

Original Article

Effects of tanshinone combined with valsartan on hypertensive nephropathy and its influence on renal function and vascular endothelial function

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Abstract: Objective: To investigate the curative effects of tanshinone combined with valsartan on hypertensive nephropathy and its influence on renal and endothelial damage. Methods: A total of 102 hypertensive nephropathy patients who were admitted to our hospital from October 2015 to November 2019 were recruited and divided into a monotherapy group (MG, n=54) and a combined group (CG, n=48), in accordance with the treatment methods. Based on routine treatment, patients in the CG received treatment of tanshinone combined with valsartan, while patients in the MG received treatment of valsartan only. The clinical efficacy, adverse reactions, blood pressure, renal function indexes, vascular endothelial injury indexes, levels of inflammatory cytokines and stress response indexes of the two groups were compared. Results: After treatment, the effective rate in the CG was higher than that in the MG, and the levels of systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine (Scr), blood urea nitrogen (BUN) and microalbumin (mAlb) in the CG were lower than those in the MG ($P < 0.05$). After treatment, endothelin-1 (ET-1) and thromboxane B2 (TXB2) levels in the CG were lower than those in the MG, while nitric oxide (NO) level was higher than that in the MG ($P < 0.05$). No serious adverse reactions occurred in the two groups during treatment, with similar situations ($P > 0.05$). The serum levels of interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor (TNF- α), malondialdehyde (MDA) and advanced oxidation protein products (AOPP) in the CG were lower than those in the MG after treatment, while the level of glutathione peroxidase (GSH-Px) was higher ($P < 0.05$). Conclusion: Tanshinone combined with valsartan can treat hypertensive nephropathy safely and effectively, and reduce renal and endothelial damage by reducing inflammation and oxidative stress.

Keywords: Tanshinone, valsartan, hypertensive nephropathy, clinical treatment

Introduction

Hypertension is one of the most common chronic diseases in the world and its incidence is increasing annually with the development of aging society, the change of diet structure and the gradual improvement of living standards [1]. Hypertension can cause a variety of complications, among which hypertensive nephropathy is the most serious one, and its incidence is increasing with the increased incidence of hypertension, and it has become a common cause of life-threatening health problems [2]. Hypertensive nephropathy occurs mainly due to the long-term influence of hypertension in small renal arteries, resulting in stenosis and

obstruction of their lumen, which in turn leads to a lack of blood supply to the kidney, and ultimately causes irreversible damage to the kidneys and overall renal function [3]. At present, the treatment of hypertensive nephropathy is mostly based on antihypertensive drug therapy, which can obviously control blood pressure, but cannot effectively improve the extrarenal symptoms and delay the progression of chronic renal failure [4, 5]. Therefore, it is still necessary to actively seek better treatment options.

Valsartan is a typical antihypertensive drug used to treat mild to moderate essential hypertension. It can not only antagonize angiotensin II receptor and relax blood vessels, but also pro-

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motes the excretion of water and sodium, so as to achieve the purpose of lowering blood pressure. At the same time, it can also reduce the glomerular filtration rate, reduce protein excretion and delay renal interstitial fibrosis [6, 7]. However, long-term clinical practice has revealed that valsartan alone cannot achieve ideal clinical efficacy in treating hypertensive nephropathy, and other drugs need to be added to enhance the efficacy [8]. Tanshinone is a preparation of active substances extracted from *Salvia miltiorrhiza*, which has many biological activities, such as anti-oxidation, anti-inflammation and improving microcirculation [9, 10]. At present, there is a lot of clinical evidence that tanshinone can safely and effectively treat many diseases including hypertensive nephropathy [11, 12]. As far as we know, there are few and incomplete clinical reports on tanshinone combined with valsartan in the treatment of hypertensive nephropathy currently, and more clinical research data are still needed.

This study explored the efficacy and safety of tanshinone plus valsartan in treating hypertensive nephropathy, aiming at finding a safer and more effective treatment scheme for patients with hypertensive nephropathy.

