Research and Report

N-of-1 Randomized Controlled Trial of Traditional Chinese Medicine for Yin-Yang Deficiency Pattern Hypertension

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Abstract:

Objective: To evaluate the clinical efficacy of the "Yin-Nourishing and Yang-Tonifying" method of Traditional Chinese Medicine based on the "Yougui Pill" formula for treating Yin-Yang Deficiency Pattern Hypertension. Methods: An N-of-1 randomized controlled trial (N-of-1 RCT) design was adopted. Patients Meeting the diagnostic criteria for Yin-Yang Deficiency Pattern in TCM with duration ≥3 months. Each patient served as their own control, undergoing 3 rounds of treatment cycles, with each cycle randomly assigned to either the trial period (modified Yougui Pill plus conventional antihypertensive drugs) or the control period (placebo plus conventional antihypertensive drugs), each lasting 4 weeks, with a 1-week washout period between phases. Primary outcome measures included office blood pressure, home self-measured blood pressure, and resting heart rate; Secondary outcome measures included Traditional Chinese Medicine (TCM) syndrome score, Pittsburgh Sleep Quality Index (PSQI), and Hospital Anxiety and Depression Scale (HADS). Statistical analysis was performed using paired t-test, Wilcoxon signed-rank test, and Bayesian hierarchical model. Results: A total of 8 patients completed the entire trial. Bayesian hierarchical model analysis showed that compared with the control period, the trial period achieved a mean reduction of 3.61 mmHg in systolic blood pressure (95% CI: -5.91, -1.34), a mean reduction of 5.97 mmHg in

diastolic blood pressure (95% CI: -6.91, -4.99), and a mean reduction of 6.29 beats/min in resting heart rate (95% CI: -6.86, -5.72), with all differences being statistically significant (P<0.05). During the trial period, patients demonstrated significantly lower Traditional Chinese Medicine (TCM) syndrome scores [8.50 (5.00, 10.50) vs. 14.00 (7.00, 23.00), P=0.033], PSQI scores (5.54±3.37 vs. 9.08±2.92, P<0.001), and HADS scores (6.38±2.34 vs. 9.33±2.97, P<0.001) compared with the control period. No serious adverse events were observed during the trial period. Conclusion: This N-of-1 trial demonstrates that for patients with Yin-Yang Deficiency Pattern Hypertension, the addition of modified Yougui Pill to conventional antihypertensive therapy can further reduce blood pressure, slow heart rate, and improve TCM syndrome presentation, sleep quality, and anxiety-depression status. This study provides high-level evidence-based support for individualized Traditional Chinese Medicine treatment.

Key Words: Traditional Chinese Medicine therapy; Hypertension; Yin-Yang Deficiency; Yougui Pill; N-of-1 randomized controlled trial;

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Hypertension remains one of the most prevalent chronic cardiovascular conditions globally, affecting an estimated 1.28 billion adults worldwide [1]. Despite advances in pharmacological therapy, a substantial proportion of patients continue to experience suboptimal blood pressure control accompanied by complex systemic symptoms that significantly impair quality of life [2]. Among the various Traditional Chinese Medicine (TCM) pattern classifications of hypertension, the Yin-Yang Deficiency Pattern represents a particularly challenging clinical phenotype, predominantly observed in middle-aged and elderly patients with long-standing disease, constitutional insufficiency, or refractory hypertension [3]. This pattern manifests clinically as vertigo, headache, soreness and weakness of the waist and knees, coexistence of aversion to cold with cold limbs and vexing heat in the five centers (chest, palms, and soles), with many patients also presenting anxiety, insomnia, and fatigue. Modern research

indicates that this pattern is closely associated with neuroendocrine disorders, endothelial dysfunction, autonomic nervous system imbalance, and accelerated vascular aging [4].

Hypertension falls under the categories of “Vertigo” and “Headache” in TCM; Yin-Yang Deficiency Pattern is one of its common patterns, manifesting as vertigo, headache, soreness and weakness of the waist and knees, coexistence of aversion to cold with cold limbs and vexing heat in the five centers (chest, palms, and soles), with some patients also presenting anxiety and insomnia [5]. Modern research suggests this pattern is closely associated with neuroendocrine disorders and endothelial dysfunction [6]. Currently, while Western antihypertensive therapy alone can control blood pressure values in such patients, it often has limitations in improving their systemic accompanying symptoms. Traditional Chinese Medicine emphasizes holistic regulation and pattern-based treatment, possessing unique advantages in “nourishing Yin and tonifying Yang, and harmonizing Yin and Yang” [7]. However, conventional large-sample Randomized Controlled Trials (RCT) aim to draw universal conclusions and are poorly suited to precisely evaluate individualized TCM efficacy that emphasizes “treatment according to individual” [8].

