Research and Report

N-of-1 randomized controlled trials of Traditional Chinese Medicine treatment for hypertension with spleen-kidney yang deficiency

Running head：N-of-1 RCTs of TCM for Hypertension with Spleen-Kidney Yang Deficiency

Sun Yaxiang [1,2], Chi Xianglin [2*]

1. School of Clinical Medical of Shandong Second Medical University, Weifang, Shan dong, 261071;

2. Department of Family Medicine, Weihai Central Hospital Affiliated to Qingdao University, Weihai, Shandong, 264400;

* Corresponding author: Professor Chi Xianglin

Address: Room 1204, Unit 2, Building 2, Xilonggang Bund, Mishan East Road, Wendeng District, Weihai City, Shandong Province. Postal Code: 264400.

Tel: 13563195807; E-mail: chixl0631@163.com

Received: August 10, 2025; Accepted: August 23, 2025

Objective: To evaluate the clinical efficacy of Traditional Chinese Medicine (TCM) employing spleen and kidney war ming and tonifying therapy for hypertens ion with spleen-kidney yang deficiency u sing N-of-1 RCT.

Methods: Five patients diagnosed with hypertension and classifi ed as having spleen-kidney yang deficiency according to TCM diagnostic criteria at the department of family medicine, Weihai Central Hospital, between January 2022 and June 2023 were selected. A single-blind, randomized and multiple crossover N-of-1 randomized con-trolled trials (SCRCT) was conducted (two patients completed the trial, and three withdrew). During the treatment period, pa-tients received conventional antihypertensive medic ation+ Jinkui Shenqi Decoction, and during the control period, patients received conventional antihypertensive medication+ placebo, 1 dose/day, prepared uniformly by the pharmacy of Weihai Central Hosp ital, with each bag containing 200 mL. Patients took one bag twice daily (morning and evening). Each patient was treate d for about 7 months to determine the curative effect.

Results: After treatment, the blood pressure, heart rate, somatic symptoms

and TCM syndromes of 2 patients were improved statistically (P)

Conclusion: Spleen and kidney warming and tonifying therapy with Traditional Chinese Medicine have a significant effect on hypertension with spleen-kidney yang deficiency. N-of-1 RCT can be used as a scientific research method to evaluate the clinical efficacy of TCM for hypertension.

Keywords: traditional Chinese medicine; hypertension; spleen-kidney yang deficiency Type; N-of-1 RCT

Fund Program: Weihai Traditional Chinese Medicine Science and Technology Project (2021II-10); Shandong Province Traditional Chinese Medicine Science and Technology Project (M-2023112);

Traditional Chinese Medicine (TCM) classifies hypertension under the syndromes of “vertigo”and “headache”. According to different understandings of the underlying pathological, various TCM practitioners have different opinions on the classification of hypertension syndromes. However, they generally fall into seven types: (1) hyperactivity of liver yang, (2) phlegm-dampness accumulation, (3) blood stasis internally, (4) liver-kidney yin deficiency, (5) spleen-kidney yang deficiency, (6) qi and yin deficiency, and (7) yin and yang dual deficiency [1]. Among these, the phlegm-dampness accumulation type is relatively common [2]. In recent years, due to the increasing aging population, changes in lifestyles and work patterns, and the outbreak of the COVID-19 pandemic (which TCM theory considers a cold-dampness toxin), spleen-kidney yang deficiency type hypertension has markedly increased [3]. The various internal and external causes mentioned above lead to deficiency of kidney yang qi, internal generation of deficiency cold, resulting in dizziness, headache, aversion to cold and cold limbs, lower back and knee pain, poor appetite and abdominal distension, long and clear nocturia at night, dull and dull mouth, constipation, pale tongue texture, obvious tooth marks, white and greasy tongue coating, and deep and thready pulse. According to traditional Chinese medicine theory, the kidneys are the root of the innate state, responsible for storing essence and generating marrow, while the spleen and stomach are the root of the acquired state, and the source of qi and blood generation. Prolonged kidney deficiency can spread to the

spleen, leading to weakness of the spleen and stomach, with both organs being damaged. This results in loss of circulation of body fluids, and the combination of internal and external cold and dampness accumulates to form phlegm. Phlegm turbidity obstructs or, with prolonged illness, enters the collaterals, causing blood stasis. Blood becomes viscous and flows poorly, resulting in the aforementioned symptoms [4]. This is the TCM pathophysiological mechanism of hypertension with spleen-kidney yang deficiency syndrome.

As is well known, hypertension is a major risk factor of cardiovascular and cerebrovascular diseases, with a high incidence, significant harm, and far-reaching influence, making it a key disease in the field of TCM prevention and treatment. Due to the widespread heterogeneity (syndrome) of hypertension, the conclusions of TCM antihypertensive research conducted through RCTs lack universality and are difficult to guide individualized and precise prevention and treatment. N-of-1 randomized controlled trials [5] (N-of-1 RCT), are prospective clinical randomized controlled trials designed for individual patients or a series of individual patients. They use the patient as their own control, setting up multiple alternating periods of treatment and control, and follow the principles of repetition, randomization, balance, control, and blinding. The N-of-1 RCT is highly compatible with the TCM concept of individualized syndrome differentiation and treatment, making them very suitable for clinical research in TCM [6]. This study aims to explore the clinical efficacy of TCM warming and tonifying the spleen and kidney in treating hypertension of spleen-kidney yang deficiency type through N-of-1 RCT.

