Effect of valsartan combined with beraprost sodium on renal function, blood coagulation function and endothelial injury in patients with hypertension and early renal damage

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ABSTRACT

Objective: To analyze the effect of valsartan combined with beraprost sodium on renal function, blood coagulation function and endothelial injury in patients with hypertension and early renal damage. Method: A total of 200 patients with hypertension and early renal damage were divided into observation group (n=97) (received valsartan combined with beraprost sodium therapy) and control group (n=103) (received valsartan therapy alone) according to different treatment methods. Differences in renal function, blood coagulation function and endothelial injury index levels were compared between the two groups after treatment. Results: Eight weeks after treatment, CysC, β 2-MG, Fib, D-D, MPV contents in plasma and UACR, α 1-MG, NAG contents in urine of observation group were significantly lower than those of control group, ATIII contents in plasma were significantly higher than that of control group; lower limb artery Vmax value of observation group was significantly higher than those of control group, carotid artery IMT value lower limb artery RI, FMD and NMD value were significantly lower than those of control group. Conclusions: Valsartan combined with beraprost sodium can protect the renal function and avoid further disease progression in patients with hypertension and early renal damage, and it is an ideal solution to disease treatment.

1. Introduction

Poor control of hypertension in patients can cause other important viscera damage with the duration prolongation, and hypertensive renal injury is the most common. Once there is kidney injury in patients with hypertension, it will exacerbate blood pressure fluctuations and increase the difficulty in hypertension treatment, and at the same time, poor control of blood pressure will further damage the kidney function and form a vicious circle [1,2]. Renal dysfunction in patients with hypertension and early renal damage is still in the reversible phase, and active intervening measures are expected to reverse the process of renal function decline and optimize the overall treatment outcome. Valsartan is a clinical common potent antihypertensive drug that prevents angiotensin II receptor from lowering the blood pressure; beraprost sodium is prostacyclin analogue that plays a dual role of anti-platelet and dilating blood vessels through activating adenyly cyclase, inhibiting calcium ions to enter into cells and so on[3]. In the study, valsartan and beraprost sodium were used together in the treatment of patients with hypertension and early renal damage, and the effect of the treatment compatibility on patients’ renal function, blood coagulation function and endothelial injury was mainly elaborated.

2. Materials and methods

2.1. General information

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A total of 200 patients with hypertension and early renal damage treated in our hospital between December 2010 and December 2015 were included, and the inclusion criteria were: 1) with primary hypertension; 2) with urinary albumin excretion rate (UAER) and urinary albumin level in accordance with the WHO-established criteria for early renal damage; 3) patients signed the informed consent; 4) with complete data. Exclusion criteria were: 1) with diabetes, severe infection and other diseases that might damage the kidney function; 2) with malignant tumor diseases; 3) with severe cardiovascular and cerebrovascular diseases, 4) allergic to valsartan or/and beraprost sodium. 200 patients conformed to the above criteria and were included in the study, and the research process and the obtained data were retrospectively analyzed. According to different treatment methods, they were divided into observation group (n=97) and control group (n=103). Control group included 54 male cases and 49 female cases, they were 48-72 years old and (63.28±7.11) years old in average, and the course of hypertension was 6-21 years and (12.73±4.95) years in average; observation group included 52 male cases and 45 female cases, they were 50-74 years old and (64.63±7.09) years old in average, and the course of hypertension was 7-25 years and (12.96±4.88) years in average. The two groups of patients showed no statistically significant difference in the distribution of gender, age and course of hypertension (P>0.05) and could be subsequently compared.

2.2. Treatment methods

Control group received valsartan therapy alone, oral administration of valsartan capsules (80 mg/capsule, Beijing Novartis Pharmaceutical Ltd., approved by H20040217), 80 mg/time, 1 time/day. Observation group received valsartan combined with beraprost sodium therapy, which was as follows: oral administration of beraprost sodium tablets (20 µg/tablet, Beijing Tide Pharmaceutical Co., LTD., approved by H20083588), 40 µg/time, 3 times/day. Usage and dosage of valsartan were the same as those of control group. Eight weeks was a course of treatment, and treatment lasted at least one course.