Materials and methods

Research subjects

In total, 102 hypertensive nephropathy patients admitted to The Affiliated Hospital of Putian University from October 2015 to November 2019 were selected as research subjects. According to the treatment methods, they were divided into a monotherapy group (MG, n=54) and a combined group (CG, n=48). Inclusion criteria: Patients whose medical history and clinical manifestations met the diagnostic criteria related to essential hypertension [13], patients whose renal function examination met the diagnostic criteria related to chronic kidney disease [14], patients aged from 18 to 65 years, and patients and their families who had signed informed consent forms. Exclusion criteria: patients who had incomplete clinical data, severe heart, liver and lung dysfunction, contraindications of drugs used, patients who received treatment of tanshinone, angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor antagonist

(ARB) four weeks before enrollment, patients whose renal damage was caused by secondary hypertension, primary glomerular disease or other reasons, patients who had poor treatment compliance or were unable to communicate normally, and pregnant patients. This study was in line with the *Declaration of Helsinki* and approved by the Ethics Association of our hospital.

Treatment methods

Both groups of patients received routine treatment for hypertensive nephropathy, including ACEI, calcium antagonist and other antihypertensive drugs to control blood pressure. In addition to routine treatment, patients in the MG were treated with valsartan, and the details were as follows: valsartan capsules taken orally, 80 mg/time, once a day, for two weeks. In the CG, tanshinone injection (intravenous, 60 mg/time, once a day) was added on the basis of the MG. Both groups of patients were treated continuously for two weeks.

Outcome measures

Detection of blood pressure and renal function indexes: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded before treatment and after 2-week treatment. Five ml of fasting elbow venous blood was taken from the two groups of patients in the morning before treatment and after 2-weeks of treatment, it was frozen in the deep cryogenic freezer for later use after anticoagulation. Meanwhile, 24 h later urine of patients was taken and stored in the deep cryogenic freezer for later use. The contents of serum creatinine (Scr), blood urea nitrogen (BUN) and microalbumin (mAlb) in samples were determined by automatic biochemical analyzer.

Detection of endothelial function indexes and inflammatory cytokines: The endothelial function indexes and inflammatory cytokines in serum samples of patients in the two groups were determined using enzyme-linked immunosorbent assay (ELISA). The former included endothelin-1 (ET-1), thromboxane B2 (TXB2) and serum nitric oxide (NO), and the latter included interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor (TNF- α).

Detection of oxidative stress indexes: The contents of glutathione peroxidase (GSH-Px), malo-

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Table 1. Comparison of general data of patients in the two groups ($\bar{x} \pm sd$), [n (%)]

Group	Monotherapy group (n=54)	Combined group (n=48)	χ^2/t	p
Gender			0.844	0.358
Female	21 (38.89)	23 (47.92)		
Male	33 (61.11)	25 (52.08)		
Age (years)	58.69±7.86	59.38±7.23	0.460	0.647
BMI (kg/m ²)	23.21±2.33	23.66±2.18	1.003	0.318
Course of hypertension (years)	9.89±5.95	10.21±5.68	0.782	0.277
Smoking history			0.274	0.601
Present	23 (42.59)	18 (37.50)		
Absent	31 (57.41)	30 (62.50)		
Alcohol abuse history			0.429	0.512
Present	18 (33.33)	19 (39.58)		
Absent	36 (66.67)	29 (60.42)		
Work			1.316	0.251
In work	30 (55.56)	32 (66.67)		
Out of work	24 (44.44)	16 (33.33)		

ndialdehyde (MDA) and advanced oxidation protein products (AOPP) in serum were determined by radioimmunoassay. The kit was provided by Nanjing Jiancheng Bioengineering Institute.

Record of clinical efficacy evaluation and adverse reactions: The clinical efficacy of the two groups of patients was evaluated after treatment. Marked response: after treatment, patients' blood pressure returned to normal level or DBP decreased ≥ 20 mmHg, and the renal function was normal or urine protein disappeared. Effective response: after treatment, patients' blood pressure basically returned to normal, or DPB decreased less than 20 mmHg, SBP decreased less than 30 mmHg, and the renal function improved significantly or urinary protein decreased significantly. No response: after treatment, patients' blood pressure did not reach normal standards, or the renal function did not improve, and proteinuria did not decrease or even worsened. Adverse reactions of patients during treatment were recorded, including nausea, palpitation, drowsiness and loss of appetite.

