1): Sleep quality was measured by the PSQI score [20]. The PSQI contains seven domains, with scores ranging from 0 to 3, yielding a total score ranging from 0 to 21, with

Table 1
Location of acupoints in *Tongdutiaoshen* acupuncture group.

Acupoints	Location	Descriptions
Baihui (GV20)	At the vertex on the midline, in the depression 5 cun posterior to the anterior hairline and 7 cun superior to the posterior hairline	Punctured horizontally 0.3–0.5 cun
Shenting (GV24)	On the midline of the head, in the depression 0.5 cun posterior to the anterior hairline	Punctured horizontally 0.3–0.5 cun
Yintang (EX-HN3)	At midpoint of the line joining the medial ends of the two eyebrows	Punctured horizontally 0.3–0.5 cun
Shenmen (HT7)	At the wrist joint, on the radial side of flexor carpi ulnaris, in the depression at the proximal border of the pisiform bone	Punctured perpendicularly 0.5–0.8 cun
Sanyinjiao (SP6)	On the medial side of the lower leg, 3 cun superior to the prominence of the medial malleolus, in a depression close to the medial crest of the tibia	Punctured perpendicularly 1.0–1.5 cun

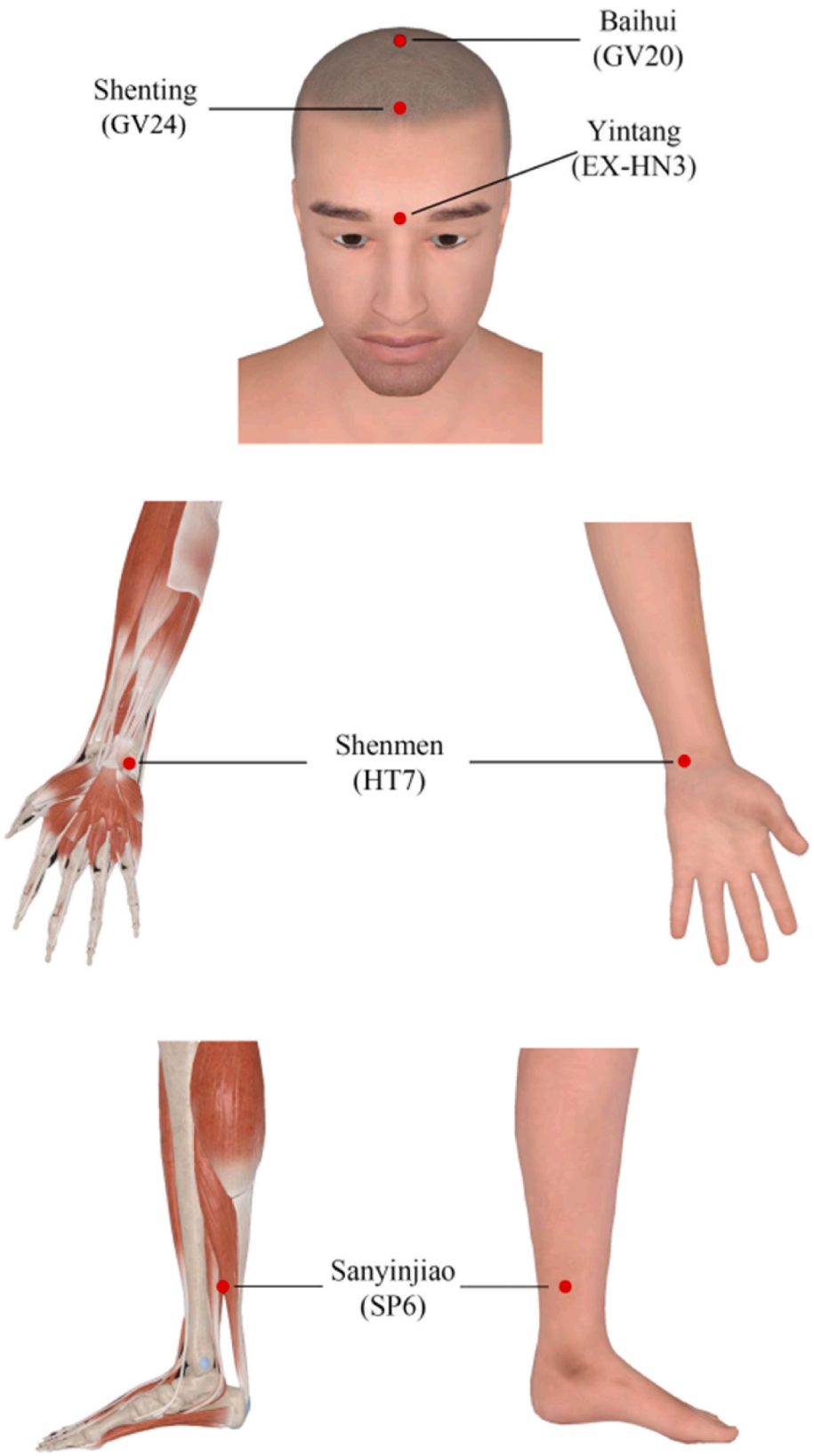

Fig. 2. All acupoints.

higher scores indicating poorer sleep quality. The reliability and validity of the Chinese version of the scale have been confirmed [21,22].

(2) HAM-A (see Attachment 2): HAM-A is a widely used, well-validated tool consisting of 14 items designed to assess the severity of a patient's anxiety [23]. Each of the 14 items in this

Fig. 3. ActiGraph wGT3X-BT and the software of Act Life 6.

clinician-rated measure is rated on a 5-point scale ranging from 0 (not present) to 4 (severe).

The PSQI and HAM-A will be assessed at baseline and at 2, 4, and 8 weeks after treatment. The schedule of each outcome assessment is presented in Table 2.

(3) TCM Syndrome Score of Insomnia (see Attachment 3): Based on the Criteria of Diagnosis and Efficacy of TCM Diseases [24], the change in the TCM Syndrome Score of Insomnia before and after treatment for patients in the two groups will be evaluated, including mainly the improvement of symptoms, such as difficulty in falling asleep, sleep time, dreaminess with easy arousal, and fatigue, followed by a categorization based on severity into four levels: null, mild, moderate, and severe. The total score was recorded, with a higher score indicating poorer sleep quality.