1. Materials and methods

1.1 diagnostic criteria

1.1.1 Diagnostic criteria for spleen-kidney yang deficiency syndrome: According to the national standard of the People's Republic of China, "Clinic Terminology of Traditional Chinese Medical Diagnosis and Treatment (Syndromes/Patterns)" [7], the main symptoms are dizziness, headache, aversion to cold and cold limbs, lower back and knee pain, and poor appetite and abdominal distension. The secondary symptoms include pale/dull

complexion, fatigue and weakness, lethargy, tinnitus, long and clear nocturia at night, dull and dull mouth, constipation, pale tongue texture, tooth marks, greasy tongue coating, and deep and thready pulse.

1.1.2 The definition of hypertension refers to the diagnostic criteria of the revised 2024 Chinese Guidelines for the prevention and treatment of hypertension [8], i.e., blood pressure should be, with systolic blood pressure (SBP) (high pressure) ≥ 140mmHg (1mmHg=0.1331kPa) and/or diastolic blood pressure (DBP) (low pressure) ≥ 90mmHg measured in the clinic on three separate days without the use of antihypertensive drugs. Systolic blood pressure ≥ 140mmHg and diastolic blood pressure<90mmHg is defined as isolated systolic hypertension.

1.1.3 Inclusion criteria

(1) Age>18 years, diagnosed with hypertension by Western medicine, and diagnosed with hypertension with spleen-kidney yang deficiency syndrome by TCM differentiation, (2) voluntarily taking traditional Chinese medicine and signing informed consent, (3) not participating in other trials in the past 3 months, (4) no acute phase of other diseases, (5) expected survival >1 year.

1.1.4 Exclusion criteria

(1) Complicated with severe cardiopulmonary or renal diseases or in the acute phase of other diseases, (2) cognitive impairment, (3) pregnancy or lactation, (4) history of gastrointestinal bleeding or bleeding in other parts and active bleeding within half a year, (5) survival <1 year.

1.1.5 Dropout criteria: (1) Withdrawal from the trial due to other reasons during the study; (2) Occurrence of acute phase of other diseases or severe complications; (3) Poor compliance and inability to adhere to taking Chinese medicine.

1.2 General information

Five patients diagnosed with hypertension by Western medicine and differentiated as spleen-kidney yang deficiency syndrome by TCM in our hospital’s outpatient clinic were selected. Three patients were dropped out (one withdrew due to inability to continue taking traditional Chinese medicine, and two withdrew due to other reasons). Finally, two patients ultimately completed the trial.

Basic information: Patient 1: Male, 53 years old, consulted due to dizziness and excessive sweating for 3 months. Height

175cm, weight 75kg, body mass index 24.49kg/m2; 15-year history of hypertension, denied hyperlipidemia and diabetes, occasional alcohol consumption, no smoking history; Main accompanying symptoms: poor appetite, abdominal distension, fatigue, back pain, knee pain, frequent urination, loose stools, general sleep, pale tongue, tooth marks, white and greasy coating, deep and weak pulse; TCM Syndrome Differentiation: Spleen-kidney yang deficiency; Blood pressure 155/92mmHg, PHQ score 15, moderate somatic problems, TCM syndrome score 31; The traditional Chinese medicine prescription: Jingui Shenqitang and the conventional antihypertensive drug Nifedipine Controlled Released Tablets 20mg qd.

Patient 2: Male, 65 years old, consulted due to chest tightness and fatigue for 3 months, worsening for 10 days. Height 172cm, weight 76kg, body mass index 25.69kg/m2; 20-year history of hypertension, 5-year history of coronary heart disease, denied diabetes, history of smoking and alcohol consumption; Main accompanying symptoms include abdominal distension, aversion to cold, leg pain, frequent urination, loose stools, poor sleep, dull tongue texture, enlarged tongue with teeth marks, white and slightly yellow tongue coating, deep and slow weak pulse; TCM Syndrome Differentiation: Spleen-kidney yang deficiency; Blood pressure 160/82mmHg, PHQ score 14, moderate somatic problems, TCM syndrome score 37. The traditional Chinese medicine prescription: Jingui Shenqitang, conventional antihypertensive drug Valsartan 80mg qd and other drugs Atorvastatin Calcium Tablets 20mg qn.

N-of-1 randomized controlled trial was conducted for a period of over 7 months, using a single-blind method, with alternating experimental and control periods. Patient self-measured blood pressure and heart rate at home every day, and went to the clinic every week for somatic symptom scoring (the somatic symptom scale used the 15 item Physical Health Questionnaire (PHQ-15) and TCM syndrome efficacy (referring to the “Guiding Principles for Clinical Research of New Chinese Medicine” clinical syndrome scoring principles).