Statistical analysis

SPSS 21.0 software package was utilized for statistical analysis, and GraphPad Prism 7 was used for illustrations of the data. Chi-square test was utilized for comparison of counting

data. Independent t-test was utilized for comparison of measurement data between the two groups, and paired t test was utilized for intra-group comparison before and after treatment. One-way analysis of variance was used to compare the measurement data of two groups or more, and the correctness of the statistical values was verified by back testing, with $P < 0.05$ being statistically significant.

Results

Comparison of clinical data

There was no remarkable difference between the two groups in general data such

as gender, age, BMI, course of hypertension, smoking history, alcohol abuse history and ability to work ($P > 0.05$). More details were shown in **Table 1**.

Comparison of blood pressure indicators

The levels of SBP and DBP were detected, and there was no remarkable difference between the two groups before treatment ($P > 0.05$), but the two levels decreased significantly in both groups after treatment, and were lower in the CG than in the MG ($P < 0.05$). More details were shown in **Figure 1**.

Comparison of renal function indexes

Detection of renal function indexes showed that there was no considerable difference in Scr, BUN and mAlb levels between the two groups before treatment ($P > 0.05$). After treatment, all the three levels were notably decreased in the two groups, and were lower in the CG than in the MG ($P < 0.05$). More details were shown in **Figure 2**.

Comparison of vascular endothelial function indexes

Detection of vascular endothelial function indexes showed that there was no remarkable difference in ET-1, TXB2 and NO levels between the two groups before treatment ($P > 0.05$).

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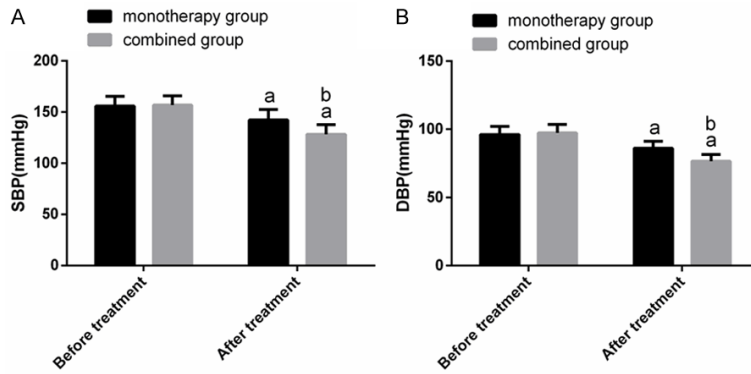


Figure 1. Comparison of blood pressure indicators. A. Comparison of SBP between the two groups before and after treatment. B. Comparison of DBP between the two groups before and after treatment. Notes: a represents the comparison between the same group and before treatment, $P < 0.05$. b represents the comparison with the monotherapy group after treatment, $P < 0.05$.

After treatment, ET-1 and TXB2 levels decreased remarkably in both groups, while the level of NO increased ($P < 0.05$). Compared with the MG, the levels of ET-1 and TXB2 in the CG were lower, but the level of NO was higher, with a statistically significant difference ($P < 0.05$). More details were shown in **Figure 3**.

Comparison of clinical efficacy

By evaluating the clinical efficacy of the two groups, it was found that the total effective rate of the CG was evidently higher than that of the MG (91.67% vs. 75.93%), and the difference was statistically significant ($P < 0.05$). More details were shown in **Table 2**.

Occurrence of adverse reactions

By recording the adverse reactions of the two groups of patients during treatment, it was found that no serious malignant adverse reactions occurred in either group, that they could be cured by symptomatic treatment or healed spontaneously, and that the occurrence of adverse reactions was similar in both groups, with no statistical difference ($P > 0.05$). More details were shown in **Table 3**.

Comparison of inflammatory cytokines

The levels of serum inflammatory cytokines showed no remarkable difference in IL-6, CRP and TNF- α between the two groups before treatment ($P > 0.05$). All three levels were sig-

nificantly decreased in the two groups after treatment, and were lower in the CG than MG ($P < 0.05$). More details were shown in **Figure 4**.

Detection of oxidative stress indexes

Before treatment, the levels of oxidative stress indexes showed that there was no remarkable difference in MDA, GSH-Px and AOPP levels between the two groups ($P > 0.05$). After treatment, the levels of MDA and AOPP in serum reduced notably in both groups, and the level of GSH-Px increased ($P < 0.05$).

