

A double-blind, placebo-controlled trial on the antihypertensive treatment effect of a quadruple single-pill combination

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Abstract

In a randomized, double-blind, placebo-controlled trial, we investigated antihypertensive treatment effect of a quadruple single-pill combination of reserpine 0.1 mg, dihydralazine 12.5 mg, hydrochlorothiazide 12.5 mg, and triamterene 12.5 mg, and changes in plasma levels of monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) in patients with grade 1 hypertension. Eligible patients with a systolic/diastolic blood pressure (BP, average of six readings at two clinic visits during a 4-week run-in period) of 140-159/90-99 mmHg were randomly assigned to the quadruple combination ($n = 30$) or placebo ($n = 30$). The randomized patients were instructed to take a pill of the combination or placebo once daily and followed up at 4, 8, and 12 weeks, respectively. Monoamine neurotransmitters were measured at baseline and 12 weeks of follow-up. After 12-week treatment, systolic/diastolic BP significantly ($p \leq .0001$) decreased from $140.8 \pm 7.9/89.5 \pm 7.5$ mmHg at baseline by $9.8 \pm 1.8/6.4 \pm 1.3$ mmHg in the combination group. The corresponding values in the placebo group were $141.3 \pm 7.9/90.3 \pm 7.3$ mmHg and $5.2 \pm 1.8/0.4 \pm 1.3$ mmHg, respectively. The between-group differences in systolic/diastolic BP changes were $-4.6/-6.0$ mmHg (95% CI, -9.7 to $0.6/-9.7$ to -2.2 mmHg, $p \leq .08$). The control rate of hypertension was higher in the combination than placebo group (63.3% vs. 16.7%, $p = .0002$). Plasma serotonin, but not norepinephrine or dopamine, changed in both treatment and placebo groups ($p \leq .01$). Nonetheless, plasma norepinephrine tended to decrease in the treatment group (-34.4 pg/ml, $p = .09$). Adverse events occurred in 5 (16.7%) and 3 (10.0%) patients in the combination and placebo groups, respectively. Our study showed that the quadruple combination reduced BP and caused some changes in plasma neurotransmitters.

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1 | INTRODUCTION

Current hypertension guidelines unequivocally recommend the use of combination therapy in the management of hypertension, preferably in single-pill formulations.^{1–3} In China, few single-pill combination drugs of newer agents, such as angiotensin receptor blockers or angiotensin-converting enzyme inhibitors with a calcium-channel blocker, have been readily available. There is a quadruple single-pill combination of reserpine 0.1 mg, dihydralazine 12.5 mg, hydrochlorothiazide 12.5 mg, and triamterene 12.5 mg, which has been used for nearly 40 years and is still commonly used in the management of hypertension in community health centers. In 2019, more than 25 million pills of this quadruple combination had been prescribed in China (data provided by China Resources Double-crane Pharmaceutical Co., Ltd.).

For historical reasons, this drug has not been studied in placebo-controlled studies for its efficacy and safety, in spite of a tremendous amount of data from the real-world setting and from non-randomized and randomized actively controlled studies. Critics often raise concerns with the use of older agents in the era with several classes of newer antihypertensive drugs. We therefore designed the present placebo-controlled trial to test the efficacy and safety of this quadruple single-pill combination in the management of hypertension. For safety reasons, we restricted our study to grade 1 hypertension and advised lifestyle modifications in all study participants. In the present analysis, we report the efficacy and safety data of the quadruple combination versus placebo, including measurements of several possibly related monoamine neurotransmitters.

2 | METHODS

2.1 | Study design and population

The study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial conducted from April 2018 to August 2019 in four hospitals in China. The study was performed under the guidance of the International Conference on Harmonization Guidelines for Good Clinical Practice local regulations and the ethical principles of the Declaration of Helsinki. The protocol of this study was approved by the ethics committees of all participating hospitals. All patients gave written informed consent.