2.3. Renal function and blood coagulation function

After treatment, 5 mL of peripheral venous blood was collected from patients in the morning and centrifuged at room temperature to get plasma and cryopreserve it at -70℃ for test; urine was collected from patients 24 hours after treatment, and the urine sediment was removed for test. (1) Renal function indexes: the urine protein and creatinine content were detected by full-automatic biochemical analyzer and urinary albumin-to-creatinine ratio (UACR) was calculated, enzyme-linked immunosorbent assay kit was used to determine plasma cystatin C (CysC), β 2 microglobulin (β 2-MG) and urine 1 microglobulin (α 1-MG) content, and rate method was used to determine urinary N-acetyl-β-D-glucosaminidase (NAG) levels. (2) Blood coagulation function indexes: full-automatic blood coagulation analyzer was used to determine the plasma fibrinogen (Fib) and antithrombin III (ATIII), ELISA method was used to determine D-dimer (D-D) and laser scattering technique was used to determine mean platelet volume (MPV).

2.4. Endothelial function

After treatment, color Doppler ultrasonic instrument was used to determine the endothelial function of two groups of patients, the probe frequency was set to 5 MHz, and during measurement, the Doppler sampling container was placed in central artery, and the Angle between the acoustic beam and the blood flow was less than 60°. The patients took supine position, carotid intima-media thickness (IMT) was measured at first, then they abduced lower limbs to expose popliteal artery (PA), anterior tibial artery (ATA) and posterior tibial artery (PTA), PA, ATA and PTA diameter (D0), ATA peak flow velocity (Vmax) and resistance index (RI) were measured under resting state, sphygmomanometer cuff was used to add the pressure to 300 mmHg and deflated after 5 min, the PA, ATA and PTA diameter (D1) were measured again after 60 s, patients took 15 min of rest for the blood vessels to return to basic state and then received sublingual administration of nitroglycerin 0.5 mg, and after 4 min, the brachial artery diameter (D2) was measured again. Flow-mediated dilation (FMD) equaled to (D2-D0)/D0, and nitroglycerin-mediated dilation (NMD) equaled to (D2-D1)/D1.

2.5. Statistical methods

The obtained data was input in SPSS21.0 for analysis and processing, measurement data was in terms of mean±standard deviation, comparison between two groups was performed by t test and P<0.05 was the standard of statistical significant differences.

3. Results

3.1. Renal function indexes of two groups

Before treatment, CysC and β 2-MG content in plasma were not significantly different between two groups; after 8 weeks of treatment, CysC and β 2-MG content in plasma of both groups were significantly lower than those before treatment, and CysC (P<0.05) and β 2-MG content in plasma of observation group after treatment were significantly lower than those of control group (P<0.05) (Table 1). Before treatment, UACR, α 1-MG and NAG content in urine were not significantly different between two groups; after 8 weeks of treatment, UACR, α 1-MG and NAG content in urine of both groups were significantly lower than those before treatment, and UACR, α 1-MG (P<0.05) and NAG content in urine of observation group after treatment were significantly lower than those of control group (Table 2) (P<0.05).

Table 1

Comparison of renal function indexes in plasma between two groups (mg/L).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Case No.</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CysC</td>
<td>β 2-MG</td>
</tr>
<tr>
<td>Observation group</td>
<td>97</td>
<td>2.14±0.29</td>
<td>3.85±0.51</td>
</tr>
<tr>
<td>Control group</td>
<td>103</td>
<td>2.21±0.27</td>
<td>3.77±0.48</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>0.247</td>
<td>0.185</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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</tbody>
</table>
3.2. Blood coagulation function of two groups

Fib, D-D and MPV levels in plasma of observation group were significantly lower than those of control group while AT[II] level was significantly higher than that of control group (P<0.05), shown in Table 3.

3.3. Endothelial function indexes of two groups

Lower limb artery Vmax value of observation group was significantly higher than those of control group, carotid artery IMT value lower limb artery RI, FMD and NMD value were significantly lower than those of control group (P<0.05), shown in Table 4.