(4) Evaluation of clinical efficacy: The criteria for evaluating the clinical efficacy in patients undergoing MHD with sleep disorders were formulated jointly by referring to the TCM Syndrome Score of Insomnia and PSQI score [25]. *Cured* is defined as the disappearance of clinical symptoms, a reduction rate of TCM syndrome ≥95%, a nocturnal sleep time ≥6 h, and a reduction in the PSQI score >5 points. *Significant response* is defined as a significant improvement in clinical symptoms, a reduction rate of TCM syndrome ≥70% and <95%, nocturnal sleep time ≥3 h and <6 h, and a reduction in the PSQI score ≥3 points and <5 points. *Response* was defined as a certain amelioration of clinical symptoms, a reduction rate of TCM syndrome ≥30% and <70% with a certain amelioration, nocturnal sleep time <3 h, and a reduction of PSQI score <3 points. *No response* was defined as the absence of amelioration or aggravation of clinical symptoms, a reduction rate of TCM syndrome of <30%, and no change in the PSQI. The overall clinical response rate = (number of cured cases + significant response + response)/number of total cases × 100%.

Table 2
The schedule of enrollment, interventions, and assessments.

		STUDY PERIOD				
		Enrolment	Allocation	Treatment period		Follow-up period
Time point	Vist	V_0	V_0	V_1	V_2	V_3
	Week	−2~0	0	2	4	8
ENROLMENT						
Demographic data		×				
Collect medical history		×				
Diagnostic criteria		×				
Inclusion/Exclusion criteria		×	×			
Informed consent		×				
Random allocation			×			
INTERVENTIONS						
Control group				⟷		
Tongdutiaoshen acupuncture group				⟷		
ASSESSMENT						
Primary outcome						
PSQI		×	×	×	×	×
HAM-A			×	×	×	×
The TCM syndrome score for insomnia			×	×	×	×
Evaluation of clinical efficacy				×	×	×
Secondary outcome						
Sleep data monitoring			×		×	×
Dialysis-related laboratory indicators			×		×	×
Safety indicators						
Vital signs monitoring			×	×	×	×
Laboratory safety indicators			×		×	×
Adverse events				×	×	×

Notes : *PSQI* Pittsburgh Sleep Quality Index. *HAM-A* Hamilton Anxiety Scale.