Eligible patients were men and women aged 18 to 75 years, who had a systolic blood pressure of 140–159 mmHg and/or diastolic blood pressure of 90–99 mmHg during a 4-week run-in wash-out period. Exclusion criteria included secondary hypertension; severe cardiac or pulmonary disease; impaired hepatic or renal function (serum aspartate aminotransferase or alanine aminotransferase ≥ 2 times the upper limit of normal value, or serum creatinine ≥ 132.6 $\mu\text{mol/L}$; serum potassium < 3.5 mmol/L or > 5.5 mmol/L; history of depression or other mental illnesses; women during pregnancy or lactation.

2.2 | Randomized treatment and follow-up

Potentially eligible patients first entered a 4-week run-in period for the determination of eligibility. Treated patients should stop their previous antihypertensive medication. All patients should take a pill of placebo once daily and be followed up at two and four weeks of the run-in period. At the end of the 4-week run-in period, patients with a systolic/diastolic blood pressure of 140–159/90–99 mmHg (mean of 6 readings at the two clinic visits) were randomly assigned to the quadruple single-pill treatment or matching placebo once daily for 12 weeks.

Clinic blood pressure and pulse rate were measured at each of the clinic visits at 4, 8, and 12 weeks of follow-up. Electrocardiogram was performed, and blood samples were collected for monoamine neurotransmitters and other laboratory measurements at baseline and 12 weeks of follow-up. Information on adverse events was collected at each clinic visit.

Patients were instructed to take medication at 8:00 to 10:00 o'clock in the morning. Other antihypertensive agents were not allowed during the whole study treatment period. In the presence of any compelling indications for any medication of blood pressure lowering action, the patient was withdrawn from the trial. Estimated glomerular filtration rate (eGFR) was calculated using the modified Chinese equation of the simplified Modification of Diet in Renal Disease (MDRD) formula.⁴

2.3 | Efficacy and safety evaluations

The primary efficacy variables were mean changes from baseline in clinic systolic and diastolic blood pressure after 12-week treatment. We also studied the blood pressure control rate as a secondary efficacy variable. We defined blood pressure control as a systolic/diastolic blood pressure below 140/90 mmHg.¹

Safety evaluations included collection of information on all adverse events and serious adverse events, electrocardiogram, and laboratory measurements. In addition, the 17-item Hamilton Depression Rating Scale (HAMD-17) was administered for the evaluation of depressive symptoms. A HAMD-17 score of ≥ 7 was defined as "depression".⁵

2.4 | Measurements of blood pressure and plasma monoamine neurotransmitters

Clinic blood pressure and pulse rate were measured three times consecutively with a 30–60 s interval, after at least 5 min rest in the seated position. A validated automated electronic blood pressure monitor (HEM-9200T, Omron, Kyoto, Japan) was used with an appropriately sized cuff in all participating hospitals. These three blood pressure and pulse rate readings at each clinic visit were averaged for analysis.

Plasma samples were collected at randomization (week 0) and the end of follow-up (week 12) or the last follow-up visit for those who withdrew from the trial. Norepinephrine and dopamine were

measured by radioimmunoassay, and serotonin by ELISA. All measurements were performed in a core laboratory.

2.5 | Statistical analysis

Data management and statistical analyses were performed using SAS 9.4 (Cary, NC, USA). Means and proportions were compared using the Student's *t* test and chi-square test, respectively. Analysis of covariance was used to calculate the least square mean change (\pm standard error [SE]) from baseline and the between-group differences (95% confidence interval [CI]) with baseline values as covariate and treatment as a factor. Scatter plot and correlation analysis were used to analyze the interrelationship between changes in monoamine neurotransmitters and that in systolic and diastolic blood pressure and pulse rate.

3 | RESULTS

3.1 | Characteristics of the randomized patients

Of the 88 potentially eligible patients who entered the 4-week run-in period, 60 were randomized to the quadruple combination ($n = 30$) or placebo ($n = 30$, Figure 1). Patient characteristics at baseline were comparable between the two randomization groups ($p \geq .06$), except for the gender distribution and body mass index ($p \leq .02$, Table 1).

