A preliminary single-blind, placebo-controlled randomized study of Tianjiu effects in patients with intradialytic hypotension

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<td>bmjopen-2015-009976</td>
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<td>Date Submitted by the Author:</td>
<td>11-Sep-2015</td>
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Huang, Yu-Chuen; China Medical University,  
Wu, Chien-Hsing; Kaohsiung Chang Gung Memorial Hospital, Nephrology  
Chen, Yung-Hsiang; China Medical University, Graduate Institute of Integrated Medicine |
| Primary Subject Heading: | Complementary medicine |
| Secondary Subject Heading: | Complementary medicine, Renal medicine |
| Keywords: | COMPLEMENTARY MEDICINE, Nephrology < INTERNAL MEDICINE, Dialysis < NEPHROLOGY |
Protocol

A preliminary single-blind, placebo-controlled randomized study of Tianjiu effects in patients with intradialytic hypotension

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Introduction: Intradialytic hypotension (IDH) is the most frequent complication of hemodialysis (HD) and may contribute to cardiovascular events and high mortality. The etiology of IDH is multifactorial; therefore, it remains a challenging problem in the management of HD patients. Because the application of Tianjiu at specific points can influence hemodynamics, we hypothesize that Tianjiu therapy at the traditionally used meridian points will reduce the severity of hypotension in patients who undergo HD.

Methods/analysis: In this clinical trial, eligible patients with IDH will be divided randomly and equally into a Tianjiu group and a control group for 4 weeks. In the Tianjiu group, the patients will have Tianjiu applied at 3 points (Conception Vessel 4, and bilateral Kidney 1) during each HD session. In the control group, patients will have clay patches applied in the same way as the Tianjiu treatment group. Both groups will be followed up for 2 weeks. The primary outcome measure will be the percentage of target ultrafiltration achieved, defined as the actual ultrafiltration volume divided by the target ultrafiltration volume. Secondary outcome measures including frequency of IDH episodes and number of nursing interventions during HD sessions, pre- and post-dialysis BP, patient’s participative assessment of the degree of fatigue after dialysis (scale from 0, not at all, to 10, extremely), and recovery time.
from fatigue after dialysis will be recorded at the 0th and 4th week.

**Ethics/dissemination:** This trial has undergone ethical scrutiny and been approved by the ethics review board of Chang Gung Memorial Hospital (Permission number: 102-4749A3 and 104-3156C). The results of this trial will help to determine whether Tianjiu is an effective and safe treatment for intradialytic hypotension, and, if so, whether it is a therapeutic effect rather than a placebo effect.

**Trial registration:** NCT02210377

**Key words:** Tianjiu, Moxibustion, Intradyalitic hypotension, Hemodialysis
INTRODUCTION

Intradialytic hypotension (IDH) has been reported in 20% to 30% of patients treated with maintenance hemodialysis (HD).\(^1\) The symptoms associated with this clinical problem, such as nausea, dizziness, and cramps, can have a negative impact on patients’ quality of life and tolerability to dialysis.\(^2\) In addition, IDH can increase patients’ morbidity and mortality by aggravating the risk of cardiovascular complications, mesenteric or cerebral ischemia, suboptimal dialysis adequacy and ultrafiltration, and left ventricular hyperthrophy.\(^3\)\(^-\)\(^5\)

The etiology of IDH is multifactorial. The main factor is rapid removal of intravascular volume by ultrafiltration (UF) and the subsequent imbalance between UF and the plasma refilling rate.\(^6\) Another possible contributor to IDH is impaired cardiovascular compensation for the reduced circulating volume, which includes increased cardiac output and contractility and increased peripheral vascular resistance.\(^7\)\(^8\) Other factors, such as the rapid reduction in plasma osmolality, autonomic dysfunction, and increased synthesis of endogenous vasodilators, have also been reported to be associated with hemodynamic instability.\(^9\)\(^-\)\(^11\)

Several approaches have been applied to prevent and manage IDH. These include accurate assessment of dry weight, avoidance of excessive interdialytic weight gain, fasting during dialysis, adequate adjustment of anti-hypertension agents, sodium and
UF profiling, cooling of the dialysate, the use of dialysate with a bicarbonate buffer or a high calcium content, pharmacological measures including α1-adrenergic agonist, and convective therapies, including hemofiltration and hemodiafiltration.\textsuperscript{12-15}

Tianjiu (also called crude herb moxibustion, auto-moxibustion, acupoint herb paste, and cold moxibustion therapy) is one type of moxibustion that is widely used in Asian countries as traditional Chinese medicine (TCM). It is a permeability treatment that involves pasting Chinese herbs as an irritant near acupoints to cause a warm and painless sensation.\textsuperscript{16} The general theory of Tianjiu is based on the generation of the warm meridian energy (Yang-Qi), which is believed to be responsible for chronic diseases associated with cold-deficiency syndrome and poor immunity.\textsuperscript{17} Tianjiu therapy has been used to modulate autonomic nervous activity, neurotransmitter levels, endogenous substance levels, and levels of inflammatory factors, and to strengthen cerebral, cardiovascular, and renal function.\textsuperscript{18-21}

In TCM theory, symptomatic IDH is etiologically caused by the derangement of Qi-blood and subsequent prostration of Yang-Qi in the human body during the rapid fluid removal of HD. Tianjiu as a therapy features a stimulating effect, and thus it should make the Yang-Qi abundant, blood circulation strong, and its autonomic nerve activity smooth and harmonized in HD patients. Accumulating evidence shows that applying Tianjiu to specific acupoints has a therapeutic effect on clinical
symptoms and quality of life in HD patients. Unfortunately, clinical trials examining Tianjiu therapy for IDH are lacking.

This proposal describes a protocol for a randomized controlled trial (RCT) that aims to test the efficacy and safety of Tianjiu therapy during HD sessions, and to determine whether the intervention can reduce the frequency of symptomatic IDH episodes and IDH-related interventions and improve dialysis adequacy, volume control, blood pressure, and quality of life. The results of this study will provide evidence for assessing the need for a large clinical trial and yield data to determine the appropriate sample size for future large-scale RCTs of Tianjiu therapy in patients with IDH.

METHODS AND ANALYSIS

Study design

A randomized, single-blinded controlled trial of Tianjiu for the treatment of IDH in dialysis patients is currently being conducted at Kaohsiung Chang Gung Memorial Hospital (KCGMH), Taiwan. All screening appointments and study visits will occur in the HD units for outpatients. This study has been ethically approved by the Institutional Review Board of CGMH and is registered with the Ethics approval numbers 102-4749A3 and 104-3156C.
The total length of the trial at KCGMH will be 2 years, from March 2014 to July 2016. We plan to recruit participants via advertisements in websites, posters and disease associations. Eligible participants meeting the criteria of IDH in this study after identification by a nephrologist will be randomly and equally assigned to the Tianjiu group or the placebo group at a 1:1 ratio. Randomization will be generated by a computerized random number function in Microsoft Excel, and the patients, program assessors, and statisticians will be unaware of the group to which they have been assigned. A block randomization procedure will be employed to ensure that group allocation is equal. Only the research assistant will know to which group each patient belongs for regulation of the application of the methods. The duration of the study will be 7 weeks, including a baseline period of 1 week (week 0–1), a treatment period of 4 weeks (week 1–4), and a follow-up period of 2 weeks (week 5–6). A flowchart of the trial procedure is presented in Fig. 1.

**Setting**

This clinical trial will be conducted in a single center, with the participant blinded to treatment allocation. All patients diagnosed with IDH in accordance with the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines will be enrolled in this trial. Symptomatic hypotension is defined as a
drop in SBP of >20 mmHg from baseline or absolute SBP <100 mm Hg accompanied
by at least one of the following: diaphoresis, nausea, vomiting, cramps, headache, or
dizziness. The whole treatment process will be carried out at Kaohsiung Chang Gung
Memorial Hospital (KCGMH), Taiwan.

