Study Protocol

The add-on effect of a Chinese herbal formula for patients with resistant hypertension: study protocol for a pilot cohort study

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ABSTRACT

BACKGROUND: Despite a recent American Heart Association (AHA) consensus statement emphasizing the importance of resistant hypertension (RH), its control is still a challenge for conventional medicine. The Chinese herbal formula, Qutan Huayu Fang, has been used effectively to assist antihypertensive agents in blood pressure control, but its effect for RH patients is still unclear. This pilot study aims to explore the effects of taking the formula in addition to antihypertensive medication in the management of RH.

METHODS/DESIGN: A prospective cohort study will be conducted in two first-class hospitals of traditional Chinese medicine (TCM). Eligible RH patients will be classified as the experimental group (n = 100) and the control group (n = 100) based on the interventions they receive. Participants taking antihypertensive agents and the Chinese herbal formula will be in the experimental group and those taking antihypertensive agents alone will be in the control group. The whole study will last 24 weeks, including an 8-week observation and follow-up at 24 weeks. The primary outcomes, assessed against patient baseline conditions, will be the reduction of systolic blood pressure and diastolic blood pressure as well as changes in TCM symptoms and signs. These outcomes will be assessed at weeks 2, 4, 6, and 8. The reductions of blood pressure will also be assessed at week 24. Cardiac events and mortality rate will be secondary outcomes and will be assessed at weeks 8 and 24. Any adverse reactions will be recorded during the study. The causal inference method will be used to assess the effectiveness of the inclusion of TCM herbal medicine in the management of patients with RH.

DISCUSSION: This study will determine whether the Chinese herbal formula is helpful for RH patients treated with antihypertensive agents and the findings will provide a basis for further confirmatory studies.

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Keywords: resistant hypertension; cohort study; medicine, Chinese traditional; Complementary therapies; study protocol

1 Introduction

Resistant hypertension (RH) is defined as the failure to achieve target blood pressure despite concurrent use of 3 antihypertensive agents of different classes\(^\text{[6]}\). Research has shown that 1 in 50 patients receiving treatment for incident hypertension will develop RH\(^\text{[7]}\). It is estimated that there are more than 16 million patients with RH in China\(^\text{[3]}\). The incidence of RH is likely to increase as the population ages and grows heavier, as older age and obesity are two of the strongest risk factors for uncontrolled hypertension\(^\text{[8]}\). Great efforts are needed to control blood pressure for RH patients who are at increased risk of stroke, cardiovascular diseases and chronic kidney diseases\(^\text{[3,4,5]}\). However, the recommendations for the pharmacological treatment of RH largely depend on clinical experience due to the lack of systematic assessment of 3 or 4 drug combinations. Conventional treatments for RH, including lifestyle modification, baroreflex activation therapy and multidrug regimens, are rarely effective and some pharmacological therapies have the potential to cause adverse side effects\(^\text{[9]}\). Thiazide diuretics can provoke hyperglycaemia and diabetes\(^\text{[10]}\), β-blockers increase the risks of fatigue and sexual dysfunction\(^\text{[11]}\) and angiotensin-converting enzyme (ACE) inhibitor may cause coughing, dizziness, headache, asthenia and nausea\(^\text{[12]}\). Studies have shown beneficial effects of renal nerve ablation on RH patients, however, long-term controlled data are still needed to explore the efficacy or sustainability of the treatment. Similarly, preliminary data set has shown potentially positive outcomes in reduction of blood pressure in response to renal denervation\(^\text{[13]}\). Effective treatment for improving the long-term clinical management of RH remains an urgent need.

In traditional Chinese medicine (TCM), RH is categorized as “dizziness” or “headache”. Recent years, 6 trials (690 participants) conducted in China suggested that use of TCM in conjunction with antihypertensive drugs generated additional positive effects\(^\text{[14-15]}\), such as reduced blood pressure, and improved TCM signs and symptoms. Although most of these trials were non-randomized and had small sample size, the results indicated a potential role for TCM in RH management.