Compared with the MG after treatment, MDA and AOPP in the CG were lower, and GSH-Px was higher ($P < 0.05$). More details were shown in **Figure 5**.

Discussion

Pathological manifestations of patients with hypertensive nephropathy are mainly renal vascular sclerosis and glomerular hyaline degeneration, thereby leading to irreversible renal failure, therefore, the main treatment direction of this disease is to select reasonable drugs to control blood pressure and protect renal function [15, 16]. This study explored the curative effects and safety of tanshinone combined with valsartan in treating hypertensive nephropathy, and found that the effective rate of treatment in the CG was higher than that in the MG, and the occurrence of adverse reactions of the two groups were similar during treatment, with no serious malignant adverse reactions, and all of which could be cured by symptomatic treatment or were healed spontaneously. The above results suggest that tanshinone combined with valsartan can be used safely and effectively in the treatment of hypertensive nephropathy.

Controlling blood pressure level is the main method to inhibit the progression of hypertensive nephropathy. Previous studies have shown that tanshinone can play the role of a vasodilator to relax blood vessels and increase blood circulation, thus lowering blood pressure. In

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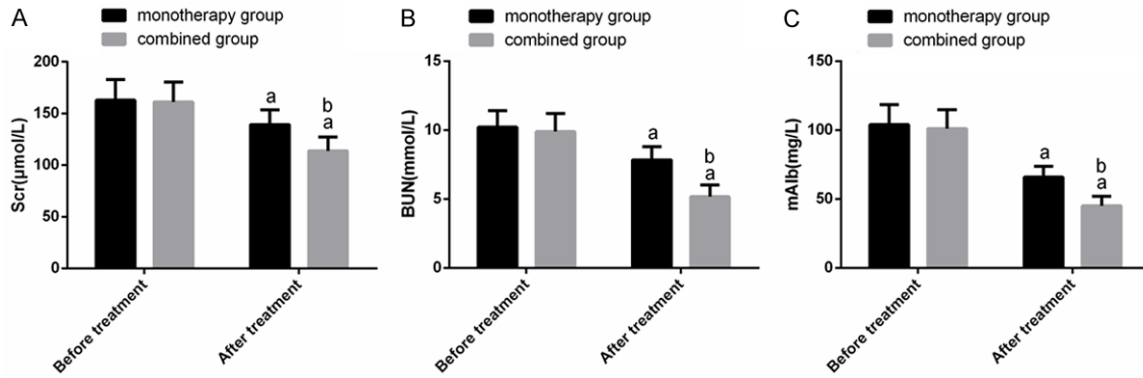


Figure 2. Comparison of renal function indexes. A. Comparison of Scr level between the two groups before and after treatment. B. Comparison of BUN level between the two groups before and after treatment. C. Comparison of mAlb level between the two groups before and after treatment. Notes: a represents the comparison between the same group and before treatment, $P < 0.05$. b represents the comparison with the monotherapy group after treatment, $P < 0.05$.