Participants

All participants who have been treated with HD for more than 3 months will be
screened for eligibility. To ensure blinding, only patients who have never received
Tianjiu before participating in this study will be included. Other inclusion criteria for
the study are as follows: age between 20 and 75 years, medically stable condition,
thrice-weekly treatment with maintenance HD for 4 hours per session, and >15% of
HD sessions in the preceding 2 months complicated by symptomatic IDH. Participants
with concurrent severe disorders of the heart, brain, liver, or the hematopoietic
system; active malignancy; mental disorders; pregnancy or lactation; hypersensitivity
skin reactions following Tianjiu therapy; or any other condition that the investigator
judges as likely to make the patient unable to complete or comply with, or otherwise
unsuitable for, the study will be excluded. Informed consent will be obtained from
each individual who agrees to participate in the study.

During the entire study period, participants will be free to withdraw from the
study at any stage without any consequences. In addition, patients who are
hospitalized for other reasons or who experience hypertensive crisis (defined as
SBP>180 mmHg or DBP > 120 mmHg) or other adverse events during the
treatment period will be excluded from Tianjiu intervention.

Interventions

Following enrollment, participants will undergo a 1-week baseline period for
comprehensive clinical assessment including dry weight reduction, medication review,
and standardization of their dialysis prescription. After randomization, patients in
both groups will receive 12 sessions of treatment over a 4-week treatment period.
The dialysis prescription, dialysate, and artificial kidney machines will not be altered
during the treatment period. UF volumes will be adapted to reach < 5% of dry weight
during each HD session. Dry weight will be determined clinically by the patient’s
attending nephrologist. Kt/V will be calculated using the Daugirdas second
generation logarithmic equation. The HD nurse assigned to each individual
participant will record hemodynamic parameters, treatment parameters, and
IDH-related interventions on standard clinical HD run-sheets.

Treatment group and placebo group
The participants in the Tianjiu group will be treated with Chinese herbal patches at acupoints on the abdomen and plantar, three times per week, for 4 hours each time during HD, and the participants in the control group will be given placebo patches (brown clay patches) on the same sites (Fig. 2). Participants will be instructed to lie supine before their HD session, and then the CV4 and bilateral KI1 will be disinfected using 75% alcohol. A Tianjiu patch (diameter 2.0 cm, depth 0.5 cm) placed on each acupoint will be covered by gauze with a non-woven adhesive plaster in the middle. The format of the placebo (clay) intervention will be the same as in the treatment group. At the end of the HD, the patches will be removed by research assistants and the surrounding skin will be checked.

Prescription and preparation of the Tianjiu paste

The prescription of Tianjiu therapy employed in this study will be referenced from Zhang Shi Yi Tong (Zhang Lu from the Qing Dynasty). The herbs will mainly include Sinapis Semen (10 g), Corydalis Rhizoma (10 g), Euphorbiae Kansui Radix (5 g), and Asari Herba Cum Radice (5 g), which will be ground into powder in an ultrafine grinder and then mixed in suitable proportions. To these herbs will be added fresh ginger juice in a ratio of 1:1 before use. The paste will be produced by the Chinese Medicine Pharmacy of KCGMH.
Selection and application of acupoints

Bilateral KI1 (Yongquan) and CV4 (Guanyuan) will be selected based on evaluation of moxibustion literature, experts’ recommendations, and the clinical experience of the researchers. KI1 is located on the points of the 1/3 and 2/3 intersection of the plantar. KI1 has the function of opening the sensory orifices, calming the spirit, recovering from unconsciousness, discharging heat, stimulating the blood pressure, and restoring yang to prevent collapse.\(^{28}^{29}\) CV4 is located on the mid-line of the abdomen, 3 cm below the center of the umbilicus, and belongs to the crossing acupoint of the conception vessel and the 3 Yin meridians. It is an important point for reducing exhaustion, promoting blood circulation, invigorating kidney Qi, and strengthening immunity.\(^{30}\)

Outcome measures

The primary outcome measure will be the percentage of target ultrafiltration achieved and will be defined as follows: \(\%\text{Target UF achieved} = \frac{\text{actual UF volume}}{\text{target UF volume}}\). Target UF volume will be the difference between the pre-dialysis weight and the dry weight. Actual UF volume will be the difference between the pre- and post-dialysis weights.
Secondary outcome measures (pre- and post-dialysis SBP, pre- and post-dialysis DBP, nadir SBP and nadir DBP, frequency of symptomatic IDH, and any IDH-related nursing interventions to treat hypotension episodes) will be recorded for each dialysis session. Blood pressure will be measured before dialysis, every 30 minutes during HD, and after dialysis in each HD session of the study. IDH-related interventions will be defined as the Trendelenburg position, manual reduction of UF rate, infusion of isotonic saline or hypertonic fluid, lowering of dialysate temperature, or dialysis cessation. Additionally, each patient’s subjective assessment of the degree of fatigue after dialysis (scale from 0, not at all, to 10, extreme) and recovery time from fatigue after dialysis (within minutes, when arriving home, at bed time, the next morning, by next HD) will be measured at the 0th and 4th week of the study period.

Data on dry weight, hematocrit, and serum albumin will be collected for all periods of the study. The outcome measurement time points are provided in detail in Table 1.

Quality control and data collection

All staff involved in the trial will receive training before implementation of the trial. The training program will include case screening and recruitment, the intervention method, outcome measures, and data processing. The research assistants will check
study protocol compliance and informed consent documents and assess the progress of the study, including participant randomization, Tianjiu patch intervention, and data quality. Dropouts and withdrawals from the study will be recorded throughout the intervention and follow-up periods.

**Patient safety**

Any adverse events (described as unfavorable or unintended signs, symptoms or diseases occurring after treatment) related to Tianjiu therapy will be observed and reported by patients and practitioners during each patient visit. In addition, all vital signs and adverse events will be measured and recorded at each visit.

**Sample size and statistical analysis**

To the authors’ knowledge, no randomized trials investigating the efficacy of Tianjiu therapy for IDH have been conducted to date. Sufficient data on estimates of the standard deviation of the proposed outcome measures in this population are not available for use in the calculation of a sample size. This pilot trial is designed to collect such data to inform the efficacy and sample size of Tianjiu therapy for a larger definitive trial in the future.

In order to collect sufficient data to inform a future sample size calculation, we
anticipate a 16 mmHg improvement due to Tianjiu therapy, and one of 0 mmHg due to sham Tianjiu therapy. Sample size calculations will be conducted using G-Power version 3.1, with an alpha value of .05 and power of 80%. The dropout rate during the study is estimated to be 10%, so a minimum of 45 participants will be needed in each group.

Baseline variables will be compared with the $\chi^2$ test for dichotomous variables and the t test or Wilcoxon rank sum test for continuous variables. Primary and secondary outcome measures will be compared with the paired t test or Wilcoxon signed rank test as appropriate. Differences in the degree of fatigue after dialysis and recovery time from fatigue after dialysis between pre-test and post-test will be analyzed by Bowker’s test. Differences will be considered statistically significant when the $P$ value is < 0.05. Analyses will be performed using SPSS version 18.0 and Microsoft Excel.

DISCUSSION

This trial is expected to provide convincing evidence that Tianjiu therapy has an effect for treating IDH. Extant literature shows that moxibustion is effective for HD patients; however, actual clinical practice has aspects that are somewhat difficult to overcome, such as unpleasant odors, burning and blistering, skin lesions, or other physical disturbances. With regard to this situation, Tianjiu therapy can prevent the
above complications and induce greater increases in skin temperature and blood perfusion than single moxibustion. In addition, stimulating the acupoints on the affected meridians can produce specific effects on regulating the corresponding organs.

