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Review Article

Effects of benazepril and valsartan on renal function, vascular endothelial function and oxidative stress factors in the treatment of renal hypertension

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Abstract: Objective: This study set out to investigate the effects of benazepril and valsartan on renal function (RF), vascular endothelial function (VEF) and oxidative stress (OS) factors in the treatment of renal hypertension (RH). Methods: A total of 109 patients diagnosed with RH and treated in our hospital were selected and included into either an observation group (OG, 61 cases) or a control group (CG, 48 cases) according to different treatment methods. The CG was given valsartan, while the OG was treated with benazepril combined with valsartan. The changes of blood pressure, VEF, RF, OS indexes, urine protein excretion (UPE) rate, endogenous creatinine clearance (ECC) rate and adverse reactions before and after treatment were recorded and compared between the two groups. Results: Compared with the CG, the OG showed significantly reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP), markedly increased NO levels, with notably reduced ET-1 levels, and dramatically declined blood urea nitrogen (BUN) and serum creatinine (Scr) after treatment. In terms of OS indicators, the levels of superoxide dismutase (SOD) were raised remarkably while malondialdehyde (MDA) was lowered significantly in both groups after treatment ($P<0.05$). Inter-group comparison demonstrated that the SOD was clearly higher while the MDA was notably lower in the OG than those in the CG. In addition, it was observed that the UPE rate and the ECC rate in the OG were significantly higher than those in the CG ($P<0.05$). The total incidence of adverse reactions did not differ markedly between the two groups ($P<0.05$). Conclusion: Benazepril combined with valsartan can effectively improve RF and VEF in patients with RH without increasing the incidence of adverse reactions.

Keywords: Benazepril, valsartan, renal hypertension, vascular endothelial function, oxidative stress factor

Preface

Renal hypertension (RH) mainly refers to the increase of blood pressure caused by renal substantial lesions and renal artery lesions; which is called renal hypertension in symptomatic hypertension [1, 2]. According to the survey, renal substantial hypertension accounts for 5%-10% of all hypertension, ranking first in secondary hypertension [3]. Since RH is secondary to renal disease, it will increase the burden on the kidney and aggravate the damage of the kidney, which in turn accelerates the rise of blood pressure, thus forming a vicious cycle and making the disease linger and difficult to cure; so it is particularly important to find appropriate treatment methods for patients with RH [4, 5].

Benazepril, is an angiotensin converting enzyme (ACE) inhibitor, it can reduce blood pressure and urinary protein by blocking angiotensin II, and can also reverse pathological manifestations such as glomerular hyaline degeneration, connective tissue hyperplasia and renal arteriostenosis [6, 7]. Research by Reams et al. found that benazepril was an effective antihypertensive agent for moderately impaired renal function (RF) in patients with hypertension [8]. While valsartan, a novel angiotensin receptor antagonist, is widely used in the treatment of hypertension and has protective effects on the heart and kidney of high-risk patients. Highly selective for angiotensin AT1 as it is, valsartan antagonizes competitively without any excitatory effect, and also inhibits AT-mediated release of aldosterone from adre-

nal globular cells, reducing vasoconstriction and water-sodium retention without affecting the degradation and inactivation of bradykinin; so it has no side effect of cough, does not affect the decline of glomerular filtration rate, and has a good protective effect on the kidney [9-11].

There have been studies on the single application either of valsartan or benazepril in the treatment of hypertension, but research on the efficacy of their combination therapy in RH treatment remains scarce [12, 13]. Therefore, this study compared the efficacy of valsartan monotherapy and valsartan combined with benazepril in the treatment of RH, and analyzed the effects of these two therapies on renal function (RF), vascular endothelial function (VEF), oxidative stress (OS) factor and serum ADMA level, in order to provide clinical reference in treating this disease.

Information and methods

General information

One hundred and nine patients diagnosed with RH in our hospital from January 2017 to March 2019 were selected. According to the treatment methods, 61 patients treated with benazepril combined with valsartan were assigned into the OG, and the other 48 patients given valsartan were included in the CG. The OG consisted of 46 males and 15 females, with an averagely age of (41.67±7.59) years. While in the CG, there were 32 males and 16 females, and the mean age was (40.89±7.83) years. This study was approved by the hospital Medical Ethics Committee, and all patients participated in the study of their own will and signed the informed consent. Inclusion criteria: Patients aged 20 to 70 years, met the diagnostic criteria for RH [14], with Scr of 132-265 mol/L, SBP of 140-180 mmHg, and DBP of 90-110 mmHg. Exclusion criteria: Patients allergic to valsartan and benazepril; Patients with malignant tumors or mental disorders; Patients with acute, severe or malignant hypertension, namely SBP≥180 mmHg, DBP≥110 mmHg, and those with essential hypertension, primary aldosterosis, pheochromocytoma, etc.; Patients with severe neurological or psychiatric diseases; Patients with severe abnormalities in lung, liver and heart function; Patients with cognitive impairment and dysfunction.