Phlegm combined with blood stasis is the main pathogenesis for RH in TCM\(^\text{[16]}\). Therefore, removing both phlegm and blood stasis is an important approach for treating RH\(^\text{[17]}\). To design this treatment approach, two TCM doctors (Shao-gong Shen, and Xue-jie Han), composed a Chinese herbal formula, named Qutan Huayu Fang (aliased as the formula). A clinical study demonstrated that Qutan Huayu Fang, combined with antihypertensive agents significantly improved the efficacy of blood pressure control for patients with chronic hypertension (5-year and 10-year)\(^\text{[18]}\). However, it is not clear whether the formula is effective for RH patients. We hypothesized that the formula could enhance the efficacy of antihypertensive agents in relieving high blood pressure, improving symptoms and signs, as well as reducing cardiac events and the overall mortality rate of patients with RH. With this purpose, we designed this trial to explore the additional effects of the formula for RH patients.

2 Methods and design

2.1 Design

This is a prospective pilot cohort study with two arms. Two-hundred participants will be recruited and divided into two groups, with 100 individuals per group. The study began in August 2013 and will last until March 2015. The first participant was recruited on August 23, 2013. Figure 1 shows the trial design.

2.2 Participants

2.2.1 Diagnosis criteria

Patients with RH are prescribed 3 or more antihypertensive medications at doctor-recommended doses, including, if possible, a diuretic. Patients will have an office blood pressure >140/90 or 130/80 mmHg when accompanied with diabetes or chronic kidney diseases. Patients requiring 4 or more antihypertensive medications may be deemed to have RH even if blood pressure is controlled\(^\text{[1]}\).

2.2.2 Inclusion criteria

Patients will be eligible to participate if they are suffering from RH; aged 18–70 years; have a TCM diagnosis of phlegm accumulating with blood stasis pattern\(^\text{[19]}\); are currently taking (within the last week) antihypertensive agents or antihypertensive agents combined with the formula and are willing to continue taking the same agents throughout the entire observation period.

2.2.3 Exclusion criteria

Patients will be excluded from the study for any of the following conditions: enrolled in other clinical trials within the previous month; pregnant, breast-feeding or preparing for pregnancy; suffering from serious complications, such as renal diseases, pheochromocytoma, stroke, coronary atherosclerotic heart diseases, diabetes or mental diseases.

2.3 Ethical consideration

The study was approved by the Institutional Review Board of the Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing, China (approval number 2012NO6).

2.4 Participant recruitment

RH patients will be recruited from outpatient and inpatient departments of two first-class TCM hospitals (Guang’anmen Hospital, and Xiyuan Hospital of China Academy of Chinese Medical Sciences) by means of posters. The patient screening will be conducted by clinicians who are not involved in the study.

If a patient meets the study criteria, the clinician who
is responsible for patient screening will provide him/her with written information, explain the study in detail in an understandable language and obtain the written consent if he/she is willing to take part in the study. Informed consent must be obtained for all patients enrolled in the study.

2.5 Grouping
The eligible RH patients will be classified as an experimental group (to receive antihypertensive agents and the herbal formula) or a control group (to receive antihypertensive agents alone) based on their interventions.

2.6 Interventions
2.6.1 Antihypertensive agents
The antihypertensive drug classes, recommended by the American Heart Association (AHA) Scientific Statement\(^1\), include thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitor and β-blocker. The following antihypertensive agents will be recommended: hydrochlorothiazide, from 50 to 100 mg/d; captopril, from 50 to 150 mg/d and betaloc, 100 mg/d. For each patient, the specific agents and their doses may be adjusted at the discretion of his or her physician but the classes are not allowed to be changed.

2.6.2 The formula
The formula comprises 11 herbs, *Uncariae Ramulus Cum Uncis* (Gouteng) 15 g, *Alismatis Rhizoma* (Zexie) 10 g, *Chuanxiong Rhizoma* (Chuanxiong) 10 g, *Salviae miltiorrhizae Radix Et Rhizoma* (Danshen) 20 g, *Semen
The indication of the formula is the phlegm accumulating with blood stasis pattern, including signs and symptoms of dizziness, headache, heavy-headedness, chest distress, vomiting phlegm-drool, dry mouth, dark-red tongue with white and greasy coating and wiry and slippery pulse. The TCM clinicians prescribe the herbal formula individually, making adjustments based on each patient’s condition. For example, Caulis Polygoni multiflori (Yejiaoteng) 30 g will be added for insomnia; Ramulus Mori (Sangzhi) 10 g for numbness in the affected limb; Ganoderma (Chilingzhi) 3 g for heavy body and lassitude; Fructus Corni (Shanyurou) 10 g and Herba Artemisiae anomala (Liujinu) 10 g for palpitation.