Many new drugs and dialysis techniques to control IDH have been developed, with all being administered during the HD itself. However, they still cannot effectively combat the side-effects of IDH because of coexisting factors such as heart disease, diabetes, old age, atherosclerosis, and impaired sympathetic response. These factors should therefore also be considered in patients prone to IDH, regardless of UF volume. Thermal therapy through acupoints to restore the balance between Yin and Yang has been shown to improve vitality in HD patients. There is also evidence that the use of Tianjiu on the Lung-Qi tonifying acupoints such as BL12 (Fengmen), BL13 (Feishu), and GV14 (Dazhui) can reduce the symptoms of allergic rhinitis and regulate the autonomous nervous system in asthma patients. Based on our experience in clinical practice, Tianjiu therapy with pasting on acupoints to activate Yang-Qi could reduce the fatigue of HD patients. Few clinical trials have been carried out to evaluate the efficacy of herb paste for HD. Thus, we designed a Tianjiu therapy at CV4 and KI1 to determine the regulatory effect for patients with IDH.

To maximally exclude the placebo effect, rigorous methodological designs are
needed. In previous studies, no examples have used valid placebo or sham methods of acupoint herb paste. However, sham-Tianjiu can be practical for blinding purposes because of the rarity of experience with Tianjiu among HD patients. For pragmatic purposes, we plan to use brown clay patches as a sham device.

In conclusion, this pilot, single-blinded RCT will investigate the efficacy and safety of Tianjiu for intradialytic hypotension, assess the feasibility and relevance of a Tianjiu therapy study design, and provide a clinical foundation for future, large-scale, pluralistic clinical trials.

Trial status

The trial is currently in the recruitment phase. Participant recruitment began in March 2015 and is expected to end in July 2016.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

MYT and CHW conceived this trial and participated in the design of this trial. MYT, SYC, and YCH planned the data analysis and drafted the manuscript. YJS and HYN will
coordinate the trial and contribute to the screening of patients. CHW, YJS, and HYN

are involved in recruitment of participants from clinics. CHW and YHC are responsible

for the design and supervision of the study and the revision of the manuscript. All

authors have read and approved the final manuscript.

Acknowledgments

We would like to express our gratitude to the people in the outpatient dialysis units

and Chinese Medicine Pharmacy of the Physical Building of Chang Gung Memorial

Hospital for their full cooperation and material support. This trial was financially

supported by the Chang Gung Memorial Hospital with grant number CMRPG

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Figure Legend

Figure 1 Flow chart of study procedure

Figure 2 Photographs of the Tianjiu therapy that will be used in this trial. (a) Actual Tianjiu sample (a traditional Chinese method that uses the warmth and irritation generated by mixed herbal patches to stimulate acupoints); (b) sham-Tianjiu sample (clay patches of the same color and size); (c) therapeutic intervention of KI1 (Yongquan); (d) therapeutic intervention of CV4 (Guanyuan)

Table 1 Timing of visits and data collection
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ABSTRACT

Introduction: Intradialytic hypotension (IDH) is the most frequent complication of hemodialysis (HD) and may contribute to cardiovascular events and high mortality. The etiology of IDH is multifactorial; therefore, it remains a challenging problem in the management of HD patients. Because the application of Tianjiu at specific points can influence hemodynamics, we hypothesize that Tianjiu therapy at the traditionally used meridian points will reduce the severity of hypotension in patients who undergo HD.

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**Ethics/dissemination:** This trial has undergone ethical scrutiny and been approved by the ethics review board of Chang Gung Memorial Hospital (Permission number: 102-4749A3 and 104-3156C). The results of this trial will help to determine whether Tianjiu is an effective and safe treatment for intradialytic hypotension, and, if so, whether it is a therapeutic effect rather than a placebo effect.

**Trial registration:** ClinicalTrials.gov NCT02210377

**Key words:** Tianjiu, Moxibustion, Intradialytic hypotension, Hemodialysis
INTRODUCTION

Intradialytic hypotension (IDH) has been reported in 20% to 30% of patients treated with maintenance hemodialysis (HD). The symptoms associated with this clinical problem, such as nausea, dizziness, and cramps, can have a negative impact on patients’ quality of life and tolerability to dialysis. In addition, IDH can increase patients’ morbidity and mortality by aggravating the risk of cardiovascular complications, mesenteric or cerebral ischemia, suboptimal dialysis adequacy and ultrafiltration, and left ventricular hyperthrophy.

The etiology of IDH is multifactorial. The main factor is rapid removal of intravascular volume by ultrafiltration (UF) and the subsequent imbalance between UF and the plasma refilling rate. Another possible contributor to IDH is impaired cardiovascular compensation for the reduced circulating volume, which includes increased cardiac output and contractility and increased peripheral vascular resistance. Other factors, such as the rapid reduction in plasma osmolality, autonomic dysfunction, and increased synthesis of endogenous vasodilators, have also been reported to be associated with hemodynamic instability.

Several approaches have been applied to prevent and manage IDH. These include accurate assessment of dry weight, avoidance of excessive interdialytic weight gain, fasting during dialysis, adequate adjustment of anti-hypertension agents, sodium and...
UF profiling, cooling of the dialysate, the use of dialysate with a bicarbonate buffer or a high calcium content, pharmacological measures including α1-adrenergic agonist, and convective therapies, including hemofiltration and hemodiafiltration.  

Tianjiu (also called crude herb moxibustion, auto-moxibustion, herbal acupoint paste, and cold moxibustion therapy) is one type of moxibustion that is widely used in Asian countries as traditional Chinese medicine (TCM). It is a permeability treatment that involves pasting Chinese herbs as an irritant near acupoints to cause a warm and painless sensation. The general theory of Tianjiu is based on the generation of the warm meridian energy (Yang-Qi), which is believed to be responsible for chronic diseases associated with cold-deficiency syndrome and poor immunity. Tianjiu therapy has been used to modulate autonomic nervous activity, neurotransmitter levels, endogenous substance levels, and levels of inflammatory factors, and to strengthen cerebral, cardiovascular, and renal function.  

In TCM theory, symptomatic IDH is etiologically caused by the derangement of Qi-blood and subsequent prostration of Yang-Qi in the human body during the rapid fluid removal of HD. Accumulating evidence shows that applying moxibustion to specific acupoints has a therapeutic effect on clinical symptoms and quality of life in HD patients. Tianjiu, one moxibustion therapy, also features a stimulating effect. Therefore, it should make the Yang-Qi abundant, blood circulation strong, and
autonomic nerve activity smooth and harmonized in HD patients. Unfortunately, clinical trials examining Tianjiu therapy for IDH are lacking.

This proposal describes a protocol for a randomized controlled trial (RCT) that aims to test the efficacy and safety of Tianjiu therapy during HD sessions, and to determine whether the intervention can reduce the frequency of symptomatic IDH episodes and IDH-related interventions and improve dialysis adequacy, volume control, blood pressure, and quality of life. The results of this study will provide evidence for assessing the need for a large clinical trial and yield data to determine the appropriate sample size for future large-scale RCTs of Tianjiu therapy in patients with IDH.