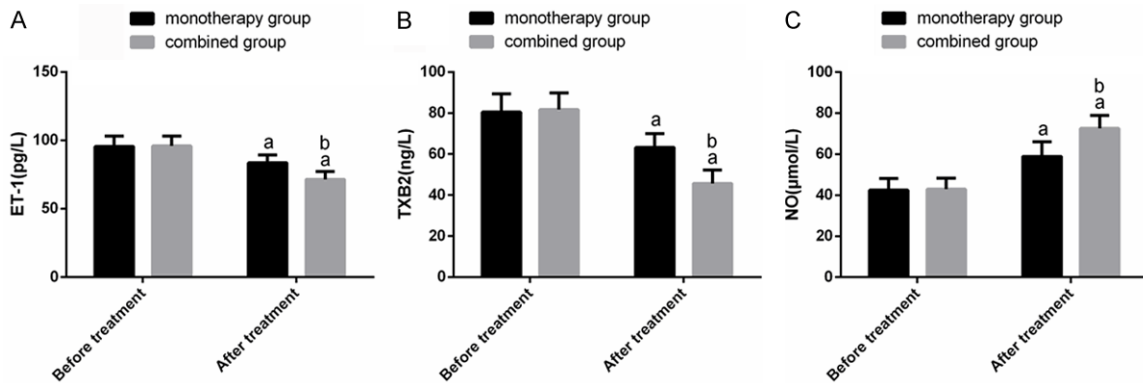


Figure 3. Comparison of vascular endothelial function indexes. A. Comparison of ET-1 level between the two groups before and after treatment. B. Comparison of TXB2 level between the two groups before and after treatment. C. Comparison of NO level between the two groups before and after treatment. Notes: a represents the comparison between the same group and before treatment, $P < 0.05$. b represents the comparison with the monotherapy group after treatment, $P < 0.05$.

Table 2. Comparison of clinical efficacy [n (%)]

Group	Marked response	Effective response	No response	Total effective rate
Monotherapy group (n=54)	12 (22.22)	29 (53.70)	13 (24.07)	41 (75.93)
Combined group (n=48)	18 (37.50)	26 (54.17)	4 (8.33)	44 (91.67)
χ^2	-	-	-	4.533
p	-	-	-	0.033

Table 3. Comparison of adverse reactions of patients during treatment [n (%)]

Group	Monotherapy group (n=54)	Combined group (n=48)	χ^2	P
Nausea	2 (3.70)	3 (6.25)	0.353	0.552
Palpitation	1 (1.85)	2 (4.17)	0.477	0.490
Drowsiness	2 (3.70)	2 (4.17)	0.014	0.904
Loss of appetite	2 (3.70)	4 (8.33)	0.984	0.321
Total number of people affected	7 (12.96)	11 (22.92)	1.732	0.188

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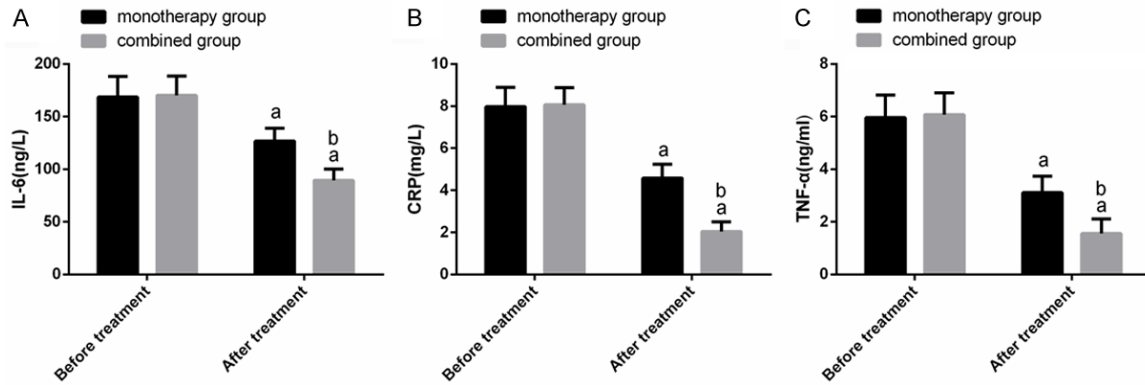


Figure 4. Comparison of inflammatory cytokines. A. Comparison of IL-6 level between the two groups before and after treatment. B. Comparison of CRP level between the two groups before and after treatment. C. Comparison of TNF- α level between the two groups before and after treatment. Notes: a represents the comparison between the same group and before treatment, $P < 0.05$. b represents the comparison with the monotherapy group after treatment, $P < 0.05$.