The formula is prepared as a decoction (Tang) according to the following procedure. Together, all herbs are brought to a boil in a 4-fold volume of distilled water. The decoction is concentrated by boiling to 180 mL, and filtered through a 5-layer gauze filter. Then another 4-fold volume of distilled water is added to the same herbs and brought to a boil, and concentrated to 180 mL over heat. This second decoction is also filtered through a 5-layer gauze filter, and mixed with the first decoction. Patients receiving the formula take 180 mL of the decoction two times a day.

**2.7 Effectiveness indicators**

**2.7.1 Primary effectiveness indicators**

In this study, the major indicators include reductions in blood pressure and changes in TCM symptoms and signs.

The systolic and diastolic blood pressures will be measured with an automated blood monitor (Panasonic EW3106W, Beijing Panasonic Electronic Co., Ltd., Beijing, China) after patients sit down and rest for 5 min. One or two minutes after the first measurement, the blood pressure will be measured a second time and the average values will be calculated.

The main TCM symptoms and signs are characterized as dizziness, headache, heavy-headedness, chest distress, vomiting phlegm-drool, dry mouth, insomnia, palpitation, numbness in the affected limb, heavy body and lassitude, pulse condition and tongue manifestation. Each symptom or sign will be given a score and the sum of all scores will be recorded (Table 1).

**2.7.2 Secondary effectiveness indicators**

The secondary indicators will include cardiac events and mortality rate. Four kinds of cardiac events, including incident myocardial infarction, heart failure, stroke and chronic kidney disease, will be recorded.

**2.7.3 Safety assessment**

Any unexpected symptom and sign, or feeling of discomfort in patients will be recorded as adverse events. For each adverse event, the starting date, ending date, degree, relationship to the trial and potential to trigger patient drop-out from the study will be carefully recorded and considered. If necessary, patients suffering from adverse effects will receive individualized treatments. If an adverse event occurs, the patient will be monitored until his/her adverse event disappears.

**2.8 Data collection**

The clinicians responsible for outcome assessment will collect and validate all case history and clinical data. Detailed contact information and assessment dates of every recruited patient will be recorded. The recruited patients will be asked to visit the clinicians 6 times for assessment of treatment.

<table>
<thead>
<tr>
<th>TCM symptoms and signs</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary symptoms and signs</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
</tr>
<tr>
<td>Heaviness of head</td>
<td>0</td>
</tr>
<tr>
<td>Oppression in the chest</td>
<td>0</td>
</tr>
<tr>
<td>Secondary symptoms and signs</td>
<td></td>
</tr>
<tr>
<td>Vomiting phlegm and saliva</td>
<td>0</td>
</tr>
<tr>
<td>Sticky mouth</td>
<td>0</td>
</tr>
<tr>
<td>Palpation</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
</tr>
<tr>
<td>Heaviness of trunk and drowsy</td>
<td>0</td>
</tr>
<tr>
<td>Numbness of the extremities</td>
<td>0</td>
</tr>
<tr>
<td>Tongue manifestation</td>
<td></td>
</tr>
<tr>
<td>Tongue coating</td>
<td>1</td>
</tr>
<tr>
<td>Tongue body</td>
<td>1</td>
</tr>
<tr>
<td>Pulse condition</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1: Scores for TCM symptoms and signs.

TCM: traditional Chinese medicine.
efficacy during the observation period (the baseline, the 2nd, 4th, 6th, 8th and 24th weeks after the first treatment). If a patient fails to visit during one of the follow-up observations, the assessor will contact him/her by phone (Table 2). All data collected using paper-based forms will be submitted to an online clinical research data-capture computer system developed by the research group (Computer Software Copyright Certificate No. 605315; http://210.76.97.115/tybz/). Only the members from the research team will have access to these data.

2.9 Sample size

This cohort study is intended to observe the additional effects of the herbal formula in RH patients. Although some trials have been conducted to evaluate the effects of TCM on RH, none of them provided enough information to accurately calculate the necessary sample size for the present study. It is necessary to conduct a pilot study to further explore the role of TCM in treating patients with RH. Because of the lack of high-quality trials for reference, 20 cardiovascular experts in integrative medicine with more than 20 years clinical experience were asked for advice. After two rounds of meetings with these experts we agreed that 200 patients should be sufficient to gather enough information in order to plan a formal clinical trial.