METHODS AND ANALYSIS

Study design

A randomized, single-blinded controlled trial of Tianjiu for the treatment of IDH in dialysis patients is currently being conducted at Kaohsiung Chang Gung Memorial Hospital (KCGMH), Taiwan. All screening appointments and study visits will occur in the HD units for outpatients. This study has been ethically approved by the Institutional Review Board of CGMH and is registered with the Ethics approval numbers 102-4749A3 and 104-3156C.
The total length of the trial at KCGMH will be 2 years, from March 2014 to July 2016. We plan to recruit participants via advertisements in our HD units. Eligible participants meeting the criteria of IDH in this study after identification by a nephrologist will be randomly and equally assigned to the Tianjiu group or the placebo group at a 1:1 ratio. Randomization will be generated by a computerized random number function in Microsoft Excel, and the patients, program assessors, and statisticians will be unaware of the group to which they have been assigned. A block randomization procedure (based on age, comorbidities such as cardiovascular disease and diabetes mellitus) will be employed to ensure that group allocation is equal and that the characteristics of the trial subjects are similar. Only the research assistant will know to which group each patient belongs for regulation of the application of the methods. The duration of the study will be 7 weeks, including a baseline period of 1 week (week 0–1), a treatment period of 4 weeks (week 1–4), and a follow-up period of 2 weeks (week 5–6). A flowchart of the trial procedure is presented in figure 1.

**Setting**

This clinical trial will be conducted in a single center, with the participant blinded to treatment allocation. All patients diagnosed with IDH in accordance with the
National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines will be enrolled in this trial. Symptomatic hypotension is defined as a drop in SBP of >20 mmHg from baseline or absolute SBP <100 mm Hg accompanied by at least one of the following: diaphoresis, nausea, vomiting, cramps, headache, or dizziness. The whole treatment process will be carried out at Kaohsiung Chang Gung Memorial Hospital (KCGMH), Taiwan.

Participants

All participants who have been treated with HD for more than 3 months will be screened for eligibility. To ensure blinding, only patients who have never received Tianjiu before participating in this study will be included. Other inclusion criteria for the study are as follows: age between 20 and 75 years, medically stable condition, thrice-weekly treatment with maintenance HD for 4 hours per session, and >15% of HD sessions in the preceding 2 months complicated by symptomatic IDH. Participants with concurrent severe disorders of the heart, brain, liver, or the hematopoietic system; active malignancy; mental disorders; pregnancy or lactation; hypersensitivity skin reactions following Tianjiu therapy; or any other condition that the investigator judges as likely to make the patient unable to complete or comply with, or otherwise unsuitable for, the study will be excluded. Informed consent will be obtained from
each individual who agrees to participate in the study.

During the entire study period, participants will be free to withdraw from the study at any stage without any consequences. In addition, patients who are hospitalized for other reasons or who experience hypertensive crisis (defined as SBP > 180 mmHg or DBP > 120 mmHg) or other adverse events during the treatment period will be excluded from Tianjiu intervention.

Interventions

Following enrollment, participants will undergo a 1-week baseline period for comprehensive clinical assessment including dry weight reduction, medication review, and standardization of their dialysis prescription. After randomization, patients in both groups will receive 12 sessions of treatment over a 4-week treatment period. The dialysis prescription, dialysate, and artificial kidney machines will not be altered during the treatment period. UF volumes will be adapted to reach < 5% of dry weight during each HD session. Dry weight will be determined clinically by the patient's attending nephrologist. Kt/V will be calculated using the Daugirdas second generation logarithmic equation. The HD nurse assigned to each individual participant will record hemodynamic parameters, treatment parameters, and IDH-related interventions on standard clinical HD run-sheets.
Treatment group and placebo group

The participants in the Tianjiu group will be treated with Chinese herbal patches at acupoints on the abdomen and plantar, three times per week, for 4 hours each time during HD. A Tianjiu patch (diameter 2.0 cm, depth 0.5 cm) placed on each acupoint will be covered by gauze with a non-woven adhesive plaster in the middle (figure 2A), and the participants in the control group will be given placebo patches (brown clay patches) (figure 2B) on the same sites. The format of the placebo (clay) intervention will be the same as in the treatment group. Participants will be instructed to lie supine before their HD session, and then the bilateral KI1 (Yongquan) (figure 2C) and CV4 (Guanyuan) (figure 2D) will be selected based on evaluation of moxibustion literature, will be disinfected using 75% alcohol. To reduce bias, the trial participants will be blinded to the intervention. Our HD nurse will be encouraged to supervise participants and to prevent them from touching the patches during each HD session.

At the end of the HD, the patches will be removed by research assistants and the surrounding skin will be checked.

 Prescription and preparation of the Tianjiu paste

The prescription of Tianjiu therapy employed in this study will be referenced from
Zhang Shi Yi Tong (Zhang Lu from the Qing Dynasty). The regimens will mainly include Sinapis Semen, Corydalis Rhizoma, Euphorbiae Kansui Radix, Asari Herba Cum Radice, and Boreneolum Syntheticum, which will be ground into powder in an ultrafine grinder and then mixed in suitable proportions of 10:10:5:5:1. To these herbs will be added fresh ginger juice in a ratio of 1:1 before use. All herbs were provided by Sheng Chang Pharmaceutical Co., Ltd. in June 2014 and can be refrigerated for up to 2 years. The paste will be produced by the Chinese Medicine Pharmacy of KCGMH on the day of use.

**Selection and application of acupoints**

Bilateral KI1 and CV4 will be selected based on evaluation of moxibustion literature, experts’ recommendations, and the clinical experience of the researchers. KI1 is located on the points of the 1/3 and 2/3 intersection of the plantar. KI1 has the function of opening the sensory orifices, calming the spirit, recovering from unconsciousness, discharging heat, stimulating the blood pressure, and restoring yang to prevent collapse. CV4 is located on the mid-line of the abdomen, 3 cm below the center of the umbilicus, and belongs to the crossing acupoint of the conception vessel and the 3 Yin meridians. It is an important point for reducing exhaustion, promoting blood circulation, invigorating kidney Qi, and strengthening
immunity.\textsuperscript{30}

**Outcome measures**

The primary outcome measure will be the percentage of target ultrafiltration achieved and will be defined as follows: %Target UF achieved will be defined as actual UF volume/target UF volume. Target UF volume will be the difference between the pre-dialysis weight and the dry weight. Actual UF volume will be the difference between the pre- and post-dialysis weights.

Secondary outcome measures (pre- and post-dialysis SBP, pre- and post-dialysis DBP, nadir SBP and nadir DBP, frequency of symptomatic IDH, and any IDH-related nursing interventions to treat hypotension episodes) will be recorded for each dialysis session. Blood pressure will be measured before dialysis, every 30 minutes during HD, and after dialysis in each HD session of the study. IDH-related interventions will be defined as the Trendelenburg position, manual reduction of UF rate, infusion of isotonic saline or hypertonic fluid, lowering of dialysate temperature, or dialysis cessation. Additionally, each patient’s subjective assessment of the degree of fatigue after dialysis (scale from 0, not at all, to 10, extreme) and recovery time from fatigue after dialysis (within minutes, when arriving home, at bed time, the next morning, by next HD) will be measured at the 0th and 4th week of the study period.
Data on dry weight, hematocrit, and serum albumin will be collected for all periods of the study. The outcome measurement time points are provided in detail in Table 1.

Quality control and data collection

All staff involved in the trial will receive training before implementation of the trial. The training program will include case screening and recruitment, the intervention method, outcome measures, and data processing. The research assistants will check study protocol compliance and informed consent documents and assess the progress of the study, including participant randomization, Tianjiu patch intervention, and data quality. Dropouts and withdrawals from the study will be recorded throughout the intervention and follow-up periods.

Patient safety

Any adverse events (described as unfavorable or unintended signs, symptoms or diseases occurring after treatment) related to Tianjiu therapy will be observed and reported by patients and practitioners during each patient visit. In addition, all vital signs and adverse events will be measured and recorded at each visit.
Sample size and statistical analysis

To the authors’ knowledge, no randomized trials investigating the efficacy of Tianjiu therapy for IDH have been conducted to date. Sufficient data on estimates of the standard deviation of the proposed outcome measures in this population are not available for use in the calculation of a sample size. This pilot trial is designed to collect such data to inform the efficacy and sample size of Tianjiu therapy for a larger definitive trial in the future.