N-of-1 randomized controlled trials (N-of-1 RCT), using a single patient as the study unit through multiple rounds of randomized, crossover, controlled design, can provide high-level efficacy evidence for specific individuals—a concept highly compatible with the individualized model of TCM pattern-based treatment [9]. This study aims to apply the N-of-1 RCT methodology, using modified Yougui Pill as the base formula, to scientifically evaluate the clinical efficacy of the “Yin-Nourishing and Yang-Tonifying” method of TCM for treating Yin-Yang Deficiency Pattern Hypertension , thereby providing high-level evidence-based support for precise integrated Chinese and Western medicine treatment in this specific population.

1. Materials and Methods

1.1 Study Design

This study adopted an N-of-1 randomized controlled trial (N-of-1 trial) design, a multi-center, single-blind,

randomized, crossover controlled trial. Each patient served as their own control, undergoing 3 rounds of treatment cycles, with each cycle consisting of a trial period (A) and a control period (B), separated by a 1-week washout period, as shown in Figure 1.

1.2 Study Subjects

1.2.1 Inclusion Criteria:

① Aged 35-75 years; ② Meeting the diagnostic criteria for essential hypertension in the "Chinese Guidelines for the Prevention and Treatment of Hypertension (2024 Revised Edition)" [10]: without antihypertensive medication, office blood pressure measured on three separate occasions in a resting state showing systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or with a documented history of hypertension; ③ Meeting the diagnostic criteria for Yin-Yang Deficiency Pattern in TCM: referring to the "Guiding Principles for Clinical Research of New Chinese Medicines (Trial)" [11], with main symptoms including headache, aversion to cold with cold limbs, soreness and weakness of the waist and knees, and vertigo; secondary symptoms including palpitations and insomnia, shortness of breath with reluctance to speak, and tinnitus; pale tongue with white coating, deep and thin pulse; ④ Duration of Yin-Yang Deficiency symptoms ≥3 months; ⑤ Able to cooperate with inquiry, tongue examination, and pulse taking; ⑥ Voluntary participation in this study with signed informed consent.

1.2.2 Exclusion Criteria:

① Secondary hypertension and malignant hypertension; ② Combined with severe cardiopulmonary or renal diseases, malignant arrhythmia, premature beats, atrial fibrillation; ③ Cognitive dysfunction, acute infectious diseases; ④ Pregnant and lactating women; ⑤ Long-term use of corticosteroids, adrenocorticotropic hormone, immunosuppressants, and other drugs; ⑥ Those with disabilities or other reasons making follow-up difficult or uncooperative.

1.2.3 Withdrawal Criteria:

① Patients who self-changed medications or experienced serious adverse events during the trial period;

② Abnormal function of vital organs, deterioration of condition, or occurrence of critical illnesses (such as cerebral hemorrhage, cerebral infarction, acute coronary syndrome, aortic dissection, etc.); ③ Subjects developing other diseases during the study period affecting efficacy and adverse event assessment; ④ Subjects with poorly controlled blood pressure requiring repeated adjustment of antihypertensive drugs; ⑤ Active withdrawal or loss to follow-up without any reason.

1.3 Sample Size

Based on the characteristics of N-of-1 trial design, combined with previous research and feasibility analysis, this study planned to enroll 12 patients. Each patient completed 3 rounds of treatment cycles, with an expected yield of 36 paired data points from treatment periods and 36 from control periods.

1.4 Randomization and Blinding

A random number table method was used to independently generate random sequences for the 3 treatment cycles for each patient (A representing the trial period, B representing the control period). Randomization schemes were developed and sealed by research personnel not involved in clinical assessment. Single-blinding was implemented for patients, meaning patients were unaware of the specific treatment regimen (Chinese medicine or placebo) received at each phase. Clinical assessors and data entry personnel were not blinded, but the final statistical analyst was blinded.

1.5 Interventions

1.5.1 Basic Treatment

All patients maintained their original antihypertensive drug regimens unchanged during the trial period, including calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, diuretics, and others. Unless blood pressure control was inadequate requiring emergency management, adjustment of the type or dosage of basic antihypertensive drugs was prohibited during the trial period.

1.5.2 Trial Period Intervention (Phase A)

On the basis of conventional antihypertensive drug therapy, modified Yougui Pill treatment was administered. Yougui Pill, originating from “Jingyue Quanshu” (Complete Works of Jingyue), has the effects of warming and tonifying

Kidney Yang, and replenishing Essence and marrow. Basic formula composition: Shu Di Huang (Radix Rehmanniae Praeparata) 24g, Shan Yao (Dioscoreae Rhizoma) 12g, Shan Zhu Yu (Fructus Corni) 9g, Gou Qi Zi (Lycii Fructus) 12g, Tu Si Zi (Semen Cuscutae) 12g, Lu Jiao Jiao (Colla Cornus Cervi) 12g (dissolved by melting), Du Zhong (Cortex Eucommiae) 12g, Dang Gui (Angelicae Sinensis Radix) 9g, Rou Gui (Cortex Cinnamomi) 6g, Zhi Fu Zi (Aconiti Lateralis Radix Praeparata) 6g (decocted first).