5.2. Secondary outcomes

(1) Collecting sleep data (ActiGraph): We plan to use an ActiGraph (Body Motion Recorder, Sleep Version; Model: wGT3X-BT, made in the USA) to collect the sleep data in this study. The ActiGraph consists of a main unit and wrist straps and is connected directly to the Software Act Life 6 (See Fig. 3). During monitoring, the equipment will be worn on the non-dialysis wrist (without catheterization) throughout the night and the bedtime and time of awakening will be documented based on a simplified Sleep Diary (see Attachment 4).

The monitored data will include sleep efficiency (SE), sleep onset latency (SOL), total sleep time (TST), wake time after sleep onset (WASO), awakening time (AT), length of awakening in minutes (LAM), and the sleep fragmentation index (SFI). The periods for monitoring these data will include days −1 to 0, 27–28, and 55–56 of enrollment, with six nights in total, and the mean at each time point of two days in pairs will be recorded.

(2) Test on the laboratory indices related to dialysis: Fasting venous blood will be sampled before 8:00 a.m. on days 0, 28, and 56 of enrollment of the patient, for a total of three times, and indices will include hepatic/renal function (albumin (ALB)), serum creatinine (Scr), serum urea (Urea), electrolytes (serum phosphorus (P), calcium (Ca) and potassium (K)), parathyroid hormone (PTH), and hemoglobin (Hb).

5.3. Safety indexes

All adverse events during the study will be documented, managed, and monitored, using methods as follows: 1) the vital signs of patients (including body temperature, pulse, respiration, and blood pressure, which will be examined post the start of dialysis, and the results will be documented in the dialysis administration system for patients). 2) The examination of the hepatic function of patients (including values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), glutamyltranspeptidase (GGT), alkaline phosphatase (ALP), which will be tested in the fasting venous blood sample taken on days 0, 28, and 56). 3) The documentation of the adverse events of acupuncture (including fainting during acupuncture, sticking of the needle, and metal allergy, which will be recorded truthfully after the end of needling, according to the actuality during the acupuncture).

5.4. Data collection and management

Prior to the start of the trial, all data assessors will be uniformly trained in order to improve the quality of the data assessment. Primary endpoints will be collected, using PSQI, HAM-A and TCM Insomnia Syndrome Scale, Actigraph (wGT3X-BT) will be used to collect sleep data in the secondary endpoints, and ELISA method will be used to test serum for laboratory indexes, with their results documented respectively in case report form.

Patients on maintenance hemodialysis will continue their dialysis after the treatment ends in this study, and a good compliance is anticipated. We will keep paying attention to the vital signs and occurrence of adverse events of the patients during the follow up. At the end of the follow up, we will collect data, and provide the last follow-up transportation subsidy. Meanwhile, we will provide a free acupuncture treatment for 4 weeks for patients in the control after unblinding at the end of the Study, as a compensation for them.

Cases will be screened using the Case screening Form (CSF) and data during the trial will be recorded using the Case Report Form (CRF). Case filters and records were trained personnel to ensure homogeneity of data records. Epidata 3.1 (EpiData Association, Denmark), which is a statistical package, will be used for data entry. All data will be double entered using the data entry program run on a software platform. The data administrator shall ensure that the data in the CRF forms are completely and truly entered into the computer.

Te data of this research may be published in medical publications, but we will keep the patients' information secret as needed by law, and personal information about the patients will not be revealed unless required by relevant laws.

5.5. Statistical analysis

Software SPSS24.0 (SPSS Inc., Chicago, IL) will be used to analyze statistically the data. Results of continuous variable will be expressed by means, standard deviation and 95% confidence interval, and those of count data will be expressed with frequency and percentage. Independent sample *t*-test or non parametric test will be used to compare baseline data, including age, sex, body mass index (BMI), disease course, PSQI score, sleep data and relevant laboratory indexes. Paired-sample *t*-test will be used for intra-cohort comparison of measurement data prior and post to the study, and non parametric test will be used in case of non-normal distribution or heterogeneity of variance. As for inter-cohort comparison, intention-to-treat (ITT) and Per-Protocol (PP) will be used with repeated measures analysis of variance (ANOVA). The count data will be tested by chi-square test, with $P \leq 0.05$ as the level of the significance.

5.6. Adverse events

Any adverse events reported by the participants will be recorded in the CRF, including the time, symptoms, signs, degree, duration, laboratory test index, treatment and outcome, follow-up, and follow-up time. Common treatment-related adverse events to be tested will include subcutaneous hematoma, continuous post-needling pain, itching at the sites of the needle insertion, and dizziness.

5.7. Trial monitoring

The academic committee of Beijing *Luhe* hospital Affiliated to Capital Medical University is responsible for reviewing the scientific nature and compliance of the protocol and making recommendations for the continuation or termination of the study. The ethics committee is responsible for reviewing the rationality of the protocol and safeguarding the rights and interests of the subjects. Both members are independent of the sponsors and researchers, and there is no conflict of interest.

6. Discussion

Insomnia is commonly observed in patients undergoing hemodialysis. Owing to the prolonged imbalance in the systemic electrolyte levels, patients undergoing MHD have a higher incidence of insomnia with more severe symptoms than the general population [26]. Moreover, prolonged insomnia can predispose patients and their families to anxiety, affecting patient survival. However, no importance has been attached to the disease by researchers, which may be related to the availability of the entire set of medications for relieving insomnia, in contrast to the little limitation on their prescription by physicians in China in clinical practice for these patients [27,28]. However, for patients on dialysis, prolonged exposure to a wide variety of oral drugs aimed at maintaining the basic stability of their physical state will undoubtedly produce a cumulative effect, which will further increase the burden on their kidneys. Therefore, patients are reluctant to take additional medications. Poor sleep quality will increase the all-cause mortality of patients [29]. Therefore, we chose a non-drug intervention (acupuncture) to solve this problem. To the best of our knowledge, this is the first high-quality randomized controlled trial to evaluate the efficacy and safety of *Tongdutiaoshen* acupuncture for insomnia in patients

undergoing MHD.

Acupuncture, a TCM therapy for insomnia, has been widely accepted in Western countries. Several clinical studies have demonstrated the efficacy of acupuncture in treating insomnia [30]. The results of a systematic review of acupuncture in treating insomnia suggested that acupuncture treatment of insomnia is efficacious, and not because of its placebo effect. For the selection of sham acupuncture, both methods were performed similarly in a clinical setting. Liu et al. [31] included 944 patients in a meta-analysis that investigated the efficacy of acupuncture in treating insomnia related to chronic pain and showed that acupuncture therapy is an effective and safe treatment for chronic pain-related insomnia (CPRI). Notably, this treatment can be recommended for managing patients with CPRI. Cheuk et al. [32] also reported that acupuncture as an auxiliary method in combination with other therapies may improve the sleep quality of patients more effectively.

Sleep monitoring is an important tool for assessing sleep quality. Polysomnography (PSG), a vital method for diagnosing diseases related to sleep disorders, has the advantage of comprehensive and accurate detection of the indices tested, including multiple items, such as electroencephalograms (EEG), electrooculograms (EOG), and electrocardiograms (ECG). However, its shortcomings are evident, including 1) the operation of PSG is complex. 2) It has limitations on site for examination, which requires the patient to show up at the sleep laboratory to receive examinations as well as monitoring and analysis by professionals and technical personnel, and the "first night effect" usually due to the maladjustment of the patient to the new environment may result in the deviation of the monitored data from the actual situation of the patient. 3) The discomforts during the examination, wherein the nasal oxygen tube and brain electrical lead easily cause interference with the patient, thereby affecting their sleep and reducing the accuracy of the examination results. 4) Expensive equipment for PSG with low availability leads to a long waiting time for the appointment. Therefore, it is necessary to develop a simpler and more convenient instrument to record the sleep status of patients [33].

The application of the ActiGraph (ACT) to the monitoring of sleep quality has been generalized, along with the development of wearable devices. With its operational principle based on the ability of human beings to keep their wrists stationary during sleep, ACT determines whether a subject is asleep or awake by collecting activity intensity data from the wrists. Once recommended by the American Association of Sleep Medicine (AASM) as an auxiliary method for sleep evaluation [34], the ACT is an effective means of assessing the objective parameters of sleep, characterized by multiple advantages, including high wearability, low price, no impact on sleep, and feasibility of prolonged monitoring [35]. Moreover, it successfully addressed the limitations of PSG technology by cooperating with the sleep diaries of patients. Sun et al. compared ACT with PSG and revealed a sensitivity of 0.96 and an accuracy of 0.88 for ACT, showing good consistency with PSG [36]. The ACT wGT3X-BT body motion recorder to be used in this study is made in ActiGraph LLC, USA. This device has been adopted by many universities and research institutions across more than 60 countries. ACT is recognized as the most accurate body motion measurement product, and the accuracy of ACT products has been demonstrated through extensive comparative studies.

Study of Wang RP et al. [1] have shown that itchy skin, dry skin and sleep disorders were the three most common symptoms in MHD patients. The occurrence of skin pruritus was positively correlated with the levels of calcium and phosphorus in blood. The higher the calcium, phosphorus and calcium-phosphorus product, the higher the frequency of pruritus. Skin itching was unbearable, and severe patients used to suffer from insomnia at night, which showed that abnormal calcium and phosphorus metabolism was one of the important factors affecting sleep quality. According to the study of Shi et al. [37], the incidences of restless legs syndrome (RLS) and insomnia were higher on MHD patients, and insomnia was closely related to the occurrence of RLS. RLS is an early symptom of peripheral neuropathy of ESRD, the pathogenesis of which is still not very clear, and may be related to the increase of microglobulin in the body and the accumulation of macromolecular toxins, especially macromolecules. Hyperparathyroidism may gradually slow down the motor nerve conduction speed, and the increase of iPTH may also be related to the peripheral nerve dysfunction [38,39]. Therefore, in this study, some biochemical indexes of MHD patients will be measured to further clarify the mechanism of treating insomnia in MHD patients with *Tongdutiaoshen* acupuncture.

This study has a few limitations. First, this is a single-center study, not a multicenter study. Dialysis needs to be performed in the same dialysis center because of the specificity of patients undergoing MHD; therefore, patients cannot be strictly separated from each other, which makes it possible for them to communicate information about the treatment they receive, thereby affecting the credibility of the results of the study. Therefore, a multisite study will be launched in the capital city to further verify this therapy's efficacy. In addition, Due to the particularity of dialysis treatment, patients need to be needled frequently and can clearly distinguish between real and sham acupuncture. If sham acupuncture is set, the blindness will be broken with a high probability, thus affecting the results of the study. Finally, only insomnia, a type of sleep disorder, was investigated in this study; however, there are other types of sleep disorders in patients on long-term hemodialysis, such as sleep apnea syndrome. Therefore, these patients should be included in a subsequent study with a larger sample size to obtain a more generalized conclusion. We hope that the results of this trial will provide reliable evidence for treating insomnia with MHD.

Protocol version

V1.0. Date of the version: Apr 19, 2022. The participants are currently being recruited for the present study since August 01, 2022, and recruitment is anticipated to be completed in August 31, 2023, approximately.

Authors' contributions

W.P., W.Z., L.M., M.SH., L.Y. and Y.C. were involved in the design of this trial. W.P., W.Z., M.SH. And L.Y. will be involved in enrolment and randomization. Y.M, W.J. and A.YC.are responsible to provide interventions. L.ZX., M. SH. And L.Y. are responsible to control the process of hemodialysis. L.H. and Y.C. is responsible to control the drug of Escrazolam tablets. A.YC. participate as the recorders of CRF, and W.P., L.M. and L.ZX. participate in drafting the work or revising it critically for intellectual content. All authors have read and approved the final structured summary.

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Ethics approval and consent to participate

Approved by the Medical Ethics Committee of Beijing *Luhe* Hospital Affiliated to Capital Medical University, Beijing, China, on May 18, 2022, with certificate No. 2022-LHKY-035-01. Before inclusion in the study, participants will be informed of the purpose of the study and of the clinical procedures required by the protocol. The researchers will explain the purpose, risks, and benefits associated with study participation. In addition, patients will be informed of their right to withdraw from the study at any time without explanation and without losing the

right to future medical care. Every patient is free to leave the study protocol at any stage of the study, may withdraw his or her consent, and may request that all of his or her data be eliminated from the database.

Consent for publication

This manuscript does not contain individual personal data from patients.

Declaration of competing interest

All authors disclosed no relevant relationship.

Data availability

No data was used for the research described in the article.

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Abbreviations

MHD	Maintenance hemodialysis
CKD	Chronic kidney disease
ESRD	End-stagerenal disease
PSQI	Pittsburgh sleep quality index
HAM-A	Hamilton anxiety scale. PSG Polysonmography
ACT	ActiGraph
CSF	Case report form
CRF	Case Report Form
RLS	restless legs syndrome

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