3.2 | Treatment effects on blood pressure and pulse rate

In the quadruple combination treatment group, systolic and diastolic blood pressure (mean \pm standard deviation [SD]) significantly ($p \leq .0001$) decreased from $140.8 \pm 7.9/89.5 \pm 7.5$ mmHg at baseline

to $131.1 \pm 12.1/83.2 \pm 9.2$ at 12 weeks of treatment (Figure 2), with a mean (\pm SE) change of $-9.8 \pm 1.8/-6.4 \pm 1.3$ mmHg (Table 2). The corresponding values in the placebo group were $141.3 \pm 7.9/90.3 \pm 7.3$, $136.0 \pm 11.2/89.7 \pm 8.1$, and $-5.2 \pm 1.8/-0.4 \pm 1.3$ mmHg, respectively. The between-group differences (95% CI) in systolic and diastolic blood pressure were -4.6 mmHg (95% CI, -9.7 to 0.6 , $p = .08$) and -6.0 (95% CI, -9.7 to -2.4 , $p = .002$), respectively. Pulse rate decreased significantly in the quadruple combination (-4.3 ± 1.5 beats/min, $p = .005$) but not placebo group ($p = .13$).

The blood pressure control rate was significantly higher in the quadruple combination than placebo group at 12 weeks of follow-up (63.3% vs. 16.7%, $p = .0002$). Similar trends were observed at four (53.3% vs. 30.0%, $p = .07$) and eight weeks of follow-up (53.3% vs. 30.0%, $p = .07$).

Further subgroup analyses did not show significant difference in systolic and diastolic blood pressure lowering effects according to several major characteristics of patients ($p \geq .06$ for interaction), except for a greater between-group difference in the changes in diastolic blood pressure in women than men (-21.2 vs. -2.3 mmHg, $p = .04$, Table 3).

3.3 | Monoamine neurotransmitters and their associations with changes in blood pressure

Plasma serotonin, but not norepinephrine or dopamine ($p \geq .09$), changed significantly ($p \leq .01$) from baseline to the end of 12-week follow-up in the quadruple combination and placebo groups (Table 4). Nonetheless, plasma norepinephrine tended to decrease in the quadruple treatment ($p = .09$) but not placebo group ($p = .94$).

The changes in systolic blood pressure tended to be positively associated with that in plasma norepinephrine and serotonin in the quadruple combination treatment ($p \leq .05$) but not the placebo group ($p \geq .12$, Figure 3). Similar trends were observed for the changes in

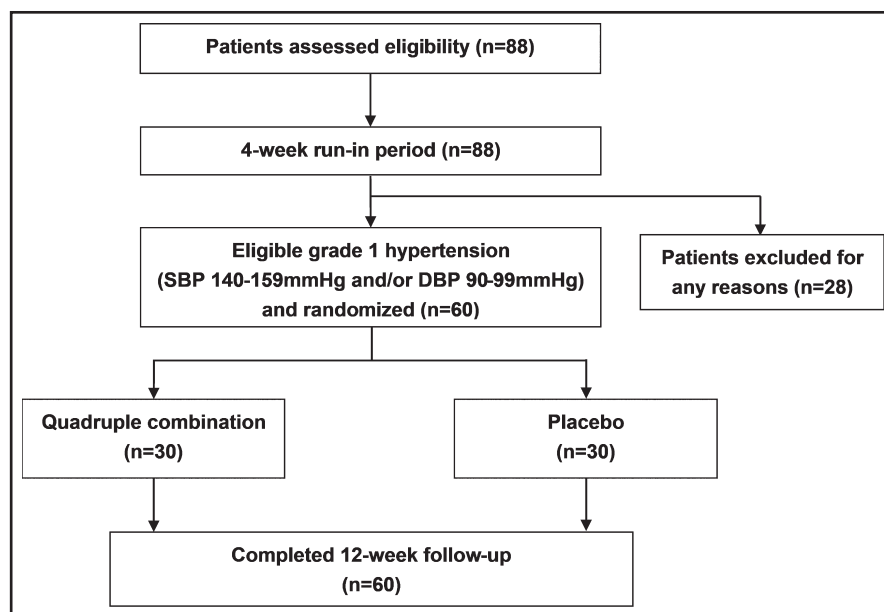


FIGURE 1 Flowchart of the trial. SBP and DBP indicate systolic and diastolic blood pressure, respectively