Modifications according to symptoms: For obvious Yin deficiency: add Sheng Di Huang (Radix Rehmanniae) 15g, Mai Dong (Radix Ophiopogonis) 12g, Wu Wei Zi (Fructus Schisandrae Chinensis) 6g; For obvious Yang deficiency: add Yin Yang Huo (Epimedii Folium) 12g, Ba Ji Tian (Radix Morindae Officinalis) 12g; For obvious Qi deficiency: add Huang Qi (Astragali Radix) 30g, Dang Shen (Radix Codonopsis) 15g; For obvious blood stasis: add Dan Shen (Salviae Miltiorrhizae Radix et Rhizoma) 15g, Chuan Xiong (Chuanxiong Rhizoma) 9g; For obvious phlegm-dampness: add Fu Ling (Poria) 15g, Bai Zhu (Atractylodis Macrocephalae Rhizoma) 12g, Chen Pi (Citri Reticulatae Pericarpium) 9g.

Administration: One dose per day, decocted with water for oral administration, taken warm in two divided doses (morning and evening), 200ml each time. Continuous administration for 2 weeks constituted one treatment period.

1.5.3 Control period Intervention (Phase B)

On the basis of conventional antihypertensive drug therapy, placebo treatment was administered. The placebo was similar in appearance, odor, and packaging to the Chinese medicine decoction, prepared from dextrin, caramel color, food flavoring, and other ingredients, containing no pharmacologically active components. Administration method was the same as the trial period.

1.5.4 Washout Period

A 1-week washout period was set between each round of treatment cycles, during which only conventional antihypertensive drug therapy was maintained, with discontinuation of trial drugs or placebo, to eliminate residual drug effects.

1.6 Outcome Measures

1.6.1 Primary Outcome Measures

1. Office blood pressure: Measured every 2 weeks using a validated upper-arm electronic sphygmomanometer. After 10 minutes of quiet rest, patients were seated and blood pressure was measured on the right upper arm for 3 consecutive times, with the average value recorded.

2. Home Self-Measured Blood Pressure: Patients measured twice daily (morning and evening), with 2 measurements each time, averaging the values and recording them, ensuring at least 2 days of valid records per week.

3. Resting Heart Rate: Measured simultaneously with blood pressure, recording beats per minute.

1.6.2 Secondary Outcome Measures

1. TCM syndrome score: Referring to the "Exploratory Study on Quantitative Diagnostic Criteria for Common TCM Patterns of Hypertension" [12], severity of symptoms was graded as follows: main symptoms scored 0, 2, 4, and 6 points for none, mild, moderate, and severe respectively; secondary symptoms scored 0, 1, 2, and 3 points for none, mild, moderate, and severe respectively; tongue and pulse characteristics scored 0 or 1 point for absence or presence. Assessed every 4 weeks. Efficacy evaluation criteria: Cured (TCM syndrome score reduction ≥95%), Markedly effective (TCM syndrome score reduction ≥70%), Effective (TCM syndrome score reduction ≥30%), Ineffective (TCM syndrome score reduction <30%).

2. Pittsburgh Sleep Quality Index (PSQI): Assessed patients' sleep quality over the past month, including 7 dimensions: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of hypnotic medications, and daytime dysfunction. Total score ranged 0-21, with higher scores indicating poorer sleep quality. Assessed every 4 weeks.

3. Hospital Anxiety and Depression Scale (HADS): Assessed patients' anxiety and depression status, including two subscales for anxiety and depression, each with 7 items scored 0-3, total score 0-21, with higher scores indicating more severe anxiety and depression. Assessed every 4 weeks.

1.7 Statistical Analysis

Statistical analysis was performed using SPSS 27.0 and R (4.4.3) software.

Descriptive statistics: Continuous variables were expressed as mean ±

standard deviation ($\bar{x} \pm s$) or median (interquartile range) [M (P25, P75)], and categorical variables were expressed as frequency (percentage).

Individual-level analysis: For continuous data with normal distribution, paired t-test was used; for non-normally distributed data, Wilcoxon signed-rank test was used to compare differences between the trial period and control period.

Individual-level analysis: Given the hierarchical data structure of N-of-1 trials (observations nested within periods, periods nested within patients), this study adopted a Bayesian hierarchical model for primary analysis.

For continuous outcome measures (blood pressure, heart rate), the following linear mixed-effects model was established:

$$Y_{ijk} = \beta_0 + \beta_1 \cdot Treatment_{ijk} + \beta_2 \cdot Period_{ijk} + \beta_3 \cdot Carryover_{ijk} + u_i + v_{ij} + \epsilon_{ijk}$$

Where, Yijk: Outcome measure for the kth observation in the jth period of the ith patient; β0: Overall intercept (baseline level of control period); β1: Core parameter, treatment effect of trial period relative to control period; Treatmentijk: Treatment indicator variable (1=trial period, 0=control period); Periodijk: Period effect (1=Round 1, 2=Round 2, 3=Round 3); ui: Patient-level random effect, ui~N (0, σ_u^2); vij: Period-level random effect, vij~N (0, σ_v^2); ϵ_{ijk} : Residual, $\epsilon_{ijk} \sim N(0, \sigma^2)$.