4. Discussion

Renal injury caused by hypertension is one of the leading causes of chronic renal failure, and without timely treatment, it can lead to irreversible kidney function damage and progressive renal failure. Relevant statistics show that there are nearly 200 million patients with hypertension in our country, those complicated with renal complications account for more than 10%, and those who eventually die of renal failure account for 1%-2.5%[4]. So, for hypertensive patients with renal impairment, early intervening in the disease and reversing its progression is the only way to optimize patient’ outcome.Valsartan is the drug that is recommended by many scholars and can be used for treatment of patients with hypertension and renal injury, valsartan is AT receptor antagonist, it can competitively antagonize I receptor without any agonistic effect, and it has been found in hypertensive rat models that valsartan treatment can maintain blood pressure levels in an ideal state for a long time[5]. But for hypertensive patients with renal injury, antihypertensive treatment alone can inhibit the further damage of hypertension on renal function, but its effect on actively optimizing kidney function and avoiding continued progression of renal injury is less. Beraprost sodium has been commonly applied in the treatment of patients with renal insufficiency, it is proved to be able to improve the glomerular ultrafiltration, reduce albumin and so on, and clinical scholars recommend adding beraprost sodium in the treatment of patients with hypertension and renal injury[6,7].

In the study, valsartan and beraprost sodium were used together, and the effect of drug combination on improving the condition of patients with hypertension and early renal damage was mainly analyzed. The most intuitive manifestations of renal injury in patients with hypertension are abnormal renal function indexes in blood and urine. Hypertension with early renal damage is characterized by glomerular filtration function and proximal convoluted tubule reabsorption function damage, and accompanied by the destruction of the proximal convoluted tubule epithelial cells. CysC is cysteine proteinase inhibitor, it is stably produced by the karyocytes in the body, it can freely cross through the glomerular filtration membrane and be reabsorbed, metabolized and degraded in the proximal convoluted tubules, and glomerular filtration function damage will cause the increased CysC content in plasma and be accompanied by protein leakage from glomeruli and increased urine protein content[8,9]; proximal convoluted tubule reabsorption function damage will cause the β 2-MG excretion disorder, characterized by increased β 2-MG content in plasma; NAG and α 1-MG are abundant in renal proximal tubule epithelium, and hypertension-induced renal proximal convoluted tubule damage will lead to increased NAG and α 1-MG protein in urine[10,11]. In the study, renal function-related index values in circulating blood and urine of the two groups were detected after treatment, and the results showed that CysC and β 2-MG content in plasma as well as UACR, α 1-MG and NAG content in urine of observation group after treatment were significantly lower than those of control group. This

### Table 2
Comparison of renal function indexes in urine between two groups before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Case No.</th>
<th>Before treatment UACR (µmol/L)</th>
<th>α 1-MG (mg/L)</th>
<th>NAG (mg/L)</th>
<th>After treatment UACR (µmol/L)</th>
<th>α 1-MG (mg/L)</th>
<th>NAG (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>97</td>
<td>29.34±3.52</td>
<td>16.49±2.26</td>
<td>7.39±0.93</td>
<td>12.42±1.85</td>
<td>8.38±1.02</td>
<td>3.14±0.52</td>
</tr>
<tr>
<td>Control group</td>
<td>103</td>
<td>30.12±4.08</td>
<td>15.93±2.14</td>
<td>7.51±0.87</td>
<td>19.58±2.29</td>
<td>12.52±1.68</td>
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<tr>
<td>t</td>
<td></td>
<td>0.392</td>
<td>0.458</td>
<td>0.257</td>
<td>5.382</td>
<td>8.293</td>
<td>6.182</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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</tbody>
</table>