The spleen-kidney yang deficiency syndrome is characterized by common symptoms such as aversion to cold and cold limbs, pale complexion, lower back

pain, abdominal coldness and pain, chronic diarrhea or undigested food in the stool, or edema with oliguria, decreased libido, pale and plump tongue, white and slippery tongue coating, and deep, slow, and weak pulse.

1.3 Overall design

The included cases adopted N-of-1 RCT design, using a random number table method. After formulating the random plan, a single-blind method (patient blinding) was adopted. Each patient underwent 3 rounds of trials, with 2 periods in each round, which were the experimental period and the control period. A 1-week washout period was set before each period. In the first month of each round, the experimental or control scheme was randomly given, and in the second month of treatment, the scheme contrasting with the first month was used for treatment. A 1-week washout period was set before and after each treatment plan (referring to previous studies [9-10]). After the cases were included, they entered the trial according to the process. The initial randomization scheme was “ABABAB”, and the process was carried out as follows (Figure 1).

On the basis of the original Western medicine antihypertensive drugs, patient in the experimental period took Chinese medicine Jingui Shenqitang with modifications to warm and tonify the spleen and kidney. The main ingredients of the Chinese medicine prescription: prepared Aconite 6-15g, 6-15g of Ramulus Cinnamomi, 6-15g of Dried Ginger, 15-30g of Poria Cocos, 6-15g of Cortex Moutan, 6-15g of Alisma, 20-30g of Rehmanniae Radix Praeparata, 6-20g of Cornus Officinalis, 20-40g of Yam, 12-20g of Salted Eucommia Ulmoides, 12-20g of Achyranthes Bidentata Blume, and 3-9g of Radix Glycyrrhizae Preparata, the specific dosage was determined according to the patient’s syndrome differentiation and type. The dosage of Western medicine antihypertensive drugs was not adjusted throughout the process; in the control period, patients were given 5% of the original medicine and 95% dextrin. Chinese herbal medicine decoction pieces were provided by our hospital's traditional Chinese medicine decoction pieces were provided by the Hanfangtang of our hospital’s Chinese medicine pharmacy, and were uniformly decocted, decocted in water, and taken orally once a day, divided into two oral

doses.

1.4 Wash off period and observation period

Due to the complex components of Chinese medicine and there is no clear half-life, the time of drug onset and the duration of drug effect were evaluated based on the physician's clinical experience. In clinical practice, most patients reported that the drug took effect on the 5th to 6th day. Before the experiment, patients were instructed on how to correctly measure blood pressure and precautions, and patients were informed to go to the clinic every week for various scores, such as telephone or WeChat communication, if they cannot not go to the clinic. During the period, the patient's blood pressure, heart rate, PHQ-15, and TCM Syndrome Score were recorded.

1.5 Randomization and blinding methods

Voluntarily take Chinese medicine treatment and sign informed consent. At the same time, N-of-1 RCT was adopted, using a random number table method. After formulating the randomization plan, a single-blind method (patient blinding) was adopted.

1.6 Observation indicators and methods

Observation indicators included blood pressure monitoring, establishment of blood pressure log card, patients measured blood pressure every day, measured right brachial artery blood pressure and heart rate after resting for 15 minutes in the morning, and evaluated TCM syndrome scores and PHQ-15 scores every week.

1.7 Efficacy criteria

The TCM syndrome standards for spleen-kidney yang deficiency syndrome refer to the "Guiding Principles for Clinical Research of New Chinese Medicine" [11] and the "Traditional Chinese Medicine Diagnosis and Treatment Plan for Hypertension (Draft)" [12]. Patients were scored based on their primary and secondary symptoms. The main symptoms were scored as 0, 2, 4, and 6 points for none, mild, moderate, and severe, respectively; the secondary symptoms were scored as 0, 1, 2, and 3 points for none, mild, moderate, and severe, respectively; the tongue and pulse were scored as 0 and 1 points according to whether they were presence or not. The blood pressure efficacy criteria were: markedly effective: diastolic blood pressure decreases by ≥ 10mmHg and reached the normal range,

or diastolic blood pressure did not reach normal but decreased by ≥ 20mmHg; effective: diastolic blood pressure<10mmHg but reached the normal range, or diastolic blood pressure decreased by 10-19mmHg but did not reach the normal range, or systolic blood pressure ≥ 30mmHg; ineffective: did not reach the above level. The TCM syndrome efficacy criteria were: markedly effective: clinical symptoms and signs were significantly improved, and the syndrome score decreased by ≥ 70%; Effective: Clinical symptoms and signs were significantly improved, and the syndrome score decreased by ≥ 30%; Ineffective: Clinical symptoms and signs were not significantly improved, or even aggravated, and the syndrome score decreased by less than 30%; Syndrome score rate= (pre-treatment score - post-treatment score)/pre-treatment score x 100%.

Somatic symptoms assessment was performed according to the Physical Health Questionnaire (PHQ-15) after each stage of treatment. The contents includes: stomach pain, back pain, arm, leg and joint pain, dysmenorrhea or other problems during menstruation, headache, chest pain, dizziness, a burst of weakness, palpitations, shortness of breath, painful sex, activity, constipation or diarrhea, intestinal discomfort, nausea or poor gas, feeling tired or lethargic, sleep disorders, etc. The above items were scored in four levels, with a total score of 30 points, 0~4 no somatic impairment, 5~9 mild somatic impairment, 10~14 moderate somatic impairment, 15 or more severe somatic impairment.