Prior distribution settings:

Weakly informative priors were adopted to ensure objectivity of results: Fixed effects: β~N (0, 10)

Random effect standard deviations: σ_u, σ_v~Half-cauchy (0, 5)

Residual standard deviation: σ~Half-cauchy (0, 5)

Analysis was completed using the brms package in R software. Model parameters were estimated through Markov Chain Monte Carlo (MCMC) method, with 4 chains run to ensure stability, and convergence diagnostics were performed. Convergence was assessed by visual inspection of MCMC chain trace plots and calculation of Gelman-Rubin convergence diagnostic statistic R-hat. All parameters showed R-hat values very close to 1(less than 1.01), indicating good model convergence and stable posterior distribution estimation. In result reporting, the treatment effect β_1 was presented as the median of its posterior distribution with 95% credible interval.

If this interval completely excluded 0, the effect was considered statistically significant. The final forest plot was generated using the ggplot2 package, with a vertical “line of no effect” (effect value=0) as reference. If the effect estimate and its interval were completely located to the left of this line, it supported the conclusion that the trial period intervention was superior.

Chart generation: Data visualization was performed using the ggplot2 package in R software. Individual blood pressure trajectory plots were established through the ggplot function for basic graphical mapping, with geom_line and geom_point geometric layers subsequently overlaid. The geom_line function drew colored lines by treatment phase for each patient through the aes (group=Patient ID, color=Treatment Period) parameter, while the geom_point () function added corresponding data points through the aes (color=Treatment Period, shape=Treatment Period) parameter. The combination of these two clearly demonstrated blood pressure trends over time and differences between treatment phases.

Significance level α=0.05, two-tailed test.

2. Results

2.1 Patient Baseline Characteristics

From July 2023 to June 2024, a total of 12 patients meeting the inclusion criteria were screened, 8 completed the entire trial cycles, and 4 withdrew midway due to personal reasons (2 lost to follow-up, 1 self-adjusted antihypertensive medication, and 1 developed acute upper respiratory tract infection). Among the 8 patients （Table 1）who completed the trial, 6 were male (75.0%) and 2 were female (25.0%); Age (54.5±10.0) years; Duration of hypertension (6.9±6.2) years.

Randomization sequences for each patient were as follows: （Table 2）

2.2 Primary Outcome Measures Analysis

2.2.1 Office Blood Pressure and Heart Rate Changes

Group-level analysis showed (Table 3) that patients in the trial period demonstrated significantly lower systolic blood pressure, diastolic blood pressure, and resting heart rate compared with the control period ($P<0.05$).

Model convergence diagnostics indicated that all parameters showed R-hat values between 1.000-1.008,

effective sample sizes (ESS) all >15,000, and MCMC trace plots showed adequate mixing of all chains, suggesting good model convergence and stable, reliable posterior estimation (Figure 2A). Compared with the control period, the trial period achieved a mean reduction of 3.61 mmHg in systolic blood pressure (95% CI: -5.91 to -1.34), a mean reduction of 5.97 mmHg in diastolic blood pressure (95% CI: -6.91 to -4.99), and the trial period showed a mean reduction of 6.29 beats/min in resting heart rate compared with the control period (95% CI: -6.86 to -5.72). The differences were statistically significant (P<0.05). The forest plot (Figure 2B) showed that effect estimates for systolic blood pressure, diastolic blood pressure, and heart rate were all located to the left of the line of no effect, suggesting that the trial period intervention was significantly superior to the control period.

Note: Dots in the figure represent effect estimates, horizontal lines represent 95% confidence intervals, and the dashed line represents the line of no effect (effect value=0). The effect values for systolic blood pressure, diastolic blood pressure, and heart rate were all negative, suggesting that the trial period (modified Yougui Pill) demonstrated better blood pressure lowering and heart rate slowing effects compared with the control period (placebo).

2.3 Secondary Outcome Measures Analysis

2.3.1 Sleep Quality and Anxiety-Depression Status（Table 4）

PSQI scores were significantly lower in the trial period compared with the control period (5.54±3.37 vs 9.08±2.92, P<0.001), suggesting that Traditional Chinese Medicine treatment could significantly improve patients' sleep quality. HADS scores were also significantly reduced (6.38±2.34 vs 9.33±2.97, P<0.001), indicating obvious improvement in anxiety and depression status.