Treatment methods

The CG was given valsartan (Huahai Pharmaceutical Co., Ltd., Zhejiang, China, H2018-3126) 160 mg/d. The method was 50 mg/d, twice a day, and the total course of treatment was 2 months. The OG was treated with benazepril (Xinya Pharmaceutical Minhang Co., Ltd., Shanghai, China, H20044840) at 10 mg/d + valsartan 80 mg/d. Patients in both groups were given the prescribed dose in the early morning for 8 weeks.

Outcome measures

Before and after treatment, the blood pressure of patients was measured three times to obtain the average value; the levels of 24-hour urinary protein excretion (UPE) and Scr in the three groups were measured before and after treatment; the adverse reactions of the two groups were compared; the changes of renal function in the two groups were observed before and after treatment; the changes of oxidative stress indices in the two groups before and after treatment were observed. Three ml of peripheral venous blood was collected from patients before and after treatment, and centrifuged at 3000 r/min for 10 min. The obtained plasma was then separated and stored at -70°C for testing. The changes of vascular endothelial function indices in the two groups before and after treatment were observed, and the above plasma samples were determined.

Statistical methods

Statistical analysis was performed using SPSS 22.0. The measurement data were expressed as mean ± standard deviation ($x \pm s$) and verified by the t-test. The counting data was represented in the form of percentage, and compared using χ^2 test. A statistically significant difference was assumed at $P<0.05$.

Results

Baseline data

The basic information, including gender, age, SBP, DBP, 24-hour UPE, Scr concentration, residence, smoking history, and alcohol history did not reveal any marked differences between the two groups ($P>0.05$) (**Table 1**).

Table 1. Basic information of patients in the two groups

Categories	OG (n=61)	CG (n=48)	t/χ^2	P
Gender			1.009	0.315
Male	46 (75.41)	32 (66.67)		
Female	15 (24.59)	16 (33.33)		
Age (years old)	41.67±7.59	40.89±7.83	0.525	0.601
BMI (kg/m^2)	24.72±3.52	23.96±3.64	1.102	0.273
SBP	156.34±8.73	156.44±8.62	0.060	0.953
DBP	99.94±4.12	100.56±4.37	0.759	0.449
24-hour UPE (g/d)	1.94±0.38	1.92±0.41	0.264	0.793
Scr concentration (μmol/L)	198.64±10.77	197.51±9.62		
Residence			0.464	0.496
Urban	37 (60.66)	26 (54.17)		
Rural	24 (39.34)	22 (45.83)		
Smoking history			1.225	0.268
Yes	24 (39.34)	14 (29.17)		
No	37 (60.66)	34 (70.83)		
Alcoholism history			0.482	0.630
Yes	11 (18.03)	7 (14.58)		
No	50 (81.97)	41 (85.42)		

Table 2. Comparison of blood pressure between the two groups before and after treatment

Groups	SBP (mmHg)		DBP (mmHg)	
	Before treatment	After treatment	Before treatment	After treatment
OG (n=61)	156.34±8.73	117.46±6.36*	99.94±4.12	75.26±5.62*
CG (n=48)	156.44±8.62	139.46±7.81*	100.56±4.37	82.41±5.54*
t	0.06	16.21	0.759	6.635
P	0.9525	<0.01	0.4493	<0.01

Note: *indicates P<0.05 compared with that before treatment.