1.8 Statistics

SPSS 25.0 statistical software was used. Normally distributed data were expressed as mean ± standard deviation (x ± s), non-normally distributed data were expressed as median (P25~P75), and paired t-test were used for normally distributed measurement data between groups; Paired sample Wilcoxon rank sum test was used for non-normally distributed measurement data between groups, and paired sample Wilcoxon rank sum test was also used for measurement data in which only one group conformed to normal distribution, with $P<0.05$ indicating statistically significant differences.

2. Result

2.1Comparison of blood pressure between experimental and control

periods after patient treatment (Table 1): Comparison of results after each round of the trial showed that the diastolic blood pressure of patient 2 in the first round were no statistically significant (P>0.05); (Table 2): After three rounds of treatment, the results were statistically significant (P<0.001 or 0.05).

2.2 Comparison of heart rate between experimental and control periods after patient treatment (Table 3): Comparison of results after each round of the trial showed that, except for the third round results of patient 1, which were not statistically significant (P>0.05), the results of the remaining rounds of the trial were statistically significant (P<0.001 or 0.05); (Table 4): After three rounds of the trial, the comparison of heart rate between the experimental period and control periods of the patients showed that the results were statistically significant (P<0.001).

2.3 Comparison of somatic symptoms between experimental and control periods after patient treatment (Table 5). The PHQ-15 scores of patients in the experimental period were significantly lower than those in the control period, and the difference was statistically significant (P<0.05).

2.4 Comparison of TCM syndrome scores between experimental and control periods after patient treatment (Table 6): The TCM syndrome scores of patients in the experimental period were significantly lower than those in the control period, and the difference was statistically significant (P<0.05).

2.5 Analysis of safety results

Before the trial, patients' blood pressure, pulse rate, respiration rate, routine blood tests, liver and kidney function, electrocardiogram, urine routine, blood glucose, blood lipids, etc. were routinely tested. The above examination indicators of the patients in this study were referenced from the national elderly physical examination project indicators or the unit's physical examination report. At the same time, each patient underwent the Self-Rating Anxiety Scale (SAS) and the Self-Rating Depression Scale (SDS) before the trial. After evaluation, the included patients had no anxiety or depression (anxiety and depression scores<50). After the end of the trial, patients rechecked relevant indicators and scores, and there were no significant abnormalities in the routine blood tests, liver and kidney function,

etc. of the two patients compared to before.

3. Discussion

This study used N-of-1 randomized controlled trials to verify the antihypertensive effect of TCM. A total of 5 patients were included in the study, and 2 patients completed the trial. The results showed that the blood pressure, heart rate, somatic symptoms, and TCM syndromes of the 2 patients were significantly improved in the experimental period compared with the control period, and the results were statistically significant ($P<0.05$). The systolic and diastolic blood pressure of the 2 patients after the third round of the experimental period were significantly lower than before the experiment (130.9mmHg<142.0mmHg, 77.5mmHg<87.0mmHg; 148.9mmHg<160.0mmHg, 80.0mmHg<97.0mmHg), and the blood pressure efficacy criteria were all effective (patient 1 diastolic blood pressure reached the normal standard, and patient 2 diastolic blood pressure decreased by 17mmHg); the TCM syndrome integral rates of the 2 patients were all markedly effective (80.6% and 83.8%). This study indicates that the traditional Chinese medicine compound Jingui Shenqitang with modifications based on disease and syndrome differentiation can not only effectively reduce blood pressure and improve blood pressure control rate, but also stabilize heart rate, change somatic discomfort, and reduce TCM syndrome scores, with few adverse reactions and high safety.

Jingui Shenqitang is a classic famous prescription derived from Jin Kui Yao Lue. It can warm and tonify the spleen and kidney, unblock the meridians, and transform qi and promote water circulation [13]. In theory, it can achieve the effect of diuresis and antihypertension by starting from the pathogenesis. Jingui Shenqitang is composed of aconite, Ramulus Cinnamomi, Poria Cocos, Rehmanniae Radix Praeparata, Alisma, etc. Modern medical research has found that the effective component of aconite, aconitine, can play an antihypertensive role by blocking α receptors, stimulating β receptors, dilating blood vessels, and reducing vascular resistance [14]; the effective component of Ramulus Cinnamomi, cinnamaldehyde, has negative chronotropic and inotropic

effects on the myocardium, and plays an antihypertensive role by reducing cardiac output and dilating arterial blood vessels to reduce peripheral resistance [15]; the effective component of Poria Cocos, pachymic acid, can activate Na-K-ATPase on the cell membrane to reduce water and sodium retention, and at the same time compete with aldosterone receptors, which can be used as a new type of aldosterone receptor antagonist to promote urine excretion and exert an antihypertensive effect [16]; the effective component of Alisma, alisol, can directly dilate arterial blood vessels to exert an antihypotensive effect [17]; in addition, the Eucommia ulmoides added to the Jingui Shenqitang is a commonly used antihypertensive Chinese medicine in TCM clinical practice, and also has a significant antihypertensive effects. Studies [18] have found that the effective component of Eucommia ulmoides, lignans, can regulate blood pressure by regulating nitric oxide (NO) levels and the renin-angiotensin system. At the same time, lignans have a protective effect on kidney damage caused by hypertension [19]; in addition, lignan extracts can also inhibit aldose reductase to prevent hypertensive cardiac remodeling [20].