2.3.2 TCM Syndrome Score（Table 5）

The median TCM syndrome score in the trial period was 8.50(5.00, 10.50), significantly lower than 14.00(7.00, 23.00) in the control period, with statistically significant difference (Z=-2.14, P=0.033). Among the 8 patients, 6(75%) achieved markedly effective or above criteria during the trial period (TCM syndrome score

reduction ≥70%), and 2(25%) achieved effective criteria (TCM syndrome score reduction 30%-70%).

2.4 Individual-level Analysis

Blood pressure trends across the 3 treatment cycles for each patient showed that blood pressure and heart rate were generally lower during the trial period compared with the control period, and this difference demonstrated considerable consistency across different patients. Figure 3 presents the blood pressure trajectory of a typical patient (Patient 1). From the trajectory, it can be observed that after three rounds of crossover treatment cycles, Patient 1's blood pressure gradually decreased from Grade 2 hypertension levels to the high-normal range, with superior blood pressure lowering effects during the experimental periods compared with control periods, demonstrating obvious therapeutic effects.

2.5 Safety Analysis

None of the 8 patients experienced serious adverse events during the trial period. 2 patients developed mild gastric discomfort, which resolved after adjusting medication timing (taken after meals); 1 patient developed mild diarrhea, which disappeared after reducing the dosage of Shu Di Huang (Radix Rehmanniae Praeparata). No patients showed abnormalities in laboratory examinations such as hepatic or renal dysfunction, or electrolyte disturbances.

Discussion

This study employed an N-of-1 randomized controlled trial design to systematically evaluate the efficacy and safety of the "Yin-Nourishing and Yang-Tonifying" method of Traditional Chinese Medicine, represented by modified Yougui Pill, for treating Yin-Yang Deficiency Pattern Hypertension. Results demonstrated that, on the basis of conventional antihypertensive therapy, the addition of modified Yougui Pill could further significantly reduce patients' systolic blood pressure, diastolic blood pressure, and resting heart rate, and effectively improve their TCM syndrome presentation, sleep quality, and anxiety-depression status, with good safety profiles. This provides high-quality evidence-based medical evidence for individualized Traditional Chinese Medicine treatment of such complex hypertension.

Yougui Pill originates from "Jingyue

Quanshu" (Complete Works of Jingyue) by Zhang Jingyue of the Ming Dynasty, representing a classic formula embodying the therapeutic principle of "seeking Yang within Yin". The complete formula employs Shu Di Huang (Radix Rehmanniae Praeparata), Shan Zhu Yu (Fructus Corni), Gou Qi Zi (Lycii Fructus), and others to nourish Yin and replenish Essence; Lu Jiao Jiao (Colla Cornus Cervi), Tu Si Zi (Semen Cuscutae), Du Zhong (Cortex Eucommiae), and others to warm and tonify Kidney Yang; assisted by Rou Gui (Cortex Cinnamomi) and Fu Zi (Aconiti Lateralis Radix Praeparata) to assist Yang and dissipate cold; and Dang Gui (Angelicae Sinensis Radix) to nourish blood and harmonize blood circulation. Together these achieve the effects of warming and tonifying Kidney Yang, and replenishing Essence and marrow.

This formula closely targets the core pathogenesis of Yin-Yang Deficiency—"Yin damage affecting Yang, Yang damage affecting Yin". Modern pharmacological research provides scientific explanations for the novel application of this classical formula. Catalpol in Shu Di Huang (Radix Rehmanniae Praeparata) can exert antihypertensive and renal protective effects by inhibiting the generation of AngII, a key effector molecule of the RAAS system [13]; pinoresinol diglucoside (PDG) from Du Zhong (Cortex Eucommiae) can improve endothelial function and promote NO release, serving as a definitive vascular endothelium-dependent relaxing factor [14]; while cinnamaldehyde and aconite alkaloids demonstrate regulatory effects on sympathetic nerve activity, which may partially explain the synchronous reduction of blood pressure and heart rate observed in this study [15-16].

The patient population observed in this study presented with difficult-to-control blood pressure and complex systemic symptoms, with pathophysiological processes likely involving multiple pathways. Chronic low-grade inflammation, oxidative stress, and neuroendocrine disorders are well-established mechanisms contributing to refractory hypertension and target organ damage [17]. Endothelial dysfunction, characterized by impaired NO bioavailability and increased vascular resistance, represents a crucial

pathophysiological link between Yin-Yang Deficiency Pattern and cardiovascular complications [18]. Additionally, psychosomatic problems such as anxiety and insomnia frequently coexist with hypertension and can aggravate blood pressure fluctuations through activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system overactivity[19]. The therapeutic effects demonstrated by modified Yougui Pill in this context suggest it may exert effects through multi-target, multi-system integrative regulation—not only addressing blood pressure as the "branch manifestation", but more importantly targeting the adjustment of Yin-Yang Deficiency as the "root cause", embodying the wisdom of Traditional Chinese Medicine in "treating disease by seeking the root" and the "holistic concept". The significant improvements in PSQI and HADS scores observed in this study represent a direct manifestation of this holistic regulatory effect.