In order to collect sufficient data to inform a future sample size calculation, we anticipate a 16 mmHg improvement due to Tianjiu therapy, and one of 0 mmHg due to sham Tianjiu therapy. Sample size calculations will be conducted using G-Power version 3.1, with an alpha value of .05 and power of 80%. The dropout rate during the study is estimated to be 10%, so a minimum of 45 participants will be needed in each group.

Baseline variables will be compared with the $\chi^2$ test for dichotomous variables and the t test or Wilcoxon rank sum test for continuous variables. Primary and secondary outcome measures will be compared with the paired t test or Wilcoxon signed rank test as appropriate. Differences in the degree of fatigue after dialysis and recovery time from fatigue after dialysis between pre-test and post-test will be analyzed by Bowker’s test. Differences will be considered statistically significant when the $P$ value
is < 0.05. Analyses will be performed using SPSS version 18.0 and Microsoft Excel.

**DISCUSSION**

This trial is expected to provide convincing evidence that Tianjiu therapy has an effect for treating IDH. Extant literature shows that moxibustion is effective for HD patients; however, actual clinical practice has aspects that are somewhat difficult to overcome, such as unpleasant odors, burning and blistering, skin lesions, or other physical disturbances. With regard to this situation, Tianjiu therapy can prevent the above complications and induce greater increases in skin temperature and blood perfusion than single moxibustion. In addition, stimulating the acupoints on the affected meridians can produce specific effects on regulating the corresponding organs.

Many new drugs and dialysis techniques to control IDH have been developed, with all being administered during the HD itself. However, they still cannot effectively combat the side-effects of IDH because of coexisting factors such as heart disease, diabetes, old age, atherosclerosis, and impaired sympathetic response. These factors should therefore also be considered in patients prone to IDH, regardless of UF volume. Thermal therapy through acupoints to restore the balance between Yin and Yang has been shown to improve vitality in HD patients. There is also evidence that
the use of Tianjiu on the Lung-Qi tonifying acupoints such as BL12 (Fengmen), BL13 (Feishu), and GV14 (Dazhui) can reduce the symptoms of allergic rhinitis and regulate the autonomous nervous system in asthma patients. Based on our experience in clinical practice, Tianjiu therapy with pasting on acupoints to activate Yang-Qi could reduce the fatigue of HD patients. Few clinical trials have been carried out to evaluate the efficacy of herb paste for HD. Thus, we designed a short-term Tianjiu therapy at CV4 and KI1 to determine the regulatory effect for patients with IDH. Our methods for recruitment, randomization, allocation, dialysis intervention, outcome assessment, and data collection methods have been described in detail. Other assessments including more suitable acupoint applications, long-term therapeutic courses, and data on the efficacy of different TCM syndromes in IDH patients will also be considered in a subsequent study.

To maximally exclude the placebo effect, rigorous methodological designs are needed. In previous studies, no examples have used valid placebo or sham methods of acupoint herb paste. However, sham-Tianjiu can be practical for blinding purposes because of the rarity of experience with Tianjiu among HD patients. For pragmatic purposes, we plan to use brown clay patches as a sham device.

In conclusion, this pilot, single-blinded RCT will investigate the efficacy and safety of Tianjiu for intradialytic hypotension, assess the feasibility and relevance of a
Tianjiu therapy study design, and provide a clinical foundation for future, large-scale, pluralistic clinical trials.

**Trial status**

The trial is currently in the recruitment phase. Participant recruitment began in March 2015 and is expected to end in July 2016.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

MYT and CHW conceived this trial and participated in the design of this trial. MYT, SYC, and YCH planned the data analysis and drafted the manuscript. YJS and HYN will coordinate the trial and contribute to the screening of patients. CHW, YJS, and HYN are involved in recruitment of participants from clinics. CHW and YHC are responsible for the design and supervision of the study and the revision of the manuscript. All authors have read and approved the final manuscript.

**Acknowledgments**
We would like to express our gratitude to the people in the outpatient dialysis units and Chinese Medicine Pharmacy of the Physical Building of Chang Gung Memorial Hospital for their full cooperation and material support. This trial was financially supported by the Chang Gung Memorial Hospital with grant number CMRPG 8D0341. This work was also supported in part by China Medical University (CMU104-S-37), Taiwan Ministry of Science and Technology (MOST 104-2320-B-039-016-MY3), and the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019).

Financial Disclosure

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Confidentiality

Personal information about potential and enrolled participants was collected, shared, and maintained in order to protect confidentiality before, during, and after the trial.

Declaration of interests
No financial and other competing interests for principal investigators for the overall trial.

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Figure Legends

Figure 1  Flow chart of study procedure.

Figure 2  Photographs of the Tianjiu therapy that will be used in this trial. (A) Actual Tianjiu patch (a traditional Chinese method that uses the warmth and irritation generated by mixed herbal patches to stimulate acupoints); (B) sham patch (clay patches of the same color and size); (C) therapeutic intervention of KI1 (Yongquan); (D) therapeutic intervention of CV4 (Guanyuan).

Table 1  Timing of visits and data collection.
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Figure 1 Flow chart of study procedure.
198x146mm (300 x 300 DPI)
Figure 2 Photographs of the Tianjiu therapy that will be used in this trial. (A) Actual Tianjiu patch (a traditional Chinese method that uses the warmth and irritation generated by mixed herbal patches to stimulate acupoints); (B) sham patch (clay patches of the same color and size); (C) therapeutic intervention of KI1 (Yongquan); (D) therapeutic intervention of CV4 (Guanyuan).

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Introduction

Background and rationale

6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

6b Explanation for choice of comparators

Objectives

7 Specific objectives or hypotheses

Trial design

8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting

9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Eligibility criteria

10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Interventions

11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes

12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline

13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations 13-14

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 13-14

**Methods: Assignment of interventions (for controlled trials)**

**Allocation:**

16a Sequence generation Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions 7

16b Allocation concealment mechanism Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned 7

16c Implementation Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions 7

17a Blinding (masking) Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how 7

17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial N/A

**Methods: Data collection, management, and analysis**

18a Data collection methods Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol 12

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols N/A
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<tr>
<td>Ethics and dissemination</td>
<td></td>
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<tr>
<td>Research ethics</td>
<td>24</td>
<td>Plans for seeking research ethics committee/institutional review board (REC/IRB) approval</td>
</tr>
<tr>
<td>Protocol amendments</td>
<td>25</td>
<td>Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)</td>
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<tr>
<td>Item</td>
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<tr>
<td>26a</td>
<td>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</td>
<td>8-9</td>
</tr>
<tr>
<td>26b</td>
<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
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<td>27</td>
<td>How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial</td>
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<tr>
<td>28</td>
<td>Financial and other competing interests for principal investigators for the overall trial and each study site</td>
<td>18-19</td>
</tr>
<tr>
<td>29</td>
<td>Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators</td>
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<tr>
<td>30</td>
<td>Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</td>
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<td>31a</td>
<td>Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</td>
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<tr>
<td>31b</td>
<td>Authorship eligibility guidelines and any intended use of professional writers</td>
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<tr>
<td>31c</td>
<td>Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code</td>
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<tr>
<td>32</td>
<td>Model consent form and other related documentation given to participants and authorised surrogates</td>
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<td>Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable</td>
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

N/A: Not applicable
Study protocol for a single-blind, placebo-controlled randomized trial of Tianjiu effects in patients with intradialytic hypotension

Journal: BMJ Open

Manuscript ID: bmjopen-2015-009976.R2

Article Type: Protocol

Date Submitted by the Author: 15-Feb-2016

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Chen, Yung-Hsiang; China Medical University, Graduate Institute of Integrated Medicine

Primary Subject Heading: Complementary medicine

Secondary Subject Heading: Complementary medicine, Renal medicine

Keywords: COMPLEMENTARY MEDICINE, Nephrology < INTERNAL MEDICINE, Dialysis < Nephrology
Protocol

Study protocol for a single-blind, placebo-controlled randomized trial of Tianjiu effects in patients with intradialytic hypotension

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ABSTRACT

Introduction: Intradialytic hypotension (IDH) is the most frequent complication of hemodialysis (HD) and may contribute to cardiovascular events and high mortality.