In fact, the therapeutic mechanism of compound Chinese medicine is not a simple superposition of the effects of different Chinese medicine components, but a new action of "1 +1>2" that emerges on the basis of syndrome differentiation, which is also the philosophical basis of the holistic concept of TCM. Therefore, in theory, Jingui Shenqitang with modifications can not only directly exert an antihypertensive effect through antihypertensive components, but also mainly exert an antihypertensive effect by increasing systemic metabolic function, reducing chronic inflammatory response, and improving arterial vascular compliance through overall action [21-22]. The rapidly developing TCM integrated pharmacology and network pharmacology in recent years are expected to solve this problem [23].

Randomized controlled trials (RCTs) have homogeneity in the sample, which can well represent the population [24], and are commonly used methods for group studies, but cannot represent individuals. The clinical observation indicators for N-of-1 RCT are mainly the symptoms of individual patients,

which not only increases patients' awareness of their own diseases, but also improve their enthusiasm for receiving treatment, and also make up for the lack of individualization in traditional RCT studies [25]. In this study, the two patients had a history of hypertension for more than 10 years, and conventional antihypertensive drugs did not control their blood pressure. At the same time, the patients had various somatic discomfort symptoms. After applying TCM individualized syndrome differentiation and treatment guided by N-of-1 RCT, the patients' blood pressure gradually decreased and tended to be stable, the heart rate decreased to varying degrees, and various somatic discomfort symptoms and TCM syndromes were improved. It can be seen that it is feasible to use N-of-1 RCT to evaluate the TCM individualized syndrome differentiation and treatment of hypertension.

As we all know, hypertension is one of the most common chronic non-communicable diseases and the most important risk factor for cardiovascular diseases. In recent years, medical conditions have been greatly improved, but the blood pressure control rate in various regions of China is still unsatisfactory [8]. A study [26] reported that in 2021, less than one-fifth of hypertensive patients worldwide had their blood pressure well controlled. Poor blood pressure control is not only related to patient's own bad lifestyles and unreasonable medication, but also to whether medical staff provides patients with individualized treatment plans. Numerous studies [27-29] have demonstrated the effectiveness of TCM in lowering blood pressure. It can achieve a curative effect on early and mild hypertension. For severe and refractory hypertension, combined with conventional antihypertensive drugs can increase the efficacy while reducing the types and/or doses of antihypertensive drugs and reducing their side effects. In addition, resting heart rate is positively related to the risk of hypertension, and is also an important independent risk factor for cardiovascular incidence rate and mortality [30]. Studies [29] have found that the rational application of Chinese medicine can lower blood pressure while slowing down heart rate. Finally, TCM can not only reduce blood pressure levels, but also significantly improve the somatic discomfort symptoms

complicated by hypertensive patients [28-29]. In this study, 2 patients had been taking antihypertensive drugs for many years, but their blood pressure control was poor and they had a variety of somatic discomforts. After adding Jingui Shenqitang with modifications, the blood pressure of the 2 patients tended to be target blood pressure, the heart rate decreased to varying degrees, and somatic symptoms such as headache, dizziness, palpitations, stomach discomfort, and sleep disorders, etc. were significantly improved, and TCM syndromes were significantly improved.

TCM has been used to treat diseases in China for more than 5000 years, mainly based on case records of symptom improvement and retrospective experience summaries, while the current medical concept requires strict evidence to prove the scientificity and effectiveness of the treatment method. This study conducted a scientific research process on TCM treatment of hypertension through N-of-1 RCT, proving that N-of-1 RCT is suitable as a scientific research method for studying TCM treatment of hypertension, and providing evidence for a more scientific evaluation of the clinical efficacy of TCM.

This study has some limitations: (1) the number of included patients is small and the extrapolation is limited. More patients need to be included to comprehensively evaluate the impact of traditional Chinese medicine on blood pressure reduction; (2) The composition of Chinese patent medicine are complex and the half-life is uncertain. The washout period of this trial is defined according to the medication experience of clinical physicians; (3) No long-term follow-up was set; (4) N-of-1 RCTs strictly requires a double-blind design. Due to objective limitations, this study only blinded patients, which may lead to biased results. Of course, since TCM is essentially a science of internal evidence [31], its syndrome differentiation and treatment have high subjectivity; Meanwhile, TCM has the characteristics of treating different diseases with the same treatment and treating the same disease with different treatments. Therefore, this study considered and integrated the theoretical differences between modern medicine and TCM, and reduced result bias by controlling researcher differences (that is, all hypertensive patients included in the

study throughout the trial were prescribed and adjusted syndrome differentiation prescriptions by the same doctor).