TABLE 1 Characteristics of the randomized patients at baseline

Characteristic	Quadruple combination (n = 30)	Placebo (n = 30)	p value
Women, n (%)	5 (16.7)	13 (43.3)	.024
Age, years	47.1 ± 13.0	46.0 ± 13.1	.75
Body mass index, kg/m ²	25.9 ± 3.4	23.4 ± 2.9	.003
Systolic blood pressure, mmHg	140.8 ± 7.9	141.3 ± 7.9	.83
Diastolic blood pressure, mmHg	89.5 ± 7.5	90.3 ± 7.3	.68
Pulse rate, beats/min	74.1 ± 9.7	74.7 ± 8.6	.81
Previous antihypertensive therapy, n (%)	7 (23.3%)	6 (20.0%)	.75
Calcium-channel blockers	5 (16.7%)	5 (16.7%)	.99
ACEI/ARB	2 (6.7%)	1 (3.3%)	.55
Other drug classes	0	1	.31
Hemoglobin, g/L	150 ± 12	150 ± 20	.95
Fasting plasma glucose, mmol/L	6.02 ± 2.06	5.51 ± 1.41	.27
Serum total cholesterol, mmol/L	5.16 ± 0.95	4.99 ± 0.87	.47
Serum triglycerides, mmol/L	1.83 ± 1.22	2.14 ± 2.22	.58
Serum HDL cholesterol, mmol/L	1.23 ± 0.33	1.26 ± 0.31	.74
Serum potassium, mmol/L	4.31 ± 0.25	4.30 ± 0.30	.88
Serum creatinine, μmol/L	79.5 ± 13.5	72.5 ± 14.2	.06
Serum uric acid, μmol/L	364 ± 74	328 ± 67	.13
eGFR, ml/min/1.73 m ²	118.3 ± 23.1	123.6 ± 30.6	.47
Monoamine neurotransmitter			
Serotonin, ng/ml	408 (300–475)	408 (107–500)	.80
Norepinephrine, pg/ml	326 (282–417)	306 (248–359)	.14
Dopamine, pg/ml	59.5 (56.4–72.9)	62.1 (56.9–72.7)	.62

Note: Values are presented as mean ± standard deviation, median (interquartile range) or number of patients (% of column total). Estimated GFR (eGFR) was calculated using the modified Chinese equation of the simplified Modification of Diet in Renal Disease (MDRD) formula.⁴ ACEI/ARB indicates angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; HDL, high-density lipoprotein.

The p value is for the comparison between the quadruple combination therapy group and the placebo group.

diastolic blood pressure in relation to both the changes in plasma norepinephrine ($p = .06$) and serotonin ($p = .19$).

the placebo group (-0.28 mmol/L, 95% CI -0.49 to -0.08 mmol/L, $p = .009$, Table 4).

3.4 | Safety

During the 12-week double-blind follow-up period, adverse events occurred in 5 (16.7%, headache [$n = 2$], bradycardia [$n = 2$], and insomnia [$n = 1$]) and 3 patients (10.0%, bradycardia [$n = 2$], and tachycardia [$n = 1$]) in the quadruple combination treatment and placebo groups, respectively ($p = .45$, Table 5). No serious adverse event or depression was reported in either group. No patient had hyperkalemia or hypokalemia. Nonetheless, serum potassium concentration was significantly lower in the quadruple combination group than

4 | DISCUSSION

Our randomized, double-blind, placebo-controlled trial demonstrated blood pressure lowering efficacy and safety of a conventional quadruple single-pill combination in grade 1 hypertension. In addition, our study on monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) showed interesting findings. An unexpected finding was the significant increase in serotonin. The quadruple combination slightly decreased norepinephrine. The changes in both serotonin and norepinephrine were associated with the changes in blood pressure.