The etiology of IDH is multifactorial; therefore, it remains a challenging problem in the management of HD patients. Because the application of Tianjiu at specific points can influence hemodynamics, we hypothesize that Tianjiu therapy at the traditionally used meridian points will reduce the severity of hypotension in patients who undergo HD.

Methods/analysis: In this clinical trial, eligible patients with IDH will be divided randomly and equally into a Tianjiu group and a control group for 4 weeks. In the Tianjiu group, the patients will have Tianjiu applied at 3 points (Conception Vessel 4, and bilateral Kidney 1) during each HD session. In the control group, patients will have clay patches applied in the same way as the Tianjiu treatment group. Both groups will be followed up for 2 weeks. The primary outcome measure will be the percentage of target ultrafiltration achieved, defined as the actual ultrafiltration volume divided by the target ultrafiltration volume. Secondary outcome measures including frequency of IDH episodes and number of nursing interventions during HD sessions, pre- and post-dialysis BP, patient’s participative assessment of the degree of fatigue after dialysis (scale from 0, not at all, to 10, extremely), and recovery time.
from fatigue after dialysis will be recorded at the 0th and 4th week.

**Ethics/dissemination:** This trial has undergone ethical scrutiny and been approved by the ethics review board of Chang Gung Memorial Hospital (Permission number: 102-4749A3 and 104-3156C). The results of this trial will help to determine whether Tianjiu is an effective and safe treatment for intradialytic hypotension, and, if so, whether it is a therapeutic effect rather than a placebo effect.

**Trial registration:** ClinicalTrials.gov NCT02210377

**Key words:** Tianjiu, Moxibustion, Intradialytic hypotension, Hemodialysis
INTRODUCTION

Intradialytic hypotension (IDH) has been reported in 20% to 30% of patients treated with maintenance hemodialysis (HD). The symptoms associated with this clinical problem, such as nausea, dizziness, and cramps, can have a negative impact on patients’ quality of life and tolerability to dialysis. In addition, IDH can increase patients’ morbidity and mortality by aggravating the risk of cardiovascular complications, mesenteric or cerebral ischemia, suboptimal dialysis adequacy and ultrafiltration, and left ventricular hyperthrophy.

The etiology of IDH is multifactorial. The main factor is rapid removal of intravascular volume by ultrafiltration (UF) and the subsequent imbalance between UF and the plasma refilling rate. Another possible contributor to IDH is impaired cardiovascular compensation for the reduced circulating volume, which includes increased cardiac output and contractility and increased peripheral vascular resistance. Other factors, such as the rapid reduction in plasma osmolality, autonomic dysfunction, and increased synthesis of endogenous vasodilators, have also been reported to be associated with hemodynamic instability.

Several approaches have been applied to prevent and manage IDH. These include accurate assessment of dry weight, avoidance of excessive interdialytic weight gain, fasting during dialysis, adequate adjustment of anti-hypertension agents, sodium and
UF profiling, cooling of the dialysate, the use of dialysate with a bicarbonate buffer or a high calcium content, pharmacological measures including α1-adrenergic agonist, and convective therapies, including hemofiltration and hemodiafiltration.\textsuperscript{12-15}

Tianjiu (also called crude herb moxibustion, auto-moxibustion, herbal acupoint paste, and cold moxibustion therapy) is one type of moxibustion that is widely used in Asian countries as traditional Chinese medicine (TCM). It is a permeability treatment that involves pasting Chinese herbs as an irritant near acupoints to cause a warm and painless sensation.\textsuperscript{16} The general theory of Tianjiu is based on the generation of the warm meridian energy (Yang-Qi), which is believed to be responsible for chronic diseases associated with cold-deficiency syndrome and poor immunity.\textsuperscript{17} Tianjiu therapy has been used to modulate autonomic nervous activity, neurotransmitter levels, endogenous substance levels, and levels of inflammatory factors, and to strengthen cerebral, cardiovascular, and renal function.\textsuperscript{18-21}

In TCM theory, symptomatic IDH is etiologically caused by the derangement of Qi-blood and subsequent prostration of Yang-Qi in the human body during the rapid fluid removal of HD. Accumulating evidence shows that applying moxibustion to specific acupoints has a therapeutic effect on clinical symptoms and quality of life in HD patients.\textsuperscript{22,23} Tianjiu, one moxibustion therapy, also features a stimulating effect. Therefore, it should make the Yang-Qi abundant, blood circulation strong, and
autonomic nerve activity smooth and harmonized in HD patients. Unfortunately, clinical trials examining Tianjiu therapy for IDH are lacking.

This proposal describes a protocol for a randomized controlled trial (RCT) that aims to test the efficacy and safety of Tianjiu therapy during HD sessions, and to determine whether the intervention can reduce the frequency of symptomatic IDH episodes and IDH-related interventions and improve dialysis adequacy, volume control, blood pressure, and quality of life. The results of this study will provide evidence for assessing the need for a large clinical trial and yield data to determine the appropriate sample size for future large-scale RCTs of Tianjiu therapy in patients with IDH.

METHODS AND ANALYSIS

Study design

A randomized, single-blinded controlled trial of Tianjiu for the treatment of IDH in dialysis patients is currently being conducted at Kaohsiung Chang Gung Memorial Hospital (KCGMH), Taiwan. All screening appointments and study visits will occur in the HD units for outpatients. This study has been ethically approved by the Institutional Review Board of CGMH and is registered with the Ethics approval numbers 102-4749A3 and 104-3156C.
The total length of the trial at KCGMH will be 2 years, from March 2014 to July 2016. We plan to recruit participants via advertisements in our HD units. Eligible participants will be identified by a nephrologist as meeting the criteria of IDH in this study and will be randomly and equally assigned to the Tianjiu group or the placebo group at a 1:1 ratio. Randomization will be generated by a computerized random number function in Microsoft Excel, and the patients, program assessors, and statisticians will be unaware of the group to which they have been assigned. A block randomization procedure (based on age, comorbidities such as cardiovascular disease and diabetes mellitus) will be employed to ensure that group allocation is equal and that the characteristics of the trial subjects are similar. Only the research assistant will know to which group each patient belongs for regulation of the application of the methods. The duration of the study will be 7 weeks, including a baseline period of 1 week (week 0–1), a treatment period of 4 weeks (week 1–4), and a follow-up period of 2 weeks (week 5–6). A flowchart of the trial procedure is presented in figure 1.

Setting

This clinical trial will be conducted in a single center, with the participant blinded to treatment allocation. All patients diagnosed with IDH in accordance with the
National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines will be enrolled in this trial. Symptomatic hypotension is defined as a drop in SBP of >20 mmHg from baseline or absolute SBP <100 mmHg accompanied by at least one of the following: diaphoresis, nausea, vomiting, cramps, headache, or dizziness. The whole treatment process will be carried out at Kaohsiung Chang Gung Memorial Hospital (KCGMH), Taiwan.

Participants

All participants who have been treated with HD for more than 3 months will be screened for eligibility. To ensure blinding, only patients who have never received Tianjiu before participating in this study will be included. Other inclusion criteria for the study are as follows: age between 20 and 75 years, medically stable condition, thrice-weekly treatment with maintenance HD for 4 hours per session, and >15% of HD sessions in the preceding 2 months complicated by symptomatic IDH.