Traditional large-sample parallel-controlled RCTs, while serving as the “gold standard” for efficacy evaluation, have limitations when assessing individualized TCM therapies: difficulty in reflecting the flexibility of pattern-based treatment, restricted generalizability due to strict inclusion criteria, and inability to provide direct evidence for treatment decisions in individual patients. The N-of-1 trial design adopted in this study, with individualization as its core characteristic, is highly compatible with the concept of TCM pattern-based treatment. By having patients serve as their own controls through multiple rounds of crossover treatment, it maximally controls inter-individual heterogeneity and provides high-level efficacy evidence for specific individuals. This study further employed Bayesian hierarchical models to pool data from multiple N-of-1 trials, preserving individualized information while achieving effective estimation of overall population effects, thereby providing a methodological paradigm for scientific evaluation of individualized TCM efficacy.

However, analysis of N-of-1 trial data faces unique challenges: small sample sizes (typically multi-round data from single patients), and the ultimate need to derive conclusions with some

generalizability from a series of individual trials. The Bayesian hierarchical model employed in this study is key to addressing this challenge. Unlike frequentist statistics relying on P-values and null hypotheses, Bayesian analysis directly provides the posterior distribution of the treatment effect β_1. We report its median and 95% credible interval (CI). For example, the systolic blood pressure effect was -3.64 mmHg (95% CrI: -5.89, -1.39), which can be intuitively understood as: based on existing data, we have 95% confidence that the true effect value lies between -5.89 and -1.39 mmHg, and since this interval is entirely negative, it does not support the null hypothesis of "no effect". This formulation more directly reflects "how large is the effect" and "how confident we are about it", aligning more closely with clinical decision-making thinking. Meanwhile, the MCMC method used in this study constructs a Markov chain whose stationary distribution exactly equals the target posterior distribution, then performs extensive iterative sampling through computer simulation, using the distribution of these samples to approximate the true posterior distribution. This study ran 4 independent Markov chains and assessed their convergence through the Gelman-Rubin statistic (R-hat) (R-hat<1.01), ensuring the stability and reliability of parameter estimation. MCMC enables inference for complex Bayesian models and serves as the technical cornerstone of data analysis in this study.

Of course, this study has several limitations that need to be considered when interpreting the results. First, although the N-of-1 design enhanced statistical power, the final completed sample size was small (n=8), which may limit the generalizability of findings to broader populations and also reduces the ability to analyze subgroup characteristics. Second, due to inherent differences in odor and taste between Chinese medicine decoctions and placebo, despite implementation of single-blinding, some patients might still guess their group assignment, thereby introducing performance bias. Third, with a total observation period of 6 months, the follow-up duration remains insufficient for evaluating the long-term efficacy and safety of TCM treatment for hypertension, particularly regarding

effects on cardiovascular endpoint events. Fourth, this study was primarily based on clinical scales and blood pressure measurements, lacking dynamic monitoring data of objective biomarkers such as vascular endothelial function, inflammatory cytokine profiles, and RAAS system activity. The explanation of mechanisms underlying modified Yougui Pill remains at the level of literature-derived inference, awaiting further experimental confirmation.

Despite these limitations, the conclusions of this study have clear clinical significance. They suggest that for hypertensive patients in clinical practice who experience aggravated blood pressure fluctuations accompanied by typical Yin-Yang Deficiency symptoms (such as coexistence of aversion to cold and vexing heat, insomnia, fatigue), combining conventional Western medicine optimization with Yin-nourishing and Yang-tonifying Chinese medicine based on Yougui Pill may represent a feasible strategy that can effectively synergistically lower blood pressure, improve systemic symptoms, and enhance quality of life.

Future related research can be advanced in depth along the following directions: Conduct multi-center, large-sample series of N-of-1 trials or pragmatic randomized controlled trials to validate and deepen the conclusions of this study; Utilize metabolomics, proteomics, and network pharmacology technologies to systematically elucidate the material basis and pathway networks through which the “Yin-Nourishing and Yang-Tonifying” method regulates blood pressure; Based on real-world data, further optimize the pattern differentiation-based medication specifications, dosage regimens, and safety profiles of this therapeutic method; And conduct health economic evaluations to assess the cost-effectiveness of this integrated Chinese and Western medicine regimen, thereby providing more comprehensive evidence for clinical decision-making and health policy formulation.