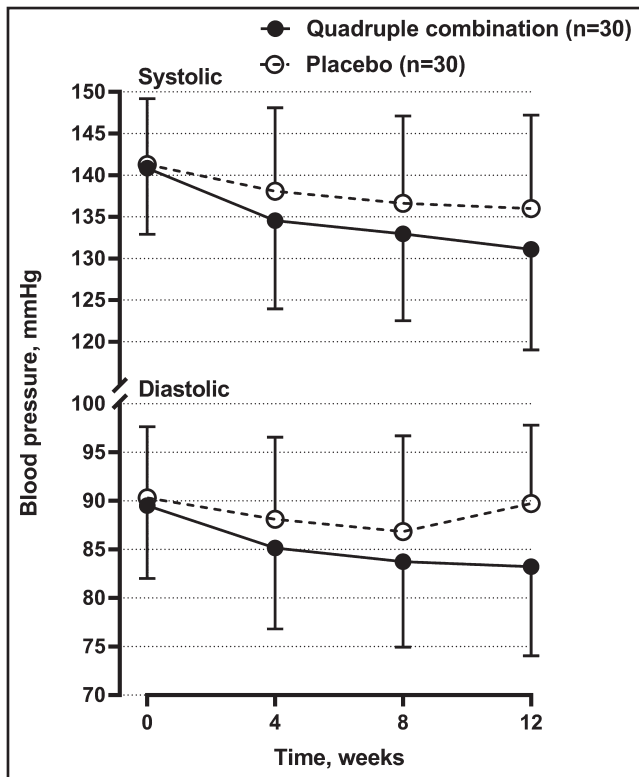


FIGURE 2 Systolic and diastolic blood pressure during follow-up by randomization group. Symbols denote the mean values of the quadruple combination (dots with solid line) and placebo groups (circles with dashed line). Vertical lines denote standard deviations

Our study is the first placebo-controlled trial on this quadruple combination. The study results are in keeping with the findings of a large-scale single-arm study.⁶ Indeed, in 1529 hypertensive patients, this quadruple combination reduced systolic/diastolic blood pressure by 8.8/4.8 mmHg after 6 months of treatment, with a blood pressure control rate of 60.2%. In addition, although the blood pressure lowering effect was generally consistent in the subgroups of patients according to several baseline characteristics, such as age, body mass index, pulse rate, serum creatinine, and serum uric acid, the diastolic blood pressure lowering effect was greater in women than men. This observation is incompletely understood.

Our study showed an acceptable safety profile of this quadruple combination, with some known side effects. There was a tiny but statistically significant decrease in serum potassium combination. This should be the consequence of the known potassium-depleting side effect of the component drug hydrochlorothiazide. This side effect was mild. None of the randomized patients had hypokalemia. The potassium sparing diuretic, triamterene, probably had some compensatory effect on potassium-depletion induced by hydrochlorothiazide. In addition, we did not observe any negative effect on depressive symptoms. The previously reported depression in relation to the use of reserpine was probably because of overdosing of this neurotransmitter depletion agent.⁷ Indeed, reserpine had been used at an average dose of up to 1.36 mg daily, which was >10 times greater than the 0.1 mg daily dose in the quadruple combination. In a recent dedicated multicenter cross-sectional study on depression,⁸ hypertensive patients

TABLE 2 Mean changes in blood pressure and pulse rate from baseline by randomization group

Follow-up time and variable	Quadruple combination (n = 30)	Placebo (n = 30)	Between-group difference (95% CI)	p value
Week 4				
Systolic blood pressure, mmHg	-6.36 ± 1.68**	-3.10 ± 1.68	-3.26 (-8.00, 1.49)	.17
Diastolic blood pressure, mmHg	-4.50 ± 1.25**	-2.07 ± 1.25	-2.43 (-5.96, 1.11)	.17
Pulse rate, beats/min	-0.54 ± 1.63	0.37 ± 1.63	-0.90 (-5.53, 3.72)	.70
Week 8				
Systolic blood pressure, mmHg	-7.95 ± 1.68**	-4.56 ± 1.68**	-3.39 (-8.16, 1.37)	.16
Diastolic blood pressure, mmHg	-5.90 ± 1.42**	-3.36 ± 1.42*	-2.54 (-6.56, 1.47)	.21
Pulse rate, beats/min	-0.68 ± 1.50	-0.07 ± 1.50	-0.60 (-4.86, 3.66)	.78
Week 12				
Systolic blood pressure, mmHg	-9.78 ± 1.82**	-5.22 ± 1.82**	-4.56 (-9.71, 0.59)	.08
Diastolic blood pressure, mmHg	-6.43 ± 1.32**	-0.44 ± 1.32	-5.99 (-9.74, -2.24)	.002
Pulse rate, beats/min	-4.32 ± 1.49**	-2.29 ± 1.49	-2.04 (-6.26, 2.18)	.34

Note: Values are least square mean ± standard error, unless otherwise indicated. CI = confidence interval.

Significance of the difference from baseline, *p < .05, **p < .01.

Subgroup	Number of patients	Systolic blood pressure, mmHg		Diastolic blood pressure, mmHg	
	Quadruple combination /Placebo	Between-group difference (95% CI)	p_{int}	Between-group difference (95% CI)	p_{int}
Age, years					
≥45	16 / 15	1.5 (-13.0, 16.2)	.07	-9.1 (-20.6, 2.2)	.40
<45	14 / 15	-13.7 (-28.4, 1.0)		-14.4 (-25.7, -3.1)	
Gender					
Men	25 / 17	-3.0 (-14.5, 8.5)	.60	-2.3 (-10.9, 6.3)	.04
Women	5 / 13	-9.1 (-30.2, 11.9)		-21.2 (-37.6, -4.9)	
Body mass index, kg/m ²					
≥25	16 / 7	-9.2 (-25.8, 7.4)	.43	-13.3 (-26.2, -0.4)	.63
<25	14 / 23	-2.9 (-15.1, 9.2)		-10.3 (-19.8, -0.7)	
Previous treatment					
Yes	8 / 5	-4.1 (-14.5, 6.1)	.70	-8.7 (-16.8, -0.6)	.41
No	22 / 25	-7.9 (-27.4, 11.5)		-14.8 (-29.8, 0.2)	
Pulse rate at baseline, beats/min					
≥74.0	16 / 16	-4.0 (-20.9, 13.0)	.64	-18.2 (-31.2, -5.3)	.06
<74.0	14 / 14	-8.2 (-21.3, 5.0)		-5.3 (-15.3, 4.7)	
Serum creatinine at baseline, μmol/L					
≥76.0	19 / 11	-12.0 (-29.7, 5.7)	.22	-18.2 (-32.1, -4.3)	.10
<76.0	11 / 19	-0.1 (-13.2, 13.1)		-5.3 (-15.5, 4.8)	
Uric acid at baseline, μmol/L					
≥381 (male) or 285 (female)	10 / 11	-6.4 (-19.2, -6.4)	.93	-10.1 (-20.0, -0.2)	.55
<381 (male) or 285 (female)	9 / 10	-5.7 (-21.0, 9.5)		-13.5 (-25.5, -1.4)	

Note: The between-group difference (95% confidence interval [CI]) was computed in a multiple linear regression model with the randomization group and all the subgroup and interaction variables included. Age, pulse rate, and serum creatinine and uric acid at baseline were dichotomized according to median. p_{int} indicates the p value for interaction between the subgroups and the randomization group in relation to systolic and diastolic blood pressure.

treated with reserpine 0.1 mg/day ($n = 787$) had similar mean depression score (40.4 vs. 40.6, $p = .70$) and depression prevalence (12.4% vs. 11.8%, $p = .86$) as those not on reserpine treatment ($n = 787$).