Participants with concurrent severe disorders of the heart, brain, liver, or the hematopoietic system; active malignancy; mental disorders; pregnancy or lactation; hypersensitivity skin reactions following Tianjiu therapy; or any other condition that the investigator judges as likely to make the patient unable to complete or comply with, or otherwise unsuitable for, the study will be excluded. Informed consent will
be obtained from each individual who agrees to participate in the study. In addition, patients who are hospitalized for other reasons or who experience hypertensive crisis (defined as SBP>180 mmHg or DBP > 120 mmHg) or other adverse events during the treatment period will be excluded from Tianjiu intervention.

Interventions

Following enrollment, participants will undergo a 1-week baseline period for comprehensive clinical assessment including dry weight reduction, medication review, and standardization of their dialysis prescription. After randomization, patients in both groups will receive 12 sessions of treatment over a 4-week treatment period. The dialysis prescription, dialysate, and artificial kidney machines will not be altered during the treatment period. UF volumes will be adapted to reach < 5% of dry weight during each HD session. Dry weight will be determined clinically by the patient’s attending nephrologist. Kt/V will be calculated using the Daugirdas second generation logarithmic equation. The HD nurse assigned to each individual participant will record hemodynamic parameters, treatment parameters, and IDH-related interventions on standard clinical HD run-sheets.

Treatment group and placebo group
The participants in the Tianjiu group will be treated with Chinese herbal patches at acupoints on the abdomen and plantar, three times per week, for 4 hours each time during HD. A Tianjiu patch (diameter 2.0 cm, depth 0.5 cm) placed on each acupoint will be covered by gauze with a non-woven adhesive plaster in the middle (figure 2A), and the participants in the control group will be given placebo patches (brown clay patches) (figure 2B) on the same sites. The format of the placebo (clay) intervention will be the same as in the treatment group. Participants will be instructed to lie supine before their HD session, and then the bilateral KI1 (Yongquan) (figure 2C) and CV4 (Guanyuan) (figure 2D) will be selected based on evaluation of moxibustion literature and will be disinfected using 75% alcohol. To reduce bias, the trial participants will be blinded to the intervention. Our HD nurse will be encouraged to supervise participants and to prevent them from touching the patches during each HD session. At the end of the HD, the patches will be removed by research assistants and the surrounding skin will be checked.

**Prescription and preparation of the Tianjiu paste**

The prescription of Tianjiu therapy employed in this study will be referenced from *Zhang Shi Yi Tong* (Zhang Lu from the Qing Dynasty). The regimens will mainly include *Sinapis Semen, Corydalis Rhizoma, Euphorbiae Kansui Radix, Asari Herba Cum Radice,*
and *Boreneolum Syntheticum*, which will be ground into powder in an ultrafine
grinder and then mixed in suitable proportions of 10:10:5:5:1.\(^\text{27}\) Fresh ginger juice
will be added to these herbs in a ratio of 1:1 before use. All herbs were provided by
Sheng Chang Pharmaceutical Co., Ltd. in June 2014 and can be refrigerated more
than 2 years. The paste will be produced by the Chinese Medicine Pharmacy of
KCGMH on the day of use.

**Selection and application of acupoints**

Bilateral KI1 and CV4 will be selected based on evaluation of moxibustion
literature, experts’ recommendations, and the clinical experience of the researchers.
KI1 is located on the points of the 1/3 and 2/3 intersection of the plantar. KI1 has the
function of opening the sensory orifices, calming the spirit, recovering from
unconsciousness, discharging heat, stimulating the blood pressure, and restoring
yang to prevent collapse.\(^\text{28,29}\) CV4 is located on the mid-line of the abdomen, 3 cm
below the center of the umbilicus, and belongs to the crossing acupoint of the
conception vessel and the 3 Yin meridians. It is an important point for reducing
exhaustion, promoting blood circulation, invigorating kidney Qi, and strengthening
immunity.\(^\text{30}\)
Outcome measures

The primary outcome measure will be the percentage of target ultrafiltration achieved and will be defined as follows: %Target UF achieved will be defined as actual UF volume/target UF volume. Target UF volume will be the difference between the pre-dialysis weight and the dry weight. Actual UF volume will be the difference between the pre- and post-dialysis weights.

Secondary outcome measures (pre- and post-dialysis SBP, pre- and post-dialysis DBP, nadir SBP and nadir DBP, frequency of symptomatic IDH, and any IDH-related nursing interventions to treat hypotension episodes) will be recorded for each dialysis session. Blood pressure will be measured before dialysis, every 30 minutes during HD, and after dialysis in each HD session of the study. IDH-related interventions will be defined as the use of Trendelenburg position, manual reduction of UF rate, infusion of isotonic saline or hypertonic fluid, lowering of dialysate temperature, or dialysis cessation. Additionally, each patient’s subjective assessment of the degree of fatigue after dialysis (scale from 0, not at all, to 10, extreme) and recovery time from fatigue after dialysis (within minutes, when arriving home, at bed time, the next morning, by next HD) will be measured at the 0th and 4th week of the study period. Data on dry weight, hematocrit, and serum albumin will be collected for all periods of the study. The outcome measurement time points are provided in...
Quality control and data collection

All staff involved in the trial will receive training before implementation of the trial. The training program will include case screening and recruitment, the intervention method, outcome measures, and data processing. The research assistants will check study protocol compliance and informed consent documents and assess the progress of the study, including participant randomization, Tianjiu patch intervention, and data quality. Dropouts and withdrawals from the study will be recorded throughout the intervention and follow-up periods.

Patient safety

Any adverse events (described as unfavorable or unintended signs, symptoms or diseases occurring after treatment) related to Tianjiu therapy will be observed and reported by patients and practitioners during each patient visit. In addition, all vital signs and adverse events will be measured and recorded at each visit.

Sample size and statistical analysis

To the authors’ knowledge, no randomized trials investigating the efficacy of
Tianjiu therapy for IDH have been conducted to date. Sufficient data on estimates of
the standard deviation of the proposed outcome measures in this population are not
available for use in the calculation of a sample size. This pilot trial is designed to
collect such data to inform the efficacy and sample size of Tianjiu therapy for a larger
definitive trial in the future.

In order to collect sufficient data to inform a future sample size calculation, we
anticipate a 16 mmHg improvement due to Tianjiu therapy, and one of 0 mmHg due
to sham Tianjiu therapy. Sample size calculations will be conducted using G-Power
version 3.1, with an alpha value of .05 and power of 80%.\textsuperscript{31} The dropout rate during
the study is estimated to be 10%, so a minimum of 45 participants will be needed in
each group.

Baseline variables will be compared with the $\chi^2$ test for dichotomous variables and
the t test or Wilcoxon rank sum test for continuous variables. Primary and secondary
outcome measures will be compared with the paired t test or Wilcoxon signed rank
test as appropriate. Differences in the degree of fatigue after dialysis and recovery
time from fatigue after dialysis between pre-test and post-test will be analyzed by
Bowker’s test. Differences will be considered statistically significant when the $P$ value
is $< 0.05$. Analyses will be performed using SPSS version 18.0 and Microsoft Excel.
DISCUSSION

This trial is expected to provide convincing evidence that Tianjiu therapy has an effect for treating IDH. Extant literature shows that moxibustion is effective for HD patients; however, actual clinical practice has aspects that are somewhat difficult to overcome, such as unpleasant odors, burning and blistering, skin lesions, or other physical disturbances. With regard to this situation, Tianjiu therapy can prevent the above complications and induce greater increases in skin temperature and blood perfusion than single moxibustion. In addition, stimulating the acupoints on the affected meridians can produce specific effects on regulating the corresponding organs.

Many new drugs and dialysis techniques to control IDH have been developed, with all being administered during the HD itself. However, they still cannot effectively combat the side-effects of IDH because of coexisting factors such as heart disease, diabetes, old age, atherosclerosis, and impaired sympathetic response. These factors should therefore also be considered in patients prone to IDH, regardless of UF volume. Thermal therapy through acupoints to restore the balance between Yin and Yang has been shown to improve vitality in HD patients. There is also evidence that the use of Tianjiu on the Lung-Qi tonifying acupoints such as BL12 (Fengmen), BL13 (Feishu), and GV14 (Dazhui) can reduce the symptoms of allergic rhinitis and regulate
the autonomous nervous system in asthma patients. Based on our experience in clinical practice, Tianjiu therapy with pasting on acupoints to activate Yang-Qi could reduce the fatigue of HD patients. Few clinical trials have been carried out to evaluate the efficacy of herb paste for HD. Thus, we designed a short-term Tianjiu therapy at CV4 and KI1 to determine the regulatory effect for patients with IDH. Our methods for recruitment, randomization, allocation, dialysis intervention, outcome assessment, and data collection methods have been described in detail. Other assessments including more suitable acupoint applications, long-term therapeutic courses, and data on the efficacy of different TCM syndromes in IDH patients will also be considered in a subsequent study.

To maximally exclude the placebo effect, rigorous methodological designs are needed. In previous studies, no examples have used valid placebo or sham methods of acupoint herb paste. However, sham-Tianjiu can be practical for blinding purposes because of the rarity of experience with Tianjiu among HD patients. For pragmatic purposes, we plan to use brown clay patches as a sham device.

In conclusion, this pilot, single-blinded RCT will investigate the efficacy and safety of Tianjiu for intradialytic hypotension, assess the feasibility and relevance of a Tianjiu therapy study design, and provide a clinical foundation for future, large-scale, pluralistic clinical trials.
Trial status

The trial is currently in the recruitment phase. Participant recruitment began in March 2015 and is expected to end in July 2016.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

MYT and CHW conceived this trial and participated in the design of this trial. MYT, SYC, and YCH planned the data analysis and drafted the manuscript. YJS and HYN will coordinate the trial and contribute to the screening of patients. CHW, YJS, and HYN are involved in recruitment of participants from clinics. CHW and YHC are responsible for the design and supervision of the study and the revision of the manuscript. All authors have read and approved the final manuscript.

Acknowledgments

We would like to express our gratitude to the people in the outpatient dialysis units and Chinese Medicine Pharmacy of the Physical Building of Chang Gung Memorial.
Hospital for their full cooperation and material support. We are also grateful to Dr. Hung-Huan Ma for his professional assistance. This trial was financially supported by the Chang Gung Memorial Hospital with grant number CMRPG 8D0341. This work was also supported in part by China Medical University (CMU104-S-37), Taiwan Ministry of Science and Technology (MOST 104-2320-B-039-016-MY3), and the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019).

Financial Disclosure

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Confidentiality

Personal information about potential and enrolled participants was collected, shared, and maintained in order to protect confidentiality before, during, and after the trial.

Declaration of interests

No financial and other competing interests for principal investigators for the
overall trial.

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Figure Legends

Figure 1  Flow chart of study procedure.

Figure 2  Photographs of the Tianjiu therapy that will be used in this trial. (A) Actual Tianjiu patch (a traditional Chinese method that uses the warmth and irritation generated by mixed herbal patches to stimulate acupoints); (B) sham patch (clay patches of the same color and size); (C) therapeutic intervention of KI1 (Yongquan); (D) therapeutic intervention of CV4 (Guanyuan).

Table 1  Timing of visits and data collection.
Table 1  Timing of visits and data collection.

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Intervention

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Comparison

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Participant safety

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Figure 2 Photographs of the Tianjiu therapy that will be used in this trial. (A) Actual Tianjiu patch (a traditional Chinese method that uses the warmth and irritation generated by mixed herbal patches to stimulate acupoints); (B) sham patch (clay patches of the same color and size); (C) therapeutic intervention of KI1 (Yongquan); (D) therapeutic intervention of CV4 (Guanyuan).

186x191mm (300 x 300 DPI)
## SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

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<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
<td>1</td>
</tr>
<tr>
<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
<td>N/A</td>
</tr>
<tr>
<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
<td>N/A</td>
</tr>
<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
<td>17-18</td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
<td>1, 17</td>
</tr>
<tr>
<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
<td>17-18</td>
</tr>
<tr>
<td></td>
<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
## Introduction

### Background and rationale

6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

1-6

6b Explanation for choice of comparators

4-5

### Objectives

7 Specific objectives or hypotheses

6

### Trial design

8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

6

## Methods: Participants, interventions, and outcomes

### Study setting

9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

6-8

### Eligibility criteria

10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

8

### Interventions

11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

9-10

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

9

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

10,13

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

9-10

### Outcomes

12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

11-12

### Participant timeline

13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

7-9
<table>
<thead>
<tr>
<th>Sample size</th>
<th>14</th>
<th>Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>15</td>
<td>Strategies for achieving adequate participant enrolment to reach target sample size</td>
</tr>
</tbody>
</table>

**Methods: Assignment of interventions (for controlled trials)**

**Allocation:**

<table>
<thead>
<tr>
<th>Sequence generation</th>
<th>16a</th>
<th>Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment mechanism</td>
<td>16b</td>
<td>Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned</td>
<td>7</td>
</tr>
<tr>
<td>Implementation</td>
<td>16c</td>
<td>Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions</td>
<td>7</td>
</tr>
</tbody>
</table>

**Blinding (masking):**

<table>
<thead>
<tr>
<th>Blinding (masking)</th>
<th>17a</th>
<th>Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17b</td>
<td>If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Methods: Data collection, management, and analysis**

<table>
<thead>
<tr>
<th>Data collection methods</th>
<th>18a</th>
<th>Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18b</td>
<td>Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Data management 19

Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Statistical methods 20a

Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

20b

Methods for any additional analyses (eg, subgroup and adjusted analyses)

20c

Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring 21a

Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b

Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms 22

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing 23

Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval 24

Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Protocol amendments 25

Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>page(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26a</td>
<td>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</td>
<td>8-9</td>
</tr>
<tr>
<td>26b</td>
<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
<td>N/A</td>
</tr>
<tr>
<td>27</td>
<td>How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial</td>
<td>18</td>
</tr>
<tr>
<td>28</td>
<td>Financial and other competing interests for principal investigators for the overall trial and each study site</td>
<td>18-19</td>
</tr>
<tr>
<td>29</td>
<td>Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators</td>
<td>N/A</td>
</tr>
<tr>
<td>30</td>
<td>Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</td>
<td>N/A</td>
</tr>
<tr>
<td>31a</td>
<td>Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</td>
<td>N/A</td>
</tr>
<tr>
<td>31b</td>
<td>Authorship eligibility guidelines and any intended use of professional writers</td>
<td>N/A</td>
</tr>
<tr>
<td>31c</td>
<td>Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Appendices**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>page(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>Model consent form and other related documentation given to participants and authorised surrogates</td>
<td>N/A</td>
</tr>
<tr>
<td>33</td>
<td>Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license. N/A: Not applicable*
Study protocol for a single-blind, placebo-controlled randomised trial of Tianjiu effects in patients with intradialytic hypotension

Ming-Yen Tsai, Yu-Jen Su, Hwee-Yeong Ng, Shih-Yu Chen, Yu-Chuen Huang, Chien-Hsing Wu and Yung-Hsiang Chen

BMJ Open 2016 6:
doi: 10.1136/bmjopen-2015-009976

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