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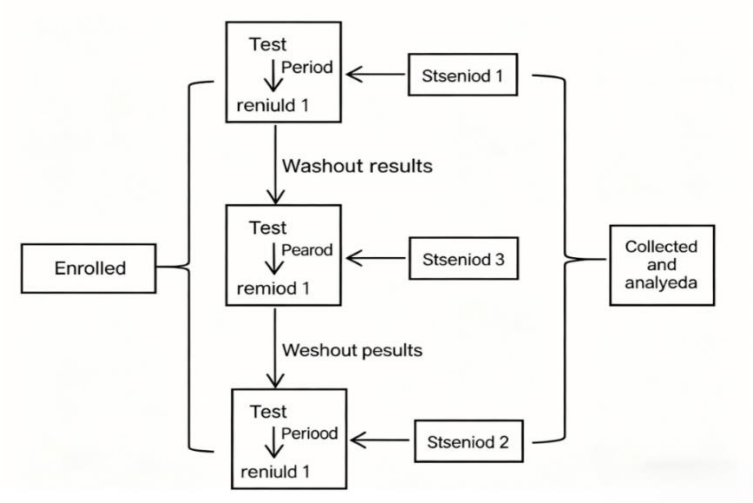

Figure 1

Table 1 Patient Baseline Characteristics (n=8)

Patients	Gender	Age (years)	Duration (years)	Office Blood Pressure (mmHg)	Heart rate (beats/min)	TCM Syndrome Presentation	PSQI	HADS
1	Male	57	5	162/100	86	18	12	7
2	Male	72	20	166/90	84	22	9	12
3	Female	48	8	175/94	90	19	14	8
4	Male	43	1	155/88	70	17	10	10
5	Male	47	1	169/117	64	23	7	11
6	Female	51	7	178/110	74	22	15	9
7	Male	66	10	152/88	68	17	11	14
8	Male	52	3	159/113	91	21	18	6

Table 2 ： Randomization sequences for each patient

Patients	Round 1	Round 2	Round 3
1	A-B	B-A	A-B
2	A-B	B-A	B-A
3	A-B	A-B	B-A
4	A-B	A-B	B-A
5	A-B	A-B	A-B
6	B-A	A-B	A-B

7	B-A	A-B	B-A
8	B-A	B-A	A-B

Note: A, Trial Period (modified Yougui Pill); B, Control Period (placebo)

Table 3: Systolic blood pressure, diastolic blood pressure, and resting heart rate Between Trial Period and Control Period

Indicator	Control Period (n=24)	Trial Period (n=24)	Statistic	P-value
Systolic Blood Pressure (mmHg)	142.00±4.64	138.36±2.78	t=3.29	0.002
Diastolic Blood Pressure (mmHg)	89.16±2.09	83.20±1.00	t=12.58	<0.001
Heart Rate (beats/min)	82.92±1.10	76.62±0.82	t=22.42	<0.001