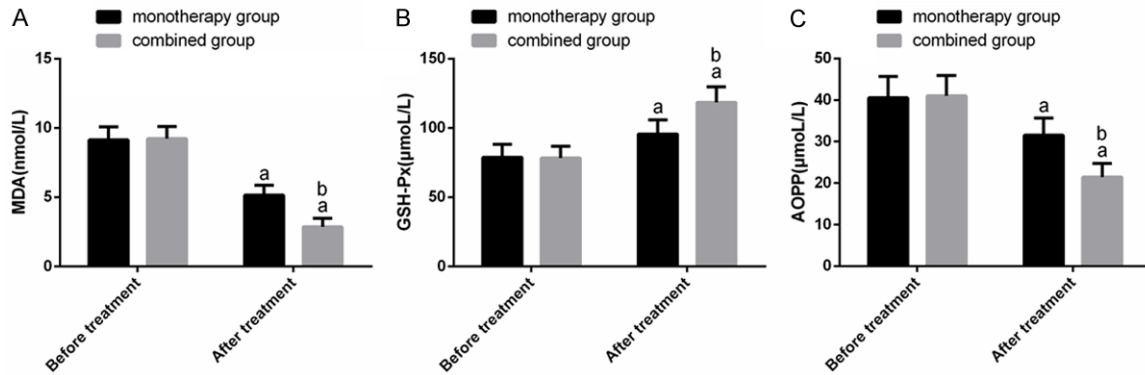


Figure 5. Detection of oxidative stress indexes. A. Comparison of MDA level between the two groups before and after treatment. B. Comparison of GSH-Px level between the two groups before and after treatment. C. Comparison of AOPP level between the two groups before and after treatment. Notes: a represents the comparison between the same group and before treatment, $P < 0.05$. b represents the comparison with the monotherapy group after treatment, $P < 0.05$.

addition, tanshinone IIA sodium sulfonate, which is the main component of tanshinone, can effectively increase the activity and level of PAI-1 in blood, thus exerting fibrinolysis in blood [17, 18]. Valsartan, an ACEI antihypertensive drug, has a completely different antihypertensive mechanism from tanshinone, and may have a synergistic effect. This study found that SBP and DBP levels in the CG were lower than those in the MG after treatment, suggesting that tanshinone combined with valsartan can control blood pressure more effectively when compared with valsartan alone. Hypertension can lead to long-term high pressure in glomerulus, resulting in impaired vascular endothelial cell function, increased renal vascular resistance, thus causing renal ischemia

and accelerating the occurrence and development of hypertensive nephropathy [19]. Compared with the MG, the levels of Scr, BUN, mAlb, ET-1, TXB2 in the CG after treatment were lower, while its NO level was higher, indicating that tanshinone combined with valsartan can effectively help patients with hypertensive nephropathy control blood pressure and improve renal function and endothelial function.

Inflammation and oxidative stress are the characteristics of chronic renal disease. They are inseparable and can influence each other, driving the progress of chronic renal disease together [20]. Oxidative stress can not only lead to apoptosis of podocytes and subsequent

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segmental glomerulosclerosis, but also induce the accumulation of myofibroblasts in kidney and the remodeling of extracellular matrix of tubulointerstitial, leading to renal damage [21]. Inflammatory reactions will cause endothelial dysfunction in hypertensive patients [22]. Therefore, many scholars believe that the use of anti-inflammatory drugs and antioxidants is one of the ways to treat hypertensive nephropathy [23, 24]. Tanshinone, as an agent with both antioxidant and anti-inflammatory effects, may be effective in reducing inflammation and oxidative stress in patients with hypertensive nephropathy. In this study, the inflammatory cytokines and oxidative stress markers in the serum of patients were detected, and it was found that IL-6, CRP, TNF- α , MDA and AOPP levels decreased after treatment, while GSH-Px level increased, and the first five indexes in the CG were lower than those in the MG, while the level of GSH-Px was higher than that in MG. The results above indicate that tanshinone combined with valsartan can effectively reduce inflammation and oxidative stress in patients with hypertensive nephropathy, which was analyzed to be directly related to the anti-inflammatory and antioxidant free radical properties of tanshinone. It also explains why the indexes of renal function and vascular endothelial function of patients were better in the CG than in the MG.

There are still some shortcomings in this study. For example, the subjects included in this study are all aged around 60. In view of the fact that patients with hypertensive nephropathy are getting younger, we believe that it is necessary to explore the efficacy of tanshinone combined with valsartan in the treatment of younger patients. Besides, the best dose of the two combined in treating hypertensive nephropathy was not explored. What's more, there is no economic analysis of the treatment cost of the two treatment methods. These deficiencies are expected to be supplemented in future studies.

To sum up, tanshinone combined with valsartan can treat patients with hypertensive nephropathy safely and effectively, and reduce the damage of the kidney and the endothelium by reducing inflammation and oxidative stress.

Disclosure of conflict of interest

None.

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