It is worth mentioning that in the real world, many hypertensive patients are of the Yin Yang deficiency type. We often add Yin-nourishing Chinese medicines such as oysters, Anemarrhena asphodeloides, Phellodendron chinense, and Ophiopogon japonicus to the above prescriptions to exert a better overall regulatory effect, and the antihypertensive effect is more obvious. In addition, relatively speaking, compound Chinese medicine decoctions are more suitable for short-term use or for diseases with more severe and/or complex clinical symptoms. Therefore, most ordinary hypertensive patients in clinical practice can't tolerate long-time oral Chinese medincine decoctions. We often give them different combinations of commonly used Chinese patent medicines such as Jinkui Shenqi wan, Jisheng Shenqi wan, and Yougui wan, and so on, according to their specific diseases, and have achieved significant clinical effects. This study included 5 patients, and only 2 completed the trial, which far exceeded the dropout rate of 20% in regular clinical studies, which is related to the particularity of N-of-1 RCT research on the one hand, and to the uncontrollability of real-world clinical research on the other hand. The subsequent adjustment of the patients' oral administration of the above pills orally is essentially the application of Jingui Shenqitang with modifications, but the drug dosage form is different, and in principle it is still consistent with this study. Therefore, if there are no emergencies during the treatment process, the patient's syndrome type does not change much, and the medical institution conditions permit, it is entirely possible to consider modulating the Chinese medicine decoction into a paste or pill. In future studies, for hypertensive patients with milder symptoms or relatively simple diseases, the aforementioned pills can be directly administered orally after syndrome differentiation, or the corresponding paste or pills can be directly administered orally, which can not only improve patient tolerance, but also reduce the dropout rate of the study sample.

In summary, this study indicates that it is feasible to apply Chinese medicine

Jingui Shenqitang with modifications to treat hypertension on the basis of conventional antihypertensive drugs, which can reduce blood pressure, improve patients' somatic discomfort, and improve quality of life. At the same time, N-of-1 RCT provides evidence-based medicine evidence for TCM treatment of hypertension, which is helpful for the promotion and popularization of TCM worldwide. Therefore, it is necessary to further conduct clinical studies on hypertension and other diseases with larger sample sizes and more TCM syndromes through N-of-1 RCT design, in order to provide more evidence-based medicine evidence for the TCM individualized and precise prevention and treatment of hypertension and other diseases.

References

[1] Lu Jing, Meng Xia, Liu Hongyan. Progress in Traditional Chinese Medicine Dialectical Classification and Dialectical Treatment of Hypertension [J]. Journal of Sichuan of Traditional Chinese Medicine, 2020, 38 (6): 220-222.

[2] Wen Zhenfang. Correlation Study of Traditional Chinese Medicine Syndrome Differentiation Patterns in Primary Hypertension with Ambulatory Blood Pressure Monitoring and China PAR Model [D]. Tianjin University of Traditional Chinese Medicine, 2023.

[3] Zhang Xiaoqing, Liu Lu, Xu Xiaobai, et al. Discussion on Acupuncture Prevention and Cure Strategy for COVID-19 from "Cold-Damp Epidemic" [J]. Acta Chinese Medicine, 2021, 36 (3): 453-456.

[4] Guan Yulong, Deng Fan, Wang Xiaoqin. Wang Xiaoqin's Experience in Treating Renal Hypertension Based on Syndrome Differentiation [J]. Liaoning Journal of Traditional Chinese Medicine, 2024, 51(5): 29-31.

[5] Shang Hongcai, Tian Guihua. N-of-1 Trial [M]. Beijing: People's Medical Publishing House, 2019: 1-10.

[6] Hu Jiayuan, Li Jiang, Zhai Jingbo, et al. CONSORT extension for reporting N-of-1 trials for traditional Chinese medicine (CENT for TCM): recommendations, explanation and elaboration [J]. Chinese Journal Of Evidence-based Medicine, 2021, 21 (3): 338-346.

[7] Clinic Terminology of Traditional Chinese Medical Diagnosis and Treatment PART 2: Syndromes/ Patterns

[S]. State Administration for Market Regulation, National Standardization Administration, 2021-11-26.

[8] Chinese Guidelines for the Prevention and Treatment of Hypertension Revision Committee, Chinese Hypertension League, Hypertension Branch of China International Exchange and Promotive Association for Medical and Health Care, et al. Chinese Guidelines for the Prevention and Treatment of Hypertension (Revised 2024 Edition) [J]. Chinese Journal of Hypertension (Chinese and English), 2024, 32 (7): 603-700.

[9] Peng Bin, Wen Yi, Zhang Shijing, et al. N-of-1 Trial of Jianpiqingrehuashi Granular Decoction with Mesalamine in the Treatment of Ulcerative Colitis in Remission with Spleen Deficiency-induced Damp-heat Syndrome [J]. Chinese General Practice, 2022, 25 (3): 293-297.

[10]Huang Lingling, Zhao Xiaofeng, Guo Lizhong. Modified Liangxue Huayu Recipe in the Treatment of Essential Thrombocytosis:A N of One Trial [J]. Journal of Traditional Chinese Medicine, 2019, 60 (8): 680-683.

[11]Zheng Xiaoyu. Guiding Principles for Clinical Research of New Chinese Medicine (Trial) [M]. Beijing: China Medical Science Press, 2002: 73-77.