### Table 3
Comparison of blood coagulation function indexes in plasma between two groups after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Case No.</th>
<th>Fib (g/L)</th>
<th>ATIII (g/L)</th>
<th>D-D (µg/L)</th>
<th>MPV (fl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>97</td>
<td>2.87±0.34</td>
<td>90.25±9.17</td>
<td>168.39±18.52</td>
<td>9.95±1.02</td>
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<tr>
<td>Control group</td>
<td>103</td>
<td>3.56±0.41</td>
<td>85.48±9.03</td>
<td>191.41±21.64</td>
<td>10.76±1.89</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>5.834</td>
<td>6.192</td>
<td>8.293</td>
<td>6.384</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Table 4
Comparison of endothelial function indexes between two groups after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Case No.</th>
<th>IMT (mm)</th>
<th>Vmax(cm/s)</th>
<th>RI</th>
<th>FMD</th>
<th>NMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>97</td>
<td>1.18±0.14</td>
<td>47.38±5.12</td>
<td>0.95±0.08</td>
<td>5.43±0.62</td>
<td>7.85±0.82</td>
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<tr>
<td>Control group</td>
<td>103</td>
<td>1.26±0.17</td>
<td>40.92±4.76</td>
<td>1.07±1.12</td>
<td>7.01±0.78</td>
<td>9.76±0.95</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>5.382</td>
<td>8.293</td>
<td>6.182</td>
<td>7.384</td>
<td>8.253</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
means that valsartan combined with beraprost sodium has optimized the glomerular and renal tubular function, which is speculated to be because that the antihypertensive effect of valsartan and the vascular dilation effect of beraprost sodium can improve glomerular capillary diameter and glomerular blood flow.

Study has shown that there has been prethrombotic state in patients with hypertension and early renal damage, which is mainly associated with blood coagulation system activation, anticoagulant system function weakening, stimulating hyperfibrinolysis, etc. Persistent progression of hypercoagulable state in patients can affect the renal hemorheology, reduce the renal blood supply and further result in the decline in kidney function. In the study, the levels of systemic coagulation indexes in patients were detected after treatment, and the results showed that Fib, D-D and MPV levels in plasma of observation group were lower while ATⅢ level was higher after treatment. Studies have found that Fib is positively correlated with the blood pressure levels in patients with hypertension, D-D can directly reflect the blood’s coagulation and fibrinolysis function, and high level of D-D indicates the redoubled risk of thromboembolism in patients; MPV is the index of platelet activation, and high level of MPV indicates that bone marrow megakaryocytes are in the proliferation hyperfunctional stage and platelet adhesion and aggregation function are enhanced; ATⅢ is the important natural anticoagulant agent in the human body, it is the inhibitor of blood coagulation factors X, XI, IX, X and other proteases that contain serine, and it forms the ATⅢ-thrombin complex to make the enzyme inactivate and play the role of inhibiting blood coagulation and fibrinolysis[12,13]. The above results indicate that valsartan combined with beraprost sodium treatment can significantly reduce the hypercoagulable state in patients with hypertension and early renal damage, which is mainly because that the beraprost sodium acts on the prostacyclin receptor of platelet and exerts antiplatelet effect.

Persistent hypertension can lead to endothelial injury, thickened artery intima and increased blood flow resistance, and eventually lead to the luminal stenosis or occlusion. Foreign study has found that hypertensive patients with long-term poor blood pressure control are with the decreased renal vascular blood flow velocity, increased vascular wall stiffness and other phenomena of vascular endothelial damage[14]. Numerous domestic studies have also found that hypertensive patients with complications are mostly accompanied by carotid artery intima thickening, and the probability of long-term cerebrovascular diseases in such patients is far higher than that in patients with good blood pressure control. Hypertensive patients with early renal damage are mostly with poor blood pressure control, and the probability of combination of vascular endothelial function damage is extremely great[15]. In the study, color Doppler ultrasound was applied to detect the vascular blood flow velocity and resistance as well as vasomotor function of the two groups after treatment, and it was found the lower limb artery Vmax value of observation group were higher while carotid artery IMT value and lower limb artery RI, FMD and NMD value were lower after treatment, showing that after valsartan combined with beraprost sodium treatment, the macrovascular intima thickness decreases, lower extremity artery blood flow velocity increases and the vasomotor function is optimized.

To sum up, it is concluded as follows: valsartan combined with beraprost sodium can protect the renal function and avoid further disease progression in patients with hypertension and early renal damage, and it’s worth popularization and application in clinical practice in the future.

References