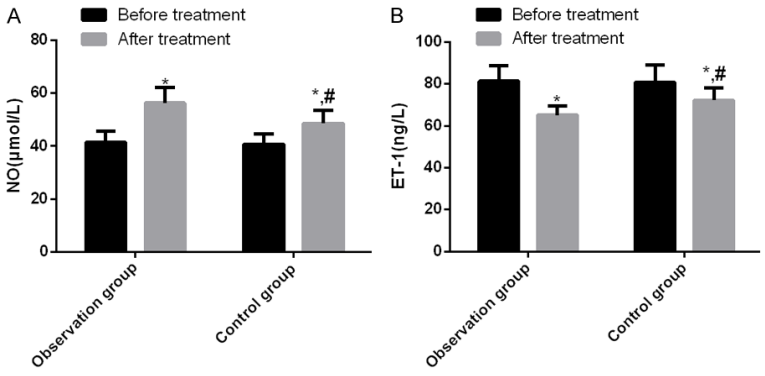

Figure 1. Comparison of vascular endothelial function between the two groups before and after treatment. A. Comparison of NO level changes between the two groups before and after treatment. There was no significant difference in NO level between the two groups before treatment (P>0.05). While the NO level elevated markedly in both groups after treatment, and the NO level in the OG was significantly higher than that in the CG. B. Comparison of ET-1 changes before and after treatment between the two groups. No significant difference was found in ET-1 level between the two groups before treatment (P>0.05), and the ET-1 level significantly decreased in both groups after treatment (P<0.05). The post-treatment ET-1 level in the OG was notably lower than that in the CG (P<0.05). Note: * indicates P<0.05 compared with that before treatment; # indicates P<0.05 compared with the OG after treatment.

Comparison of blood pressure between the two groups before and after treatment

Before treatment, the blood pressure indices of SBP, DBP did not reveal any marked difference between the two groups (P>0.05). While the blood pressure dropped notably in both groups after treatment (P<0.05), and the SBP

Table 3. RF in the two groups before and after treatment

Groups	BUN (mmol/L)		Scr (μmol/L)	
	Before treatment	After treatment	Before treatment	After treatment
OG (n=61)	9.43±0.82	6.32±0.41*	98.43±7.21	64.32±4.26*
CG (n=48)	9.52±0.77	7.64±0.53*	99.21±8.14	82.41±5.54*
t	0.584	14.66	0.53	19.28
P	0.56	<0.01	0.597	<0.01

Note: *indicates P<0.05 compared with that before treatment.

Table 4. Comparison of changes of OS indexes between the two groups before and after treatment

Groups	SOD (μmol/L)		MDA (ng/L)	
	Before treatment	After treatment	Before treatment	After treatment
OG (n=61)	37.54±4.32	68.41±5.67*	17.82±2.31	11.34±1.42*
CG (n=48)	38.06±5.21	51.39±5.26*	18.06±2.51	14.67±1.92*
t	0.570	16.060	0.518	10.410
P	0.570	<0.01	0.605	<0.01

Note: *indicates P<0.05 compared with that before treatment.

and DBP in the OG were significantly lower than those in the CG, (**Table 2**).

Comparison of VEF between the two groups before and after treatment

No clear difference was observed in NO and ET-1 levels between the two groups before treatment (P>0.05). While the level of NO increased dramatically and the level of ET-1 declined notably in both groups after treatment (P<0.05). The NO level in the OG was higher than that in the CG, while the ET-1 level was remarkably lower than that in the CG (**Figure 1**).

RF in the two groups before and after treatment

Comparison of RF revealed that the BUN and Scr levels did not differ significantly between the two groups before treatment (P>0.05), while after treatment, these two were noticeably lower in both groups (P<0.05), and the post-treatment BUN and Scr were lower in the OG than in the CG (**Table 3**).

Comparison of changes of OS indexes between the two groups before and after treatment

The SOD and MDA did not differ significantly between the two groups before treatment (P>0.05). While the post-treatment SOD was remarkably elevated, and the SOD level in the OG was markedly higher than the CG (P<0.05). In terms of post-treatment MDA, it decreased notably after treatment (P<0.05), and the MDA level in the OG was remarkably lower than that in the CG after treatment (P<0.05) (**Table 4** and **Figure 2**).

Comparison of UPE rate and ECC rate between the two groups before and after treatment

There were no marked differences in UPE rate and ECC rate between the OG and CG groups before treatment (P>0.05). While after treatment, the UPE rate in the two groups decreased significantly, and the UPE rate in the OG was noticeably lower than that in the CG (P< 0.05). As to ECC rate, it presented at clearly higher levels in the OG than the CG (P<0.05) (**Figure 3**).

Comparison of adverse reactions between the two groups

The comparison of the occurrence of adverse reactions exhibited that complications occurred in 5 cases (8.2%) in the OG and 4 cases (8.33%) in the CG, and there was no marked difference in the total incidence of adverse reactions between the two groups (P<0.05), (**Table 5**).

Discussion

Renal hypertension (RH) is the main component of secondary hypertension, with the main

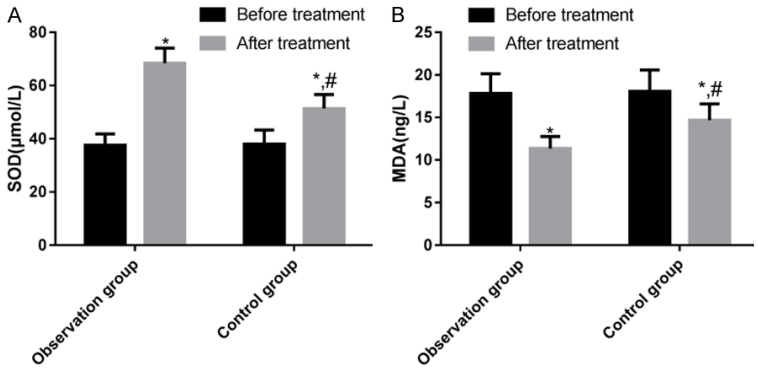

Figure 2. Comparison of changes of oxidative stress indexes between the two groups before and after treatment. A. Comparison of SOD changes between the two groups before and after treatment. There was no significant difference in SOD between the two groups before treatment, but the SOD level increased significantly in the two groups after treatment, and the SOD in the OG was noticeably higher than that in the CG after treatment. B. Comparison of MDA changes in the two groups before and after treatment. The MDA level did not differ significantly between the two groups before treatment ($P>0.05$), while it increased remarkably in both groups after treatment ($P<0.05$), and the MDA in the OG was clearly lower than that in the CG ($P<0.05$). Note: * indicates $P<0.05$ compared with that before treatment; # indicates $P<0.05$ compared with the OG after treatment.

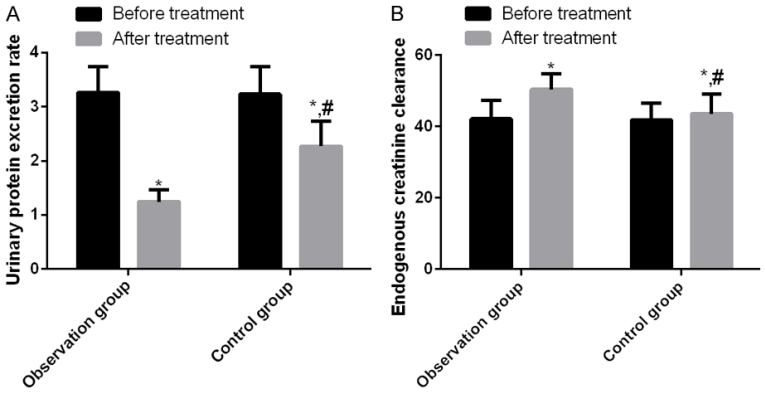

Figure 3. Comparison of UPE rate and ECC rate between the two groups before and after treatment. A. Comparison of UPE rate before and after treatment between the two groups. There was no significant difference in the UPE rate between the two groups before treatment ($P>0.05$), but the UPE rate dropped dramatically in the two groups after treatment ($P<0.05$), and the UPE rate in the OG was significantly lower than that in the CG after treatment ($P<0.05$). B. Comparison of changes in ECC rate before and after treatment between the two groups. Before treatment, there was no significant difference in the ECC rate between the two groups ($P>0.05$). While the ECC rate increased greatly in both groups after treatment ($P<0.05$), and the ECC rate in the OG was noticeably higher than that in the CG ($P<0.05$). Note: * indicates $P<0.05$ compared with that before treatment; # indicates $P<0.05$ compared with the OG after treatment.

clinical manifestations of headache, dizziness, blurred vision, bad temper, palpitations, insomnia, tinnitus, low back pain, hematuria, proteinuria, and edema [15-17]. At present, there are many kinds of clinical drugs for the treatment of RH, whose main purpose is to effectively reduce the patient's blood pressure, delay the progress of the patient's kidney disease and bring down the incidence of cardiovascular and cerebrovascular diseases [18, 19].

Report of the Joint National Committee (JNC) has confirmed that angiotensin converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) can hold the progression of nephropathy in patients with chronic nephropathy and diabetic nephropathy; both of which are strong indications for hypertension in patients with chronic nephropathy [20, 21]. Benazepril is a ACEI drug, which can be hydrolyzed in the liver into active metabolite benazepril, a mercapto-free ACEI that can inhibit the conversion process of angiotensin and slow the degradation of bradykinin, as well as to reduce peripheral vascular resistance [22, 23]. However, in addition to ACE pathway, angiotensin II can also be synthesized by chymoprotein, cathepsin G and other non-ACE pathways, so its effect on RH is not complete. Apart from that, the long-term use of benazepril reduces the level of angiotensin II in the blood and increases the sensitivity of angiotensin receptor, resulting in unfavorable therapeutic effects [24]. While valsartan is an ARB drug that can antagonize angiotensin II receptors specifically, thus completely blocking the RAAS system. Its mechanism of action is to selectively antagonize the AT1 receptor subtype and increase the angiotensin II

Table 5. Comparison of adverse reactions between the two groups

Categories	OG (n=61)	CG (n=48)	χ^2 value	P
Cough	4 (6.56)	3 (6.25)		
Nausea and vomiting	3 (4.92)	1 (2.08)		
Hyperkalemia	1 (1.64)	1 (2.08)		
Total incidence rate	5 (8.2)	4 (8.33)	0.026	0.9795

level, thereby increasing its binding to the AT2 receptor and exerting a positive effect [25, 26]. However, the down side is that valsartan has no effect on the production of bradykinin and can cause hypotension [27]. From the above brief introduction, we can see that the combination therapy of the two can play a complementary role; that is, while blocking the RAAS system, it can also reduce the level of angiotensin, which in turn effectively lowers the blood pressure, thus better playing a role in the improvement of RF and blood pressure. Therefore, this study comparatively analyzed the efficacy of benazepril combined with valsartan with that of valsartan monotherapy in the treatment of RH. The results showed that the post-treatment SBP and DBP in both groups were remarkably reduced (P<0.05), and the SBP and DBP in the OG were significantly lower than those in the CG. In addition, changes in VEF play a vital part in the occurrence and progress of RH [28]. Vascular endothelial cells help to maintain the internal stability of vasoconstriction, and participate in the regulation of inflammation, coagulation and fibrinolysis, vasoconstriction and other functions. Elevated blood pressure in RH will lead to the damage of vascular endothelial cells, which will inevitably result in the imbalance of its synthesized and secreted NO and ET-1, triggering the imbalance of vascular tension regulation, thus forming a vicious circle and aggravating the increase of blood pressure [29]. In this study, NO increased markedly while ET-1 decreased notably in the two groups after treatment, and compared with the CG, the NO level in the OG was clearly higher while the ET-1 was notably lower, indicating that the improvement of blood pressure and vascular endothelial cells in the OG was greater than that in the CG. The imbalance between the endothelium-derived vasodilator and vasoactive active substances caused by vascular endothelial dysfunction or decline is an important cause of renal hypertension. Vascular endothelial dysfunction promotes the occurrence of renal hypertension, while renal hypertension also accelerates the decline of vascular endothelial function. The RF, UPE rate, ECC rate and adverse reactions of the two groups were compared before and after treatment. It was found that, BUN and Scr were noticeably decreased in the two groups after treatment (P<0.05), and these two were lower in the OG than in the CG. The post-treatment UPE rate of the two groups decreased significantly, and the UPE rate in the OG was noticeably lower than that in the CG (P<0.05). As to ECC rate, it raised markedly in the two groups after treatment, and the ECC rate in the OG was significantly lower than that in the CG. No significant difference was noticed in the overall incidence of adverse reactions between the two groups. All these findings suggested that benazepril combined with valsartan could effectively improve RF without increasing the incidence of adverse reactions. Ruggenenti et al. [30] compared the efficacy of benazepril monotherapy and combination therapy of valsartan and benazepril in patients with type 2 diabetes and nephropathy using a prospective randomized controlled trial, and found that the combination therapy did not increase the incidence of adverse events and was more effective in delaying the occurrence of end-stage renal disease.

SOD is a major enzyme that removes free radical system *in vivo*, and its activity level can indirectly reflect the degree of free radical damage to cells [31]. While MDA is mainly a metabolic product of lipid peroxidation damage, which can better mirror the degree of cell oxidative damage [32]. Thus, both SOD and MDA can reflect the degree of peroxidative damage to a certain extent. In this study, SOD was clearly elevated while MDA was clearly declined in the two groups after treatment (P<0.05), and SOD was markedly higher while MDA was notably lower in the OG than in the CG, indicating that the combined treatment of benazepril and valsartan effectively reduced oxidative damage.

Although this study demonstrated the effect of the combined treatment of benazepril and valsartan on RF, VEF, and OS factors in RH, there are still some limitations. The specific mechanism of the treatment in RH has not

been thoroughly analyzed, the prognostic factors of patients with RH have not been studied, and the specific relationship between endothelial function, oxidative stress factors and renal function in patients with renal hypertension has not elucidated. We hope to address these deficiencies in future studies.

In conclusion, the combination therapy of benazepril and valsartan can effectively enhance renal function and vascular endothelial function in renal hypertension without increasing the occurrence of adverse reactions.

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Disclosure of conflict of interest

None.

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