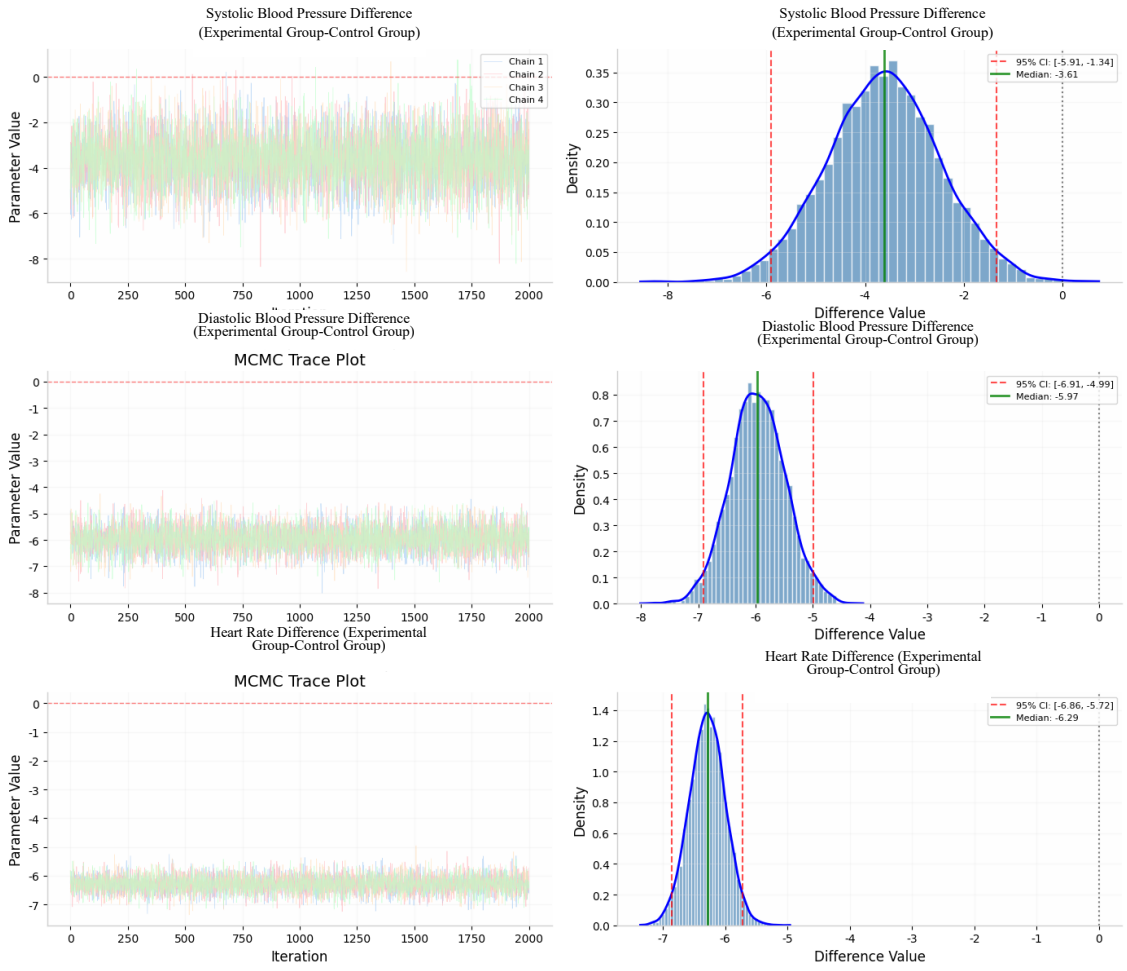

Figure 2A MCMC Chain Trace Plots for N-of-1 Randomized Controlled Trial

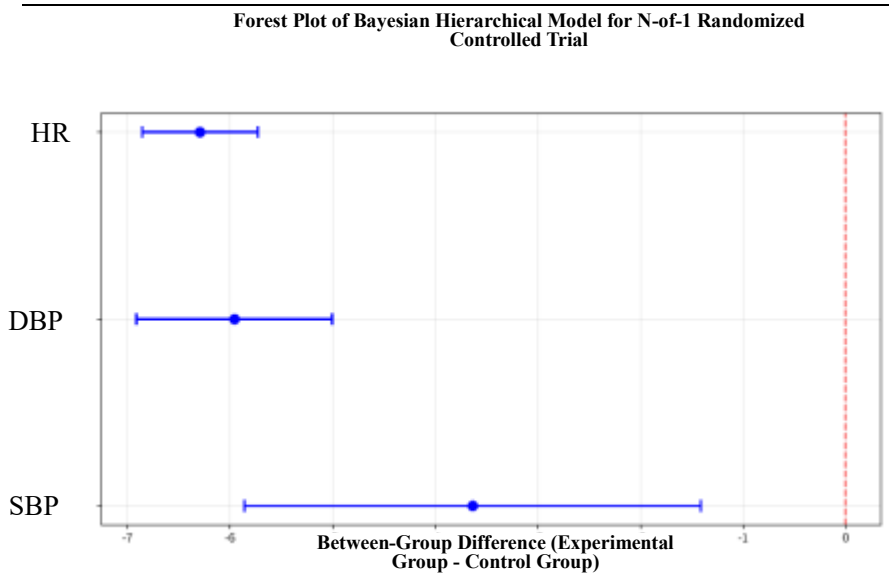

Figure 2B Forest Plot of Bayesian Hierarchical Model for N-of-1 Randomized Controlled Trial

Table 4 Comparison of PSQI and HADS Scores Between Trial Period and Control Period (x±s)

Indicator	Control Period (n=24)	Trial Period (n=24)	Statistic	P-value
PSQI Score	9.08 ± 2.92	5.54 ± 3.37	t=3.89	<0.001
HADS Score	9.33 ± 2.97	6.38 ± 2.34	t=3.83	<0.001

Table 5 Comparison of TCM Syndrome Scores Between Trial Period and Control Period

Indicator	Control Period (n=24)	Trial Period (n=24)	Statistic	P-value
TCM Syndrome Score	14.00 (7.00, 23.00)	8.50 (5.00, 10.50)	Z=-2.14	0.033

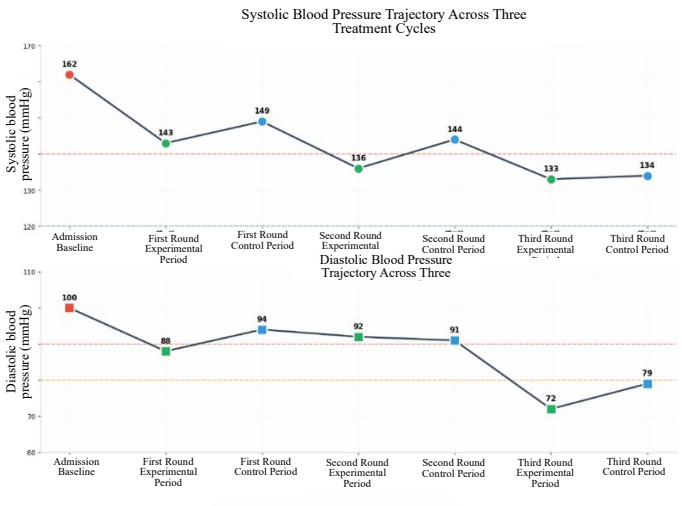

Figure 3