Effect of nifedipine controlled-release tablet combined with valsartan treatment on serological indicators in type 2 diabetic nephropathy patients with hypertension

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ABSTRACT

Objective: To analyze the effect of nifedipine controlled-release tablet combined with valsartan treatment on serological indicators in type 2 diabetic nephropathy patients with hypertension.

Methods: A total of 96 cases of type 2 diabetic nephropathy with hypertension were included in the research, and according to different clinical treatment plans, all patients were randomly divided into nifedipine group, valsartan group and combined treatment group, 32 cases in each group. After different treatment, peripheral venous blood was drawn to detect the differences in values of serum renal function-related indicators, renal blood vessel-related indicators and illness-related indexes.

Results: Serum CysC, Hcy, Chemerin and RBP-4 values of combined treatment group were significantly lower than those of nifedipine group and valsartan group (P<0.05); serum COMP, TM, vWF and mALB values of combined treatment group were significantly lower than those of nifedipine group and valsartan group while Ang-1 and Ang-2 values were higher than those of nifedipine group and valsartan group (P<0.05); serum Ghrelin, TGF-β1 and ALD values of combined treatment group were significantly lower than those of nifedipine group and valsartan group while APN and miR-21 values were higher than those of nifedipine group and valsartan group (P<0.05).

Conclusions: Nifedipine controlled-release tablet combined with valsartan treatment of type 2 diabetic nephropathy patients with hypertension can effectively optimize the illness and inhibit the progression of renal failure, and it has positive clinical significance.

1. Introduction

There are many type 2 diabetic nephropathy patients in clinical practice, and most are patients that have with more than 10-year duration of diabetes and poorly controlled blood glucose. Hypertension is an important factor aggravating diabetes and contributing to the diabetic nephropathy, and for type 2 diabetic nephropathy patients with hypertension, blood pressure must be positively controlled so as to lay a good foundation for the treatment of hyperglycemia and renal dysfunction[1]. Both nifedipine controlled-release tablet and valsartan are commonly used drugs for clinical treatment of hypertension, nifedipine can inhibit the free Ca²⁺ influx and relax vascular smooth muscle while expand peripheral small artery and reduce peripheral vascular resistance. Valsartan is angiotensin II receptor blocker, which inhibits vascular contraction and blood pressure rise through selective combination with it[2]. Given the refractoriness and harmfulness of the blood pressure in type 2 diabetic nephropathy patients with hypertension, clinical scholars suggest the application of antihypertensive drugs with different mechanism of action in order to enlarge curative effect. In the research, the effect of nifedipine controlled-release tablet combined with valsartan treatment on serological indicators in type 2 diabetic nephropathy patients with hypertension was mainly analyzed, hereby reported as follows.
2. Materials and methods

2.1. General information

A total of 96 cases of type 2 diabetic nephropathy with hypertension were included in the research, hospitalization time interval was from July 2009 to June 2015, the research contents were approved by the hospital ethics committee, and both patients and their families signed informed consent forms. Excluding criteria: 1) patients complicated with diabetic ketoacidosis; 2) patients with the complications of heart, liver, brain and other important organs; 3) patients with history of nephrotoxic drug use; 4) patients with urinary system infection; 5) pregnant women or breast-feeding women; 6) patients with mental or neurological dysfunction.

According to different clinical treatment plans, all patients were randomly divided into nifedipine group, valsartan group and combined treatment group, 32 cases in each group, and patients’ basic information was as follows: nifedipine group included 18 male cases and 14 female cases, they were 38-70 years old, the average was (52.81±7.95) years; the course of diabetes was 9-18 years, the average was (13.27±3.05) years, the course of diabetic nephropathy was 1-5 years and the average was (2.38±0.31) years; valsartan group included 17 male cases and 15 female cases, they were 37-72 years old, the average was (50.62±7.14) years; the course of diabetes was 10-19 years, the average was (13.81±3.23) years, the course of diabetic nephropathy was 1-6 years and the average was (2.42±0.33) years; combined treatment group included 19 male cases and 13 female cases, they were 41-70 years old, the average was (51.78±6.31) years; the course of diabetes was 8-18 years, the average was (12.45±4.09) years, the course of diabetic nephropathy was 1-5 years and the average was (2.63±0.37) years. Above baseline information was no significant differences among three groups (P>0.05).

2.2. Drug treatment

Three groups received routine western medicine treatment, including glucose-reducing by insulin, diabetic diet and appropriate physical activity, and orally took antihypertensive drugs according to the original plan to make blood glucose and blood pressure values reach the standard. Before treatment, three groups stopped taking antihypertensive drugs for a week, nifedipine group orally took nifedipine controlled-release tablet, 30 mg/time, 1 time a day; valsartan group orally took valsartan capsule, 80 mg/time, 1 time a day. Combination group orally took nifedipine controlled-release tablet and valsartan capsule, same dose and frequency as above. Three groups of patients received drug treatment for 6 months as a course of treatment.

2.3. Serological detection

After three groups underwent different treatments for one course of treatment, 5ml of peripheral venous blood was drawn in the morning and centrifuged under normal temperature (37 °C) and with high speed to obtain supernatant and cryopreserve it in -70 °C refrigerator for detection. Renal function-related indexes were detected: cystatin C (CysC), homocysteine (Hcy), chemerin and retinