Combination treatment of captopril and prazosin to treat patients with gestational hypertension

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Abstract. Gestational hypertensive disorder is a complication of pregnancy, which adversely affects mother-child health. Captopril and prazosin are two agents that are frequently applied for the treatment of patients with gestational hypertension. However, the cooperative efficacy of captopril and prazosin has been not investigated in a previous study. In the present study, the comprehensive treatment of captopril and prazosin for the treatment of patients with gestational hypertension was investigated. A total of 324 patients with gestational hypertension were recruited to analyze the therapeutic effects of captopril and prazosin in patients with gestational hypertension. The duration of the treatment, dose-limiting toxicities and maximum tolerated dose of captopril and prazosin were examined in this cohort. Furthermore, the levels of blood pressure and proteinuria were also examined in patients with gestational hypertension who received treatment with captopril and/or prazosin with placebo as a control. Serum levels of vasodilation-converting enzyme and α-adrenergic receptor were also examined prior to and during the 4-week post-treatment period. It was observed that the most common treatment-emergence adverse events were hypertension and proteinuria following 4-week treatments. The data revealed that captopril or prazosin treatments significantly ameliorated gestational hypertension and symptoms compared with placebo ($P<0.01$). Notably, the combination of captopril and prazosin treatments significantly ameliorated hypertension and proteinuria and reduced the expression levels of vasodilation-converting enzyme and α-adrenergic receptor (all $P<0.01$), which contributed to beneficial effects on complications and blood coagulation mechanism compared with either captopril or prazosin treatment. In conclusion, the present clinical study indicated that combination treatment of captopril and prazosin exhibited more efficient outcomes than the single agent by improving gestational hypertension, indicating that a comprehensive therapeutic regimen of captopril and prazosin may be a potential clinical opinion for patients with gestational hypertension.

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Introduction

Gestational hypertension is a disease that occurs during pregnancy and leads to symptoms including hypertension, preeclampsia, eclampsia and chronic hypertension (1,2). This disease adversely affects maternal and fetal health (3). Gestational hypertension is one of the leading causes of maternal, fetal and neonatal morbidity and mortality (4,5). A previous report has suggested that the incidence rate of gestational hypertension is 7-12% in China, which is higher than the worldwide average (3.2-5.0%) (6). It has been demonstrated that clinically assisted reproductive technology treatment may increase the incidence of gestational hypertension and preeclampsia (7). In addition, there are a number of factors that induce gestational hypertension and have been identified to serve a role in the etiology of these hypertensive disorders, including work stress, depression and anxiety (8,9). Furthermore, reports have indicated that vasodilation-converting enzyme and α-adrenergic receptor serve a crucial role in the process of gestational hypertension and may be potential targets for the treatment of patients with gestational hypertension in the clinic (10-12).

Antihypertensive drugs are typically used in clinical treatment for remission of patients with hypertension during the gestation period (13). Notably, the mechanisms of formation of gestational arterial hypertension for women during pregnancy have previously been investigated and results have indicated that vasodilation-converting enzyme contributes to the progression of gestational hypertension (14). Therefore, the angiotensin-converting enzyme inhibitor was investigated and the efficacy for hypertension in the clinic has been studied. Tovar-Rodriguez *et al* (12) have previously investigated a combination therapy with an angiotensin-converting enzyme inhibitor and a diuretic that was highly effective in hypertension. Furthermore, the influence of the treatment of angiotensin-converting enzyme inhibitor on baroreflex sensitivity and flow-mediated vasodilation of the brachial artery has also been demonstrated previously in essential hypertension (15). Captopril is an antihypertensive agent that targets angiotensin converting enzyme for the treatment of gestational

hypertension (16). In the present study, the efficacy of captopril for the treatment of gestational hypertension, compared with prazosin, was investigated.

Prazosin is an α-adrenergic receptor inhibitor, which is used for the treatment of hypertension and heart failure (17). It has previously been revealed that a higher expression of α-adrenergic receptor is associated with the aggravation of gestational hypertension and α-adrenergic receptor blockers are beneficial for patients with hypertension (18). The present study further analyzed the therapeutic effects of prazosin on patients with gestational hypertension compared with captopril. Although the effects of prazosin on patients with diabetic nephropathy may induce positive α-adrenergic receptor autoantibodies, the efficacy of prazosin is evident on the improvement of gestational hypertension (19). Furthermore, it was observed that prazosin as an α-adrenergic receptor blocker, significantly reduced hypertension, heart failure and symptoms induced by gestational hypertension.

The aim of the present clinical study was to evaluate the combined treatment of captopril and prazosin for patients with gestational hypertension in a relatively large sample of pregnant outpatients (n=324) who had undergone gestational hypertension. The present study also investigated the potential molecular mechanism of captopril and prazosin in the processes of gestational hypertension. The results indicate that combination treatment with captopril and prazosin is more efficient for gestational hypertension than treatment with either captopril or prazosin. These clinical outcomes indicate that a therapeutic regimen of captopril and prazosin may be a potential therapeutic option for patients with gestational hypertension.

Materials and methods

Ethics statement. The current phase-II study (approval no. HMCH20090236-A4) was performed between February 2009 and August 2011 in accordance with the recommendations in the Guide for Haidian Maternal and Child Healthcare. The present study was approved by the Ethics Committee of Haidian Maternal and Child Health Care Center (Beijing, China). All patients were required to review trial protocols and amendments and to provide written informed consent.

Patients. A total of 324 patients with gestational hypertension (aged 22-42 years old) were randomly divided into four groups (Captopril, n=92; Prazosin, n=88; Combination, n=94; Placebo, n=50) and double-blind trails were conducted once daily in the Haidian Maternal and Child Healthcare unit. Patients were recruited between February 2009 and August 2011. A detailed description of the inclusion/exclusion criteria, allocation method and other details were provided in previously published studies (20,21). All patients were divided into four groups following the principle of random double-blind and control experiments. Patients with gestational hypertension received treatment with captopril (n=92) and prazosin (n=88), combination therapy of captopril and prazosin (n=94) or placebo (n=50). Patients with gestational hypertension received captopril (0.5 mg/kg, n=5; 1.0 mg/kg, n=5; 1.5 mg/kg, n=6; 2.0 mg/kg, n=6; 2.5 mg/kg, n=10; Sigma-Aldrich; Merck KGaA, Darmstadt, Germany), prazosin (0.02 mg/kg, n=5; 0.06 mg/kg, n=5; 0.10 mg/kg, n=7; 0.14 mg/kg, n=8; 0.18 mg/kg, n=7; Sigma-Aldrich), combined treatment (Captopril: 0.06 mg/kg and prazosin, 1.0 mg/kg) or a placebo (starch; Sigma-Aldrich; 1.0 mg/kg) that were administered orally. Patient trials were performed in a comfortable room.

Study design. The present double-blind study was performed in three phases: i) The baseline phase (consisting of 1-week of dose-titration treatment); ii) the double-blind treatment phase (consisting of 2-week dose-titration treatment); and iii) the 2-week post-treatment phase for patients with gestational hypertension who volunteered to continue to complete the study. A total of 39 patients ceased participation between phases II and III due to adverse side effects, including headache, angioedema, rash, pruritus, amblygeustia, palpitation, fever and tachycardia. Patients with gestational hypertension were randomized to undergo the double-blind treatment with captopril, prazosin, combined treatment or placebo, which were administered once daily. Patients with gestational hypertension continued to receive treatment with 0.06 mg/kg captopril, 1.0 mg/kg prazosin, combined therapy (Captopril: 0.06 mg/kg and Prazosin, 1.0 mg/kg) or placebo to achieve the final investigation throughout the post-treatment phase.

ELISA. Blood samples were collected from patients following 4-weeks treatment. Serum was separated using centrifugation at 6,000 x g at 4˚C for 15 min. Commercial ELISA kits were used to measure plasma concentration levels of vasodilation-converting enzyme using a BACE1 ELISA kit (cat. no. MA1-744; Thermo Fisher Scientific, Inc., Waltham, MA, USA) and an α-adrenergic receptor ELISA kit (cat. no. PA5-32660; Thermo Fisher Scientific, Inc.) in patients with gestational hypertension, following the manufacturer's protocol. Final results were recorded at 450 nm on an ELISA plate reader.

Activity of angiotensin vasodilation-converting enzyme. Activity of vasodilation-converting enzyme was analyzed in patients following treatment. The activity of vasodilation-converting enzyme was conducted according to a previous report (22). The serum activity of angiotensin converting enzyme was determined using the spectrophotometric method using the synthetic substrate Hip-Gly-Gly (Thermo Fisher Scientific, Inc.) (23).

Outcome measures. An automated sphygmomanometer was used to assess the function of patients with gestational hypertension. The artery-to-vein ratio was used to analyze the efficacy of captopril, prazosin and combination treatment for patients with gestational hypertension. Clinical gestational hypertension parameters were evaluated as described in a previous study (24). The data of gestational hypertension was recorded and the degree of hypertension was calculated.

Efficacy and safety assessments. Efficacy assessments, including the median percentage reduction scores and response rate were analyzed in patients with gestational hypertension from the baseline and double-blind phases in the presence of each group's respective treatment. In addition, overall safety

Table I. Characteristics of patients with gestational hypertension.

Variable	Groups			
	Captopril	Captopril	Combination	Placebo
Patients, n (%)	92 (28.4)	88 (27.2)	94 (29.0)	50 (15.4)
Age, mean ± SD	29.2±7.2	29.5±6.4	32.5±8.1	35.2±9.2
Blood pressure (mm Hg)	144±12	139±10	154±8	148±10
Coronary heart disease, n (%)	6 (6.5)	5 (5.7)	7 (7.4)	3 (6.0)
Edema (mm^3)	26.13±14.37	17.26±10.68	36.24±14.66	10.20±4.63
24 h protein, mg	35.45±20.19	24.03±14.79	52.45±19.50	13.49±6.48
Creatinine clearance, ml/min	85.45±12.45	74.24±14.76	82.78±12.68	92.34±8.06
Serum urea, mmol/l	3.67±0.48	3.86±0.73	3.65±0.43	3.49±0.56

SD, standard deviation. Data was presented as the mean ± standard deviation.

and pharmacokinetic analysis were conducted according to previous clinical studies (25,26). Furthermore, at least one safety assessment of the most frequent treatment-emergent adverse events was conducted in all randomized patients following the administration of treatment. A dose-response analysis was conducted when the last dose of drugs was administered.

Evaluation of toxicity. The toxicities of captopril and prazosin were assessed using the National Gestational Hypertension Institute Common Toxicity Criteria (27). A biochemical profile measurement of blood pressure and urinalysis were performed every 2 days during gestational hypertension treatment periods. Furthermore, electrocardiograms and biochemical detection were performed every 3 days. Toxicity was defined as any of the drug-related toxicities defined in a previous study (28).

Statistical analysis. Data are presented as the mean ± standard error of the mean, unless otherwise stated. Statistical significance of differences between mean values was assessed by Student's t-test for unpaired data. Comparisons of data between multiple groups were performed using one-way analysis of variance followed by a post-hoc Turkey honest significant difference test. Continuous variables are presented as the mean and 95% confidence interval (CI). Treatment effect is presented as median reduction in knee osteoarthritis over the treatment period. Robust nonparametric Hodges-Lehmann estimates of median drugs treatment effects and 95% CI are provided. Responder rates and treatment-emergent adverse events were analyzed by χ^2 test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 324 patients participated in the present clinical investigation to analyze the efficacy of captopril and prazosin in the treatment of gestational hypertension. The mean age of patients with gestational hypertension was 33.6±9.8 years old. The characteristics of patients with gestational hypertension are summarized in Table I. In addition, it was revealed that the percentage of patients with gestational hypertension who are ≥35 years old was significantly higher than those <35 years old (Fig. 1). Furthermore, incidence rate of coronary heart disease induced by gestational hypertension was significantly higher in patients aged >35 years old (Fig. 2). A total of 285 patients continued to complete the double-blind treatment period and the post-treatment phase.

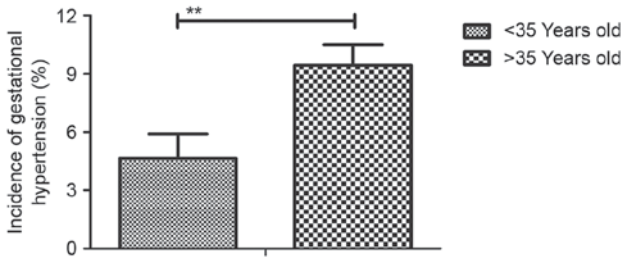

Figure 1. Incidence of gestational hypertension between groups aged >35 and <35 years old. **P<0.01.

Duration of treatment, dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of captopril and prazosin. To analyze the optimal dose of captopril and prazosin in patients with gestational hypertension, the duration of treatment, DLT and MTD of captopril and prazosin were identified. The duration of treatment with captopril and prazosin was 4 weeks in patients with gestational hypertension. The dosing cohorts were 0.5, 1.0, 1.5, 2.0 and 2.5 mg/kg for captopril and 0.02, 0.06, 0.10, 0.14 and 0.18 mg/kg for prazosin. The doses of 1.5 and 2.0 mg/kg were identified as the MTD and DLT of captopril, respectively. In addition, 0.10 and 0.14 mg/kg of prazosin were identified as the MTD and DLT of prazosin, respectively. MTD and DLT were assessed according to the Common Toxicity Criteria (version 2.0) of the National Cancer Institute, National Institutes of Health (29). It was observed that the lowest-dose cohorts of antihypertensive agents presented the lowest number of captopril or prazosin dose reductions. Common treatment-emergent adverse events of captopril were headache, angioedema, rash, pruritus, ambly-geustia, palpitation, fever and tachycardia (Table II). The common treatment-emergent adverse events of prazosin were

Table II. Treatment-emergence adverse events of captopril with an overall incidence ≥10%.

Adverse event	Total (n=32)	0.5-1.0 mg/kg (n=10)	1.0-1.5 mg/kg (n=12)	2.0 mg/kg (n=10)
Headache	4	0	2	2
Angioedema	4	1	1	2
Rash	5	1	2	2
Pruritus	4	1	1	2
Amblygeustia	4	1	1	2
Palpitation	4	1	1	2
Fever	4	1	1	2
Tachycardia	5	1	2	2

Treatment-emergent adverse events were analyzed using the χ^2 test.

Table III. Treatment-emergence adverse events of prazosin with an overall incidence ≥10%.

Adverse event	Total (n=32)	0.02-0.06 mg/kg (n=10)	0.10-0.14 mg/kg (n=15)	0.18 mg/kg (n=7)
Palpitation	5	1	2	2
Orthostatic hypotension	4	1	1	2
Nausea	6	1	2	3
Tinnitus	5	1	2	2
Vomiting	5	1	1	3
Sleepiness	4	1	1	2
Diarrhea	4	1	1	2

Treatment-emergent adverse events were analyzed via χ^2 test.

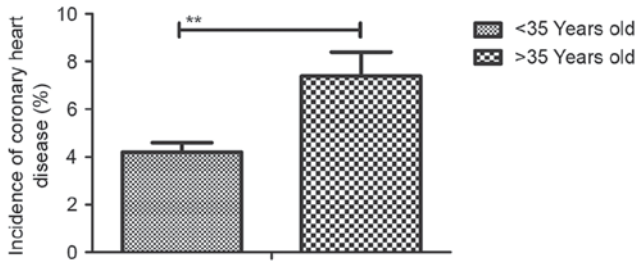

Figure 2. Incidence of coronary heart disease between groups aged >35 and <35 years old. **P<0.01.

palpitation, orthostatic hypotension, nausea, tinnitus, vomiting, sleepiness and diarrhea (Table III). Notably, the majority of patients with gestational hypertension required a reduced drug dosage to combat cumulative toxicity following treatment with the MTD dose (data not shown). Therefore, patients were administered 1.0 mg/kg captopril and 0.06 mg/kg prazosin to complete the present study.

Treatment-emergent adverse events of comprehensive treatment of captopril and prazosin. The treatment-emergent adverse events of comprehensive treatment of captopril and prazosin were analyzed in patients with gestational hypertension. Patients with gestational hypertension in each group received at least one dose of their respective group's treatment and a post-baseline safety evaluation, which included analysis of toxic events. As depicted in Table IV, following the last dose of captopril and prazosin, the most common treatment-emergent adverse events in single agent treatment and combination treatment were rash and palpitation (≥10% each). These side effects were catabolic and were resolved following termination of the treatment.

Efficacy of comprehensive treatment of captopril and prazosin for gestational hypertension. Following analysis of the treatment-emergent adverse events of comprehensive treatment of captopril and prazosin, the therapeutic effects of captopril and/or prazosin were examined on blood pressure, proteinuria, artery-to-vein ratio and edema for patients with gestational hypertension. As depicted in Fig. 3, it was observed that blood pressure was significantly improved in patients treated with captopril or prazosin compared with placebo. However, combination treatment of captopril and prazosin was significantly more effective compared with either captopril or prazosin alone. Similar results were also observed in proteinuria levels in patients with gestational hypertension, which recovered to healthy levels (80-120 mm Hg) in the captopril and/or prazosin groups, compared with placebo treatment (Fig. 4). In addition, it was revealed that the artery-to-vein ratio was significantly increased by the treatment of captopril or prazosin compared with placebo and combination treatment induced a significant increase compared with either single

Table IV. Treatment-emergent adverse events for hypertension and proteinuria by common toxicity criteria grade.

Adverse event	Total (n=32)	Captopril (n=10)	Prazosin (n=10)	Combination (n=12)
Rash	9	2	3	4
Grade 1	3	1	1	1
Grade 2	2	0	1	1
Grade 3	4	1	1	2
Palpitation	10	5	4	2
Grade 1	4	1	1	2
Grade 2	3	1	1	1
Grade 3	3	0	1	2

Treatment-emergent adverse events were analyzed via χ^2 test.

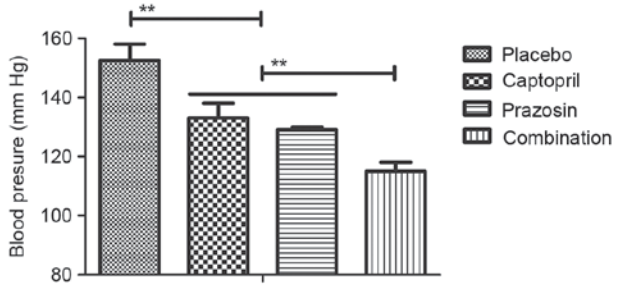

Figure 3. Analysis of blood pressure of patients with gestational hypertension following treatment with captopril, prazosin, combination or placebo. Data are presented as the mean ± standard error of the mean for three independent experiments. **P<0.01.

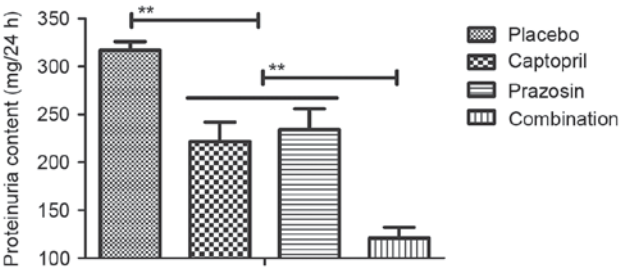

Figure 4. Proteinuria levels in patients with gestational hypertension following treatment with captopril, prazosin, combination or placebo. Data are presented as the mean ± standard error of the mean for three independent experiments. **P<0.01.

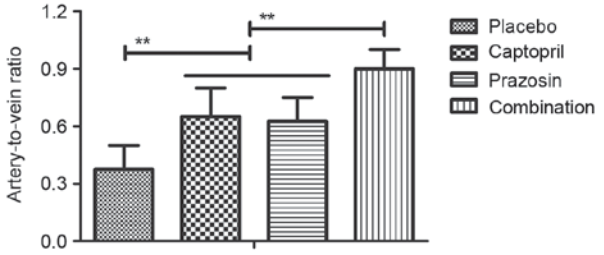

Figure 5. Artery-to-vein ratio in patients with gestational hypertension following treatment with captopril, prazosin, combination or placebo. Data are presented as the mean ± standard error of the mean for three independent experiments. **P<0.01.

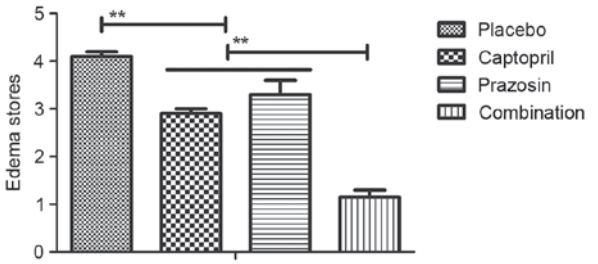

Figure 6. Edema stores of patients with gestational hypertension. Data are presented as the mean ± standard error of the mean for three independent experiments. **P<0.01.

agent (Fig. 5). Furthermore, the edema stores of patients with gestational hypertension were significantly reduced following treatment with captopril or prazosin compared with placebo and combination treatment induced a significant decrease compared with either single agent (Fig. 6). Together, these clinical outcomes revealed that combination therapy with captopril and prazosin significantly ameliorated the clinical features of gestational hypertension.

