Research Protocol

The effect of acupuncture on hemodialysis patients with restless legs syndrome(RLS)

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Principal Investigator:
Principal Investigator(s): Jia-Ming Chen
Institution: CHANGHUA CHRISTIAN HOSPITAL,TAIWAN
Protocol No. : Y_105_0300 / CCH IRB No. : 170217
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Address: 135 Nanxiao St., Changhua City, Changhua County 500, Taiwan (R.O.C.)
Tel: 886-4-723-8595

The effect of acupuncture on hemodialysis patients with restless legs syndrome(RLS) study protocol for a randomized crossover trial

I. Study Objectives

To our knowledge, there have been no studies on the impact of acupuncture therapy on RLS in patients undergoing hemodialysis. Therefore, the present study was conducted to determine the effect of acupuncture on the severity of RLS in hemodialysis patients. The study is a randomized crossover trial.

II. Background and Rationale

Restless legs syndrome (RLS), a common sensorimotor movement disorder first described in detail by Ekbom, ranges in severity from merely causing annoyance in the patient to affecting sleep and quality of life severely enough to warrant medical treatment. Remarkable differences in prevalence rates of RLS can be observed across countries and geographic regions. Epidemiological research demonstrates that the prevalence of RLS in adults (18 years or more) ranges from less than 1% in Singapore to approximately 10% in Europe and the United States. In 1995, a uniform diagnosis of RLS was made possible worldwide, based on the criteria proposed by the International RLS Study Group (IRLSSG). According to the most recently revised diagnostic criteria, the four clinical manifestations mandatory for the diagnosis are:

(1) an urge to move the legs, accompanied or caused by uncomfortable and unpleasant sensations in the legs;
(2) the urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity;
(3) the urge to move or the unpleasant sensations are partially or totally relieved by movement;
(4) the urge to move or the unpleasant sensations are worse in the evening or night or only occur in the evening or night.

Acupuncture, an ancient Chinesemedical therapy used in the prevention and treatment of disease, is another useful method for treating RLS. It involves inserting needles into specific points (acupoints or Xue Wei) on the human body to bring about its therapeutic effects. Conventional science suggests that acupuncture works by neurological, neurohormonal as well as psychological mechanisms, and it is thought to confer an analgesic effect. Several kinds of acupuncture methods, such as body acupuncture, auricular acupuncture, scalp acupuncture, electro-acupuncture, laser acupuncture, acupressure, acupoint injection therapy (injection of drugs into acupoints)

or a combination of the approaches mentioned above, are used in the treatment of RLS.

The mechanism of acupuncture treatment for RLS is still ill-defined. According to our preliminary research, the current practice of acupuncture forRLS ismainly based on principles ofTraditional Chinese Medicine (TCM) rather than conventional science. The traditional explanation, based on TCM theory, is that acupuncture restores the balance between Yin and Yang and regulates Qi (the essence) and blood so that integral unity can be maintained and miscellaneous diseases cured.

The development of this disorder in hemodialysis patients is progressive, affecting various physical and psychological dimensions over time. The symptoms of this syndrome are greatly intensified at rest, and are relieved by moving the extremities, especially the legs. In hemodialysis patients, the symptoms mainly occur during dialysis when the patient is at rest and cause discomfort. Evidence suggests that RLS in hemodialysis patients is associated with a risk of cardiovascular disease, osteoporosis, musculoskeletal pain, and increased mortality. In the general population and in patients with end-stage renal disease (ESRD), the potential causes of RLS include anemia, pregnancy, iron deficiency, the dysfunction of dopamine within the central nervous system, a family history of RLS, and peripheral neuropathy. In patients with ESRD, iron deficiency, anemia, and dialysis are predisposing factors that can lead to RLS.

Some clinical trials have examined the efficacy of acupuncture in the treatment of RLS and demonstrated that it was able to alleviate the clinical symptoms. To our knowledge, however, There have been no studies on the impact of acupuncture therapy on RLS in patients undergoing hemodialysis. Therefore, the present study was conducted to determine the effect of acupuncture on the severity of RLS in hemodialysis patients.

III. Procedures

A. Research and Design

Subject Selection/Sample

Inclusion criteria:

1) Patients between 18-80 years old diagnosed with RLS in hemodialysis patients according to the diagnostic criteria of the International Restless Legs Syndrome Study Group (11).

2) Subjects should have bothersome RLS symptoms, despite best medical therapy

3) Subjects should be stable on all RLS medication for at least 4 weeks prior to

enrollment
4) All subjects must be able to read and write in English in order to be able to complete home diary cards and questionnaires.
5) All women of childbearing age must be using an acceptable form of birth control, including abstinence, IUD or intrauterine system in place for at least 3 months prior to screening, subject or partner using barrier method (e.g., condom, diaphragm, or cervical cap) with spermicide from screening through study completion; partner has a documented vasectomy > 6 months prior to Baseline, Stable hormonal contraception (with approved oral, transdermal, or depot regimen) for at least 3 months prior to screening.

Exclusion criteria:
1) RLS secondary associated with end stage renal disease, iron deficiency or pregnancy
2) Does not have sufficient vision to be compliant with study procedures.
3) Any other condition (other than the primary indications), which in the opinion of the investigators might contribute to difficulty complying with the protocol

Study setting
The trials will be conducted at the Changhua Christian Hospital. This study will adhere to the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) [15] to allow for greater completeness, transparency and accuracy of reporting. The protocol for this study has been registered in the Clinical Trials register (ClinicalTrials.gov Identifier: NCT04356794).

Eligibility criteria
Subjects who voluntarily sign a consent form will undergo the trial according to the study design. When a subject is determined to be fit for participation based on inclusion and exclusion criteria, the subject will be randomly assigned to 1 of 2 groups in a ratio of 1:1. One group is the true EA experimental group and the other is the sham EA control group. Each group will receive their treatment 2 times a week for 4 weeks. After 4 weeks of treatment and a 2-week washout period, the control group will switch to the experimental group while the experimental group will switch to the control group. The subjects then undergo the treatment of their new group for another 4 weeks.
Treatment and assessment will be performed independently and the practitioners will not be involved in assessing the outcome of the treatment. The subjects, the outcome assessors and the statistician performing the data analyses will be blinded to the treatment allocation throughout the study.

Ethics
This research protocol adheres to the principles of the Declaration of Helsinki and has been approved by the institutional review boards of the Changhua Christian Hospital (No. : 170217). Informed consent will be obtained from each participant before any treatment is given. All subjects will have the right to withdraw from the study at any time.

Inclusion criteria
The inclusion criteria were as follows:
1. Informed consent to participate in the study;
2. Between the ages of 20 - 80 years;

3. A mean frequency of RLS symptoms during the last 6 months of more than twice per week;
4. A score of at least 20 on the International Restless Legs Syndrome Rating Scale(corresponding to severe RLS,IRLSRS);
5. A history of chronic renal failure treated with regular and continuous hemodialysis for at least 3 months;
6. No acupuncture treatment in the last one month.

Exclusion criteria
The exclusion criteria were as follows:
1. An unwillingness to continue to participate in the study;
2. Vascular access in the leg area, such as an arteriovenous shunt;
3. The presence of peripheral neuropathy and vascular problems in the lower extremities;
4. Currently taking drugs for RLS, such as dopamine agonists, benzodiazepines, opioids, and gabapentin;
5. A history of other motor disorders, such as Parkinson's disease, dyskinesia, and dystonia;
6. With an artificial cardiac pacemaker;
7. Pregnancy or breastfeeding.

B. Measurement/Instrumentation
1) International Restless Legs Severity Scale (12): a 40 point scale measuring severity of restless leg symptoms. Patients are asked to answer a series of 10 questions each of which have values ranging from 0 to 4 and the points are then added. Higher values are associated with more severe symptoms.
2) Insomnia Severity Index: a series of 7questions assessing quality of sleep, with values ranging from 0 to 28.
3) heart rate variability: HRV is the measure of the inconsistent gaps between each heartbeat and is used as an index for different aspects of psychology. HRV is an index of the influence of both the parasympathetic nervous system and the sympathetic nervous systems.
Outcome measures will be at baseline and at week 4,10 and 18. Medical history including demographic information and information about alcohol, drug and tobacco use will be collected at the baseline visit. Medications and vital signs will be recorded at each visit. Adverse events will be recorded at week 4,10 and 18 or as reported by the patients. Anticipated benefits for the subjects in the treatment arms will be attenuation of RLS symptoms and improvement in quality of life and sleep.

Statistical Considerations:

A. Sample Size:

A total of 112 patients will be accrued to the study with roughly equal allocation to each treatment arm. This sample size will achieve over 90% power to detect a 5 point change in the International Restless Legs Severity Scale for the main effects of acupuncture assuming a standard deviation of 4 within each cohort. Additionally we will have roughly 80% power to detect a potential interaction effect on acupuncture therapy. Every effort will be made to reduce attrition; consent documents will emphasize the importance of complete data and encourage patients to return for the follow-up visit.

B. Randomization:

Patients will be randomized to one of the two treatment options with equal allocation. In an attempt to balance severity across treatment cohorts the randomization scheme will be stratified by baseline severity of RLS symptoms as measured by the International Restless Legs Severity Scale (severe vs. very severe). The randomization scheme will be generated by the study statistician with varying block sizes and uploaded to a web-based randomization program. After the patients eligibility has been confirmed and consent documents signed the research coordinator will randomize the patient to one of the two treatment options via the web-based randomization program. The PI will not randomize patients or have access to their treatment assignments.

C. Analysis plan:

All demographic and baseline characteristics of interest will be summarized both overall and by cohort. Frequencies and percentages will be used to summarize categorical variables and means, standard deviations and other appropriate measures of spread for continuous variables. ANOVA models will be used for testing and to estimate the effects of acupuncture. Sensitivity analyses may be considered to assess the impact of baseline severity and other clinically relevant covariates on the outcomes. We will adjust for multiplicity for all contrasts. Secondary outcomes will be analyzed using a similar approach. Further details will be provided in the Statistical Analysis Plan (SAP).

For study-related patient data (case report forms) a unique identifier will be used. Study-related documents will be kept in a locked cabinet in a locked office. A separate list (paper-only) will be made containing the unique identifier and the name of each participant. This list will be kept separate from the study related documents. Study databases will be stored on a password protected computer network in a locked office and kept for 5 years.

IV. Bibliography

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