Our finding on the non-significant decrease in plasma norepinephrine can be explained by the use of reserpine as a component of the quadruple combination. Probably because of the small dosage, the observed decrease was not statistically significant. However, the change in plasma norepinephrine was still significantly associated with that in blood pressure, indicating that 0.1 mg reserpine played a major part in the blood pressure lowering effect of the quadruple combination.

The significant increase in plasma serotonin in both treatment and placebo groups is unexpected. Such increase actually diminished the blood pressure lowering effect of the drug. The mechanisms and health consequences remain unknown. There is some evidence that serotonin plays a role in placebo effect. Indeed, genetic polymorphisms in the serotonin-related pathways were associated with the placebo effect on depression,⁹ social anxiety,¹⁰ and drowsiness.¹¹ Plasma serotonin in too high concentrations

TABLE 3 Subgroup analysis on the between-group differences in systolic and diastolic blood pressure

might cause serotonin syndrome¹² and in mildly elevated concentrations had been linked with hip fracture.¹³ None of these health consequences were observed in the present relatively small-size and short-term study.

Our study should be interpreted within the context of its limitations. First, the present trial had a relatively small sample size, which to some extent might explain the unbalanced distribution in some characteristics at randomization, such as gender and body mass index, and the non-significant treatment-induced difference in systolic blood pressure. Second, we only measured office blood pressure. We did not perform ambulatory or home blood pressure monitoring, which is largely devoid of placebo effect. There was indeed a significant placebo effect on both systolic and diastolic blood pressure in the control group, similarly as observed in a recent meta-analysis of placebo-controlled trials on β -blockers.¹⁴ Third, our patients had low or no depressive symptoms at enrollment. The 12-week follow-up is probably insufficiently long to observe any treatment effect, if there is.

TABLE 4 Mean changes from baseline to 12 weeks of treatment in the monoamine neurotransmitters and several measurements by randomization group

Variable	Quadruple combination	Placebo	Between-group difference (95% CI)	<i>p</i>
Monoamine neurotransmitters				
Plasma serotonin, ng/ml	117.4 ± 44.6*	184.2 ± 46.2**	-66.7 (-195.6, 62.1)	.30
Plasma norepinephrine, pg/ml	-36.0 ± 20.8	-1.6 ± 20.8	-34.4 (-93.9, 25.2)	.25
Plasma dopamine, pg/ml	1.55 ± 2.77	-0.68 ± 2.77	2.23 (-5.63, 10.10)	.57
Hemoglobin, g/L	-2.7 ± 2.7	-4.5 ± 2.8	1.8 (-6.5, 10.0)	.66
Blood biochemistry				
Fasting plasma glucose, mmol/L	-0.18 ± 0.12	-0.11 ± 0.12	-0.07 (-0.41, 0.27)	.68
Serum potassium, mmol/L	-0.21 ± 0.07**	0.07 ± 0.07	-0.28 (-0.49, -0.08)	.009
Serum total cholesterol, mmol/L	0.11 ± 0.12	-0.03 ± 0.12	0.14 (-0.19, 0.48)	.39
Serum HDL cholesterol, mmol/L	-0.04 ± 0.03	-0.05 ± 0.03	0.01 (-0.09, 0.10)	.88
Serum triglycerides, mmol/L	0.08 ± 0.17	-0.16 ± 0.17	0.24 (-0.26, 0.74)	.33
Serum creatinine, μmol/L	-1.3 ± 2.0	1.0 ± 1.8	-2.3 (-7.9, 3.2)	.40
Serum uric acid, μmol/L	32.6 ± 14.8	6.6 ± 15.3	26.0 (-18.5, 70.5)	.45
eGFR, ml/min/1.73 m ²	3.9 ± 3.4	-0.1 ± 3.2	4.1 (-5.5, 13.6)	.39

Note: Values are least square mean ± standard error, unless otherwise indicated. eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein. Significance of the difference from baseline, **p* < .05, ***p* < .01.