Analysis of plasma concentration of vasodilation-converting enzyme and α-adrenergic receptor in patients with gestational hypertension. The expression and activity of vasodilation-converting enzyme and α-adrenergic receptor was subsequently detected in patients with gestational hypertension following treatment with captopril and/or prazosin. As demonstrated in Fig. 7, compared with the placebo group, the plasma concentration of vasodilation-converting enzyme was significantly downregulated following prazosin treatment. Treatment with captopril alone or combination treatment led to a significant decrease compared with prazosin treatment alone. It was observed that the activity of vasodilation-converting enzyme was also significantly inhibited in patients with gestational hypertension following treatment with captopril or combination treatment in comparison with both the placebo and prazosin groups (Fig. 8). In addition, it was revealed that the plasma concentration levels of α-adrenergic receptor in patients with gestational hypertension were downregulated following treatment with prazosin or combination treatment in comparison

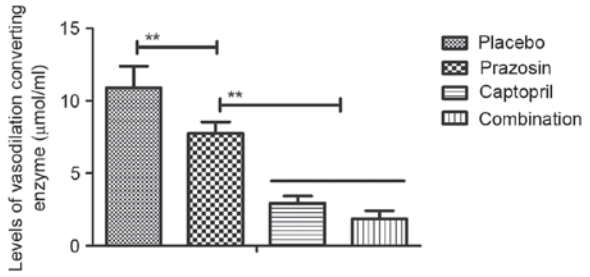

Figure 7. Plasma concentration of vasodilation-converting enzyme by the treatment of captopril, prazosin, combination or placebo. Data are presented as the mean ± standard error of the mean for three independent experiments. **P<0.01.

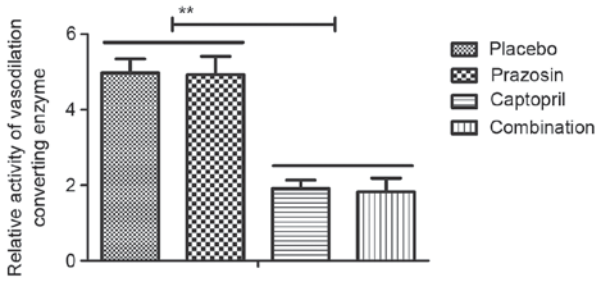

Figure 8. Activity of vasodilation-converting enzyme in patients with gestational hypertension. Data are presented as the mean ± standard error of the mean for three independent experiments. **P<0.01.

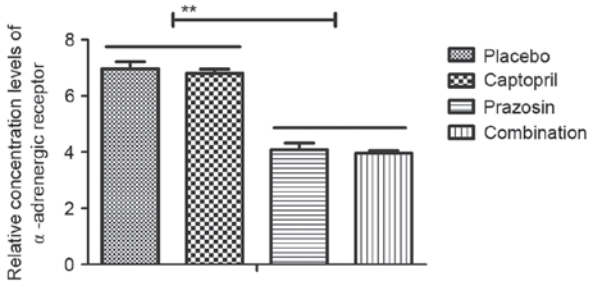

Figure 9. Plasma concentration levels of α-adrenergic receptor in patients with gestational hypertension. Data are presented as the mean ± standard error of the mean for three independent experiments. **P<0.01.

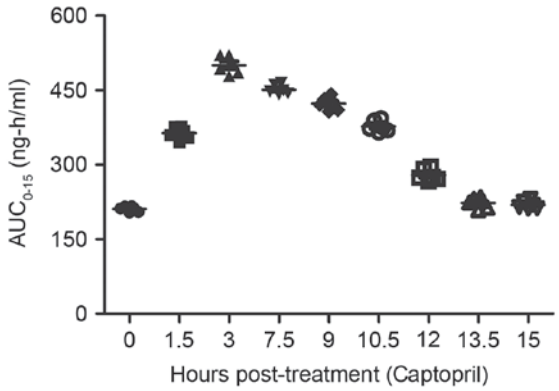

Figure 10. Plasma concentration levels of captopril in patients with gestational hypertension following captopril treatment. Data are presented as the mean ± standard error of the mean for three independent experiments. AUC, area under curve.

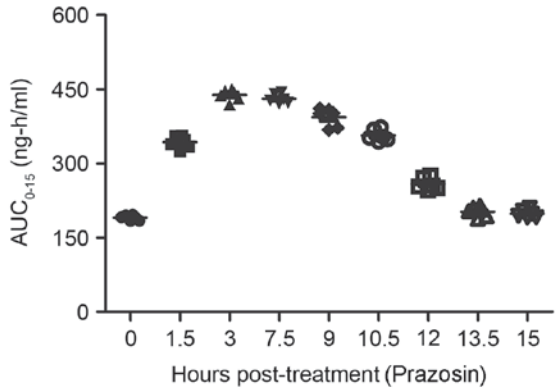

Figure 11. Plasma concentration levels of prazosin in patients with gestational hypertension following prazosin treatment. Data are presented as the mean ± standard error of the mean for three independent experiments. AUC, area under curve.

with both the placebo and captopril groups (Fig. 9). Together, these clinical outcomes indicate that expression levels of vasodilation-converting enzyme and α-adrenergic receptor may be downregulated by captopril and prazosin, respectively, which contribute to the recovery of gestational hypertension.