2.10 Statistical analysis

The causal inference method will be adopted in the data analysis. This will follow 3 steps. In step 1, a t test will be applied for continuous variables and a Chi-square test for categorical variables to find confounding factors in the baseline analysis. In step 2, propensity score methods will be used to deal with potential confounding factors found in step 1, such as age, body mass index or course of disease[20,21]. In step 3, the additional effect of the formula will be detected with causal inference based on the counterfactual model. For analysis of the final dataset, missing data will be filled using the last observation carried forward approach. Level of significance will be set to $P < 0.05$. All analyses will be performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC).

3 Discussion

The discovery of a new effective therapy in clinical practice is vital for management of RH, and the experiences of Chinese clinicians provide an important source of effective TCM therapies. TCM works better and costs less than conventional medicine for management of some common diseases[22]. The TCM treatment approach works at different levels and on different targets, while Western drugs often intended to target very specific pathways[23]. What is more, Western and TCM approaches have been used together to reach great effect worldwide[24–27]. In this study, we propose to add antihypertensive agents to an empirical Chinese herbal formula to improve the clinical management of RH. A prospective pilot cohort design is employed in the study, and 200 RH patients will be treated as subjects.

To guarantee the quality of the study programs and define any additional effects of the formula, only patients who meet inclusion criteria will be recruited. In addition, patients will be excluded if they also suffer from renal diseases, pheochromocytoma, stroke, coronary atherosclerotic heart diseases, diabetes or mental diseases; the medical therapies associated with these afflictions may interacted with the planned interventions, resulting in difficulty in interpreting clinical results.

To minimize the bias and artificial errors of human data management, an online clinical research data-capture computer system will be adopted to collect the data.

Table 2 Calendar summary

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Baseline (0 week)</th>
<th>2nd week</th>
<th>4th week</th>
<th>6th week</th>
<th>8th week</th>
<th>24th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion and exclusion criteria</td>
<td>×</td>
<td></td>
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<tr>
<td>Informed consent</td>
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<td></td>
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<tr>
<td>Demography</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past medical history and treatment history</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>TCM symptoms and signs</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Cardiac events</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Mortality rate</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
</tbody>
</table>

*: indicators to be recorded. TCM: traditional Chinese medicine.
Each patient record will be typed by two researchers and be verified before storing. Once stored, the data will be visible to the statisticians and supervisors of this study; however, they will not be able to modify data entries. The clinical appraisers and statisticians will be kept unaware of whether a participant belongs to the experimental or control group. The antihypertensive agents used in this study were recommended by the AHA. As an observational study, the experimental and control groups are not randomly assigned. In order to explore causality between the clinical outcome and the medical intervention, we employ a new method of statistical analysis, the causal inference method. In previous randomized controlled trials,\textsuperscript{26,29} the associative inference method has been used. As the correlation between the effect and the intervention method can be determined by associative inference method, using random method can remove the confounding factors and find the internal and essential connection. Propensity scores used in causal inference can balance the experimental and control group by limiting the confounding factors. This method can help scientists to evaluate health interventions more accurately and will lead to more effective treatment and prevention of health and social problems.\textsuperscript{30,31}

The outcomes in the follow-up will only include cardiac events, mortality rate and adverse events. These outcomes will be easy to assess with only a few questions. The physicians who follow the whole process of the study are familiar with patients and are experienced interviewers. These measures will guarantee the quality of the follow-up.

On one hand, a limitation of this study is that the follow-up time is relatively short. However, patients with RH are almost 50% more likely to suffer from a cardiovascular event compared to patients without RH\textsuperscript{[24]}, so the acquired data on cardiovascular events and mortality rate will be enough for the planning of subsequent trials. On the other hand, this is a pilot cohort study and the sample size is relatively small compared with a formal cohort study. However, this sample size is enough to provide reference for the further study.

In conclusion, this prospective pilot cohort study will find whether the formula is helpful for RH patients treated with antihypertensive agents and the findings will provide a basis for further confirmatory studies.

4 Acknowledgements

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5 Competing interests

The authors declare that they have no conflict of interests.

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