FIGURE 3 Scatter plot for the interrelationship between the changes in systolic blood pressure and that in plasma concentration of serotonin (left panel) and norepinephrine (right panel) by randomization group. Regression lines were drawn for the quadruple combination (dots with solid line) and placebo groups (circles with dashed line) separately. Pearson correlation coefficients (*r*) and the corresponding *p* values are given alongside the regression line. The numbers of patients per group and the *p* value for interaction between randomization group and changes in plasma concentration of serotonin or norepinephrine in relation to the changes in systolic blood pressure (*p_{int}*) are also given

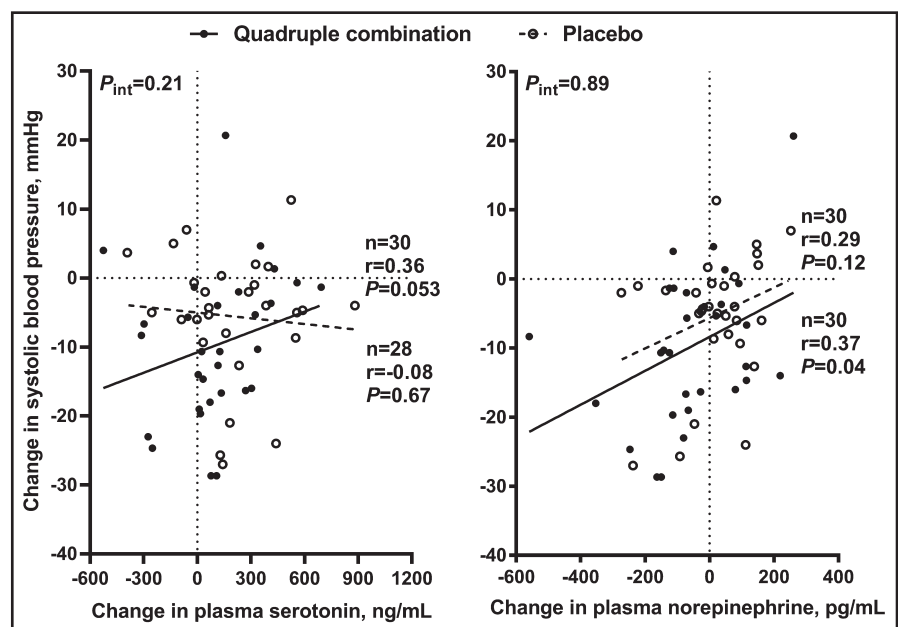


TABLE 5 Side effects of the quadruple combination

Side effect	Quadruple combination (n = 30)	Placebo (n = 30)
Headache/dizziness/swelling	2 (6.7%)	0
Bradycardia	2 (6.7%)	2 (6.7%)
Insomnia	1 (3.3%)	0
Tachycardia	0	1 (3.3%)

Note: Values are number of patients (% of column total), listed in the descending order in the quadruple combination and then placebo groups.

5 | CONCLUSIONS

In conclusion, our study showed that the single-pill quadruple combination of reserpine, dihydralazine, hydrochlorothiazide, and triamterene effectively reduced blood pressure in patients with grade 1 hypertension, with some known side effects of the component drugs, such as the changes in plasma norepinephrine and serum potassium. The finding on the changes in plasma serotonin warrants further investigation in studies involving this drug and other classes of antihypertensive drugs.

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CONFLICT OF INTEREST

Dr Wang reports receiving lecture and consulting fees from Astra-Zeneca, Novartis, Omron, Salubris, Servier, and Takeda. The other authors declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

Ji-Guang Wang contributed to the conception and design of the study. Lei-Xiao Hu performed statistical analyses and together with Ji-Guang Wang prepared the first draft of the manuscript. Dian Wang, Hua-Ling Liu, Qing-Tao Zhang, Dong-Sheng Sun, Li Zhang, Xin Chen, and Gui-Li Chang contributed to data acquisition. All authors critically commented and revised the manuscript and gave the final approval.

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