Pharmacodynamics analysis. After examining the efficacy of comprehensive treatment of captopril and prazosin, the pharmacodynamics of captopril and prazosin were analyzed in patients with gestational hypertension during the clinical therapeutic period. The plasma concentration levels of captopril and prazosin were analyzed in patients with gestational hypertension following treatment with captopril and/or prazosin. As depicted in Fig. 10, the plasma concentration levels of captopril peaked at 3 h post-treatment. In addition, the plasma concentration levels of prazosin reached a maximum 3-7.5 h following administration (Fig. 11). Furthermore, the maximum concentrations (C_{max}) of captopril or prazosin were observed to increase linearly with increasing dosages (Figs. 12 and 13). The present study presented that the median terminal elimination half-time (t½) of captopril or prazosin ranged between 1 and 12 h at the indicated dose. Furthermore, there was no drug accumulation observed after patients received captopril or prazosin by observing the C_{max} values. Together, these data indicate that captopril and prazosin exhibited efficient concentration and functional times.

Discussion

Previous studies have indicated that vasodilation-converting enzyme and α-adrenergic receptor serve a crucial role in the initiation and development of patients with gestational hypertension, which respectively target angiotensin and α-adrenergic receptor and subsequently lead to gestational hypertension (18,30). In the present study, the association among the plasma concentration levels of vasodilation-converting enzyme and α-adrenergic receptor and hypertension was investigated in patients with gestational hypertension. In addition, the efficacies of the antihypertensive drugs captopril and prazosin, which target vasodilation-converting enzyme and α-adrenergic receptor,

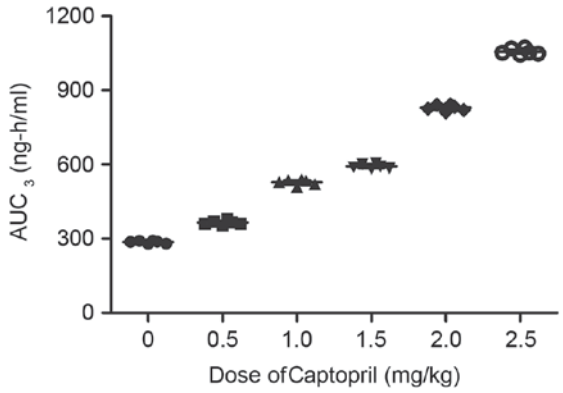

Figure 12. C_{max} concentrations of captopril in patients with gestational hypertension following different concentration levels of captopril treatment. Data are presented as the mean ± standard error of the mean for three independent experiments. AUC, area under curve.

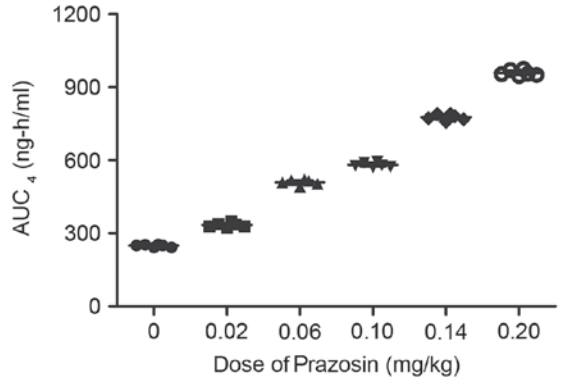

Figure 13. C_{max} concentrations of prazosin in patients with gestational hypertension following different concentration levels captopril treatment. Data are presented as the mean ± standard error of the mean for three independent experiments. AUC, area under curve.

respectively, have been examined in patients with gestational hypertension.