[12]Han Xuejie. Traditional Chinese Medicine Diagnosis and Treatment Plan for Hypertension (First Draft) [J]. China Journal of Traditional Chinese Medicine and Pharmacy, 2008 (7): 611-613.

[13]Sun Guochao. The effect of Jingui Shenqitang combined with ziprasidone on the quality of life and treatment efficacy in patients with bipolar affective disorder [J].Harbin Medical Journal, 2021, 41 (6): 132-133.

[14]Liang Xiaoyu, Shi Yujiao, Liu Yongcheng, et al. Research progress on pharmacological mechanism and attenuation and synergism of Aconite [J]. Global Traditional Chinese Medicine, 2024, 17 (7): 1428-1439.

[15]Li Xue, Zhao Jinghan, Wu Wenxuan, et al. Research Progress on Chemical Constituents and Pharmacological Effects of Ramulus Cinnamomi [J]. Acta Chinese Medicine and Pharmacology, 2023, 51 (5): 111-114.

[16]He Pengfei, Gao Min, Wen Jihong,et al. Research progress on pharmacological effects of Poria cocos [J]. Yunnan Journal of Traditional Chinese Medicine, 2024, 45 (8): 83-87.

[17]Zhang Weijun, Han Dongwei, Li Ji. Advances in Chemical Compositions and Pharmacological Effectsof Alismatis Rhizoma [J]. Acta Chinese Medicine and Pharmacology, 2021, 49 (12): 98-102.

[18]Zhang Ruizhe, Li Qian, Pei Juan, et al. Overview of the Chemical Components and Pharmacological Effects of Eucommia Ulmoides [J]. Journal of Shaanxi University of Chinese Medicine, 2024, 47 (4): 87-91.

[19]LI L, YAN J, HU K, et al. Protective effects of Eucommia lignans against hypertensive renal injury by inhibiting expression of aldose reductase [J]. J Ethnopharmacol, 2012, 139 (2): 454-461.

[20]LI ZY, GU J, YAN J, et al. Hypertensive cardiac remodeling effects of lignan extracts from Eucommia ulmoides Oliv. bark--a famous traditional Chinese medicine [J].Am J Chin Med, 2013, 41 (4): 801-815.

[21]KAO ST, WANG SD, LIN CC, Lin LJ. Jin Gui Shen Qi Wan, a traditional Chinese medicine, alleviated allergic airway hypersensitivity and inflammatory cell infiltration in a chronic asthma mouse model [J]. J Ethnopharmacol, 2018, 227: 181-190.

[22]Liang Yinglan, Zhang Qiong. Clinical Efficacy of Modified Jingui Shenqitang in Treatment of Renal Hypertension with Spleen-kidney Yang Deficiency Syndrome [J]. Chinese Journal of Experimental Traditional Medical Formulae, 2020, 26 (5): 81-86.

[23]Li Jixin, Wang Wenru, Ren Yan, et al. Study on the molecular mechanism of Linggui Zhugan Decoction in treating hypertension and obesity based on network pharmacology and molecular docking technology [J]. International Journal of Traditional Chinese Medicine, 2023, 45 (4): 456-463.

[24]SAMUEL JP, BELL CS, SAMUELS JA, et al. N-of-1 Trials vs. Usual Care in Children With Hypertension: A Pilot Randomized Clinical Trial [J]. Am J Hypertens, 2023, 36 (2): 126-132.

[25]GOLDENBERG JZ, WENNER CA. A novel N of 1 trial design and proposed utility in complementary and alternative medicine research (review) [J]. J Evid Based Complementary Altern Med, 2012, 17 (2): 126-130.

[26]NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019:

a pooled analysis of 1201 population-representative studies with 104 million participants [J]. Lancet, 2021, 398 (10304): 957-980.

[27]Wang Mengxi, Wu Chenjie, Cao Peihua, et al. Meta-analysis for Clinical Efficacy of Traditional Chinese Medicine in treating resistant Hypertension [J]. China Journal of Chinese Materia Medica, 2021, 46(3): 685-693.

[28]LI J. Traditional Chinese Medicine in Treating Hypertension[J]. Circ Cardiovasc Qual Outcomes. 2022, 15 (3): e008723.

[29]Xu Weizhen. Mechanism and Pharmacological Analysis of Modified Chaihu Shugan San in the Treatment of Hypertension Combined with Anxiety [J]. Chinese Medical Journal of Metallurgical Industry, 2020, 37 (3): 262-264.

[30]Zhang Lingyu, Xie Liangdi, Shen Yihua, et al. Relationship between resting heart rate and left ventricular mass index in the patients with essential hypertension [J]. Chinese Journal of Hypertension, 2021, 29 (12): 1272-1278.

[31]Liu Zhengqiang, Zhang Wenchun. Tracing the origin of Huangdi Neijing from the TCM inward observation and examination [J]. China Journal of Traditional Chinese Medicine and Pharmacy, 2021, 36 (12): 7015-7019.