Following a 4-week baseline, patients with gestational hypertension were randomized to a double-blind treatment with captopril, prazosin, combined therapy or placebo once daily. Although previous results indicated that treatment with captopril or prazosin was able to regulate the plasma concentrations of vasodilation-converting enzyme and α-adrenergic receptor, respectively (19,31), to the best of our knowledge, the clinical outcomes of combined captopril and prazosin have not been investigated in previous studies. Therefore, the present study aimed to evaluate the clinical application of combined treatment with captopril and prazosin. The safety, treatment-emergent adverse events, positive observations and pharmacodynamics of the comprehensive treatment of captopril and prazosin were also evaluated to make a comprehensive assessment for the therapeutic effects for patients with gestational hypertension. Treatment responses have assessed median percent reduction in hypertension that was improved with comprehensive treatment of captopril and prazosin compared to a single agent and placebo. Furthermore, the overall incidence of treatment-emergent adverse events in the presence of captopril and prazosin were rash and palpitation during the treatment of gestational hypertension, which is consistent with previous reports (32,33). The clinical data of the present study have demonstrated that captopril and prazosin are able to alleviate gestational hypertension and hypertension-related indictors.

Captopril is an inhibitor of vasodilation-converting enzyme that is used as a clinical oral drug for the treatment of hypertension in a number of countries. A number of previous studies have investigated the therapeutic effects of captopril on patients with gestational hypertension in clinical. Woodworth *et al* (29) have demonstrated the effect of long-term captopril therapy on patients with hypertension and diabetes determined by the biochemical parameters of intrarenal blood flow and renal function. In addition, Van Guilder *et al* (30) have indicated that comprehensive effects of low-dose oral spironolactone and captopril therapy present more benefits for spontaneous hypertension and heart failure. Furthermore, Reusz *et al* (31) have recently suggested the influence of captopril treatment on occupational activity of engine operators with hypertension. These outcomes indicate that captopril is an efficient drug for the treatment of hypertension in preclinical and clinical experiments. The outcomes also confirm the efficacy of captopril on gestational hypertension. Furthermore, the treatment-emergent adverse events and pharmacodynamics of Captopril were evaluated and studied to systematically analyze the drug metabolism during the treatment for patients with gestational hypertension. The outcomes indicate that captopril is a relatively efficient antihypertensive drug for the treatment of gestational hypertension.

Prazosin is an α-adrenergic receptor inhibitor that can significantly inhibit vasoconstriction by targeting the α-adrenergic receptor in the vascular endothelial cells. Previous studies have indicated that prazosin inhibits the activity of α-adrenergic receptor leading to the improvement of activity of vascular endothelial cells in patients with hypertension (34,35). In addition, Franklin *et al* (27) have demonstrated the efficacy and tolerance of prazosin in patients with hypertension and non-insulin dependent diabetes. Furthermore, Joglekar and Nanivadekar (34) also compared the efficacies of oral therapy with combined enalapril, prazosin and hydrochlorothiazide in the acute treatment of severe hypertension in Nigerian patients. The present study investigated the efficacies of combined treatment of captopril and prazosin for the treatment of gestational hypertension and it was demonstrated that prazosin treatment also inhibits the serum concentration levels of α-adrenergic receptor in patients with gestational hypertension. These results of the present study revealed that captopril and prazosin used in combination had a higher efficacy than when the drugs were administered alone in patients being treated for gestational hypertension. Furthermore, pharmacodynamic analysis indicated that captopril and prazosin may be maintained at efficient concentrations in patients with gestational hypertension.

In conclusion, the present study investigated the clinical efficacy of combination treatment with captopril and prazosin in patients with gestational hypertension in a phase-II clinical study. Although previous studies have identified a number of drugs that exhibit direct effects on gestational hypertension, it is important to investigate the overall role of captopril and prazosin in affecting hypertension and hypertension-related

indicators (36,37). The clinical outcomes presented that captopril and prazosin revealed novel options in gestational hypertension management and an increasing number of clinical reports demonstrate promising results. Of note, this clinical analysis indicates that pharmacokinetic interactions of captopril and prazosin are important determinants in optimizing therapy for gestational hypertension. Therefore, clinicians require monitoring the clinical responses and tolerability when patients undergo treatment with captopril and prazosin. Overall, the observations of the present study indicate that patients with gestational hypertension comprehensively treated with captopril and prazosin demonstrated beneficial effects on gestational hypertension.

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Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Authors' contributions

BH designed and performed experiments. XD, HI and JZ analyzed the data.

Ethics approval and consent to participate

The current phase-II study (approval no. HMCH20090236-A4) was performed between February 2009 and August 2011 in accordance with the recommendations in the Guide for Haidian Maternal and Child Healthcare. The present study was approved by the Ethics Committee of Haidian Maternal and Child Health Care Center (Beijing, China). All patients were required to review trial protocols and amendments and to provide written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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