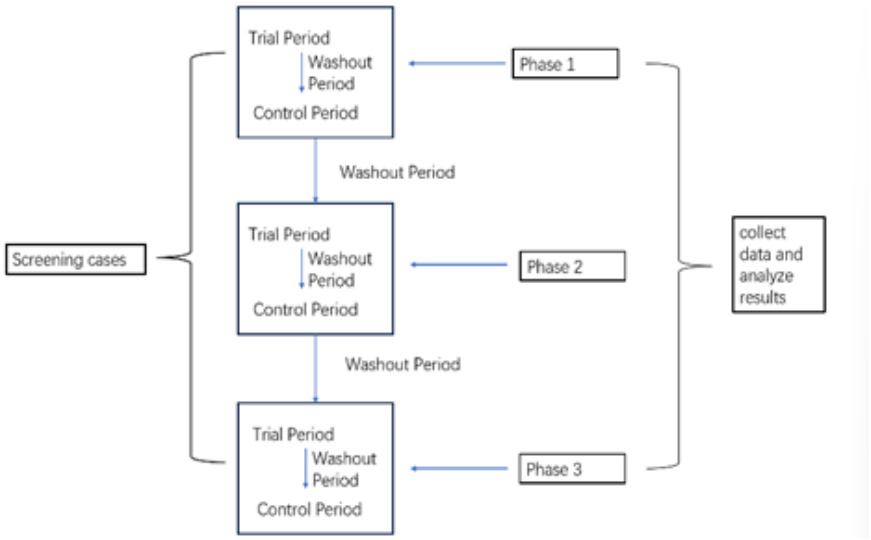

Figure 1

Table 1 Systolic and diastolic blood pressure results after each round of treatment in patients with spleen-kidney yang deficiency type hypertension

Patient		SBP (mmHg)				DBP (mmHg)			
		Experimental period	Control period	t/Z Value	P Value	Experimental period	Control period	t/Z Value	P Value
Patient 1	Round 1	137.9±2.8	139.4±1.3	-2.499	0.018	83.5±1.8	85.2±1.0	-4.610	0.001
	Round 2	134.2±3.5	136.0±0.9	-2.983	0.006	81.1±2.2	82.1±1.4	-2.211	0.035
	Round 3	130.9±2.7	134.0±1.0	-5.745	<0.001	77.5±2.0	79.0±1.2	-3.724	0.001
Patient 2	Round 1	155.5±2.7	157.2±1.0	-3.247	0.003	87.3±2.5	87.8±1.0	-1.208	0.237
	Round 2	151.8±2.8	153.5±1.0	-3.132	0.004	82.5±1.3	83.2±1.1	-2.304	0.029
	Round 3	148.9±2.5	152.1±1.6	-5.679	<0.001	80.0±1.4	80.9±1.3	-2.494	0.019

Table 2 Systolic and diastolic blood pressure results after three rounds of treatment in patients with spleen-kidney yang deficiency type hypertension

Patient	SBP (mmHg)				DBP (mmHg)			
	Experimental period	control period	Z Value	P Value	Experimental period	control period	Z Value	P Value
Patient 1	134.0 (131.0~137.3)	136.0 (134.8~138.3)	-5.280	<0.001	81.0 (78.0~83.0)	82.0 (80.0~85.0)	-5.587	<0.001
Patient 2	152.0 (149.0~155.0)	154.0 (153.0~157.0)	-4.564	<0.001	82.5 (80.8~86.0)	83.0 (81.2~87.0)	-2.953	0.003

Table 3 Heart rate after each round of treatment in patients with spleen-kidney Yang deficiency type hypertension

Patient	Period	Experimental period	control period	t/Z Value	P Value
Patient 1	Round 1	77.2±1.4	78.2±1.1	-2.892	0.007
	Round 2	74.6±1.5	76.0±1.0	-5.662	<0.001
	Round 3	75.8±1.3	76.4±1.1	-1.777	0.086
Patient 2	Round 1	85.4±1.6	86.8±1.1	-3.633	0.001
	Round 2	82.5±1.2	83.1±1.1	-2.068	0.048
	Round 3	81.0±1.8	82.6±0.8	-4.287	<0.001

Table 4 Heart rate results after three rounds of treatment in patients with splee n-kidney yang deficiency type hypertension

Patient	Experimental period	Control period	Z Value	P Value
Patient 1	76.0 (75.0~77.0)	77.0 (76.0~78.0)	-4.710	<0.001
Patient 2	83.0 (81.0~85.0)	83.5 (82.8~86.0)	-4.829	<0.001

Table 5 PHQ-15 results after three rounds of treatment in patients with spleen-ki dney yang deficiency type hypertension

patient	Experimental period	control period	Z Value	P Value
patient 1	5.5 (3.3~7.5)	8.0 (5.0~10.8)	-2.014	0.044
patient 2	3.0 (2.0~5.0)	8.0 (4.0~8.8)	-1.980	0.048

Table 6 TCM syndrome score results after three rounds of treatment in patients with spleen-kidney yang deficiency type hypertension

Patient	Experimental period	Control period	Z value	P Value
Patient 1	9.5(5.3~19.0)	13.5(6.0~24.0)	-2.051	0.040
Patient 2	9.0(2.3~19.0)	12.0(6.0~23.4)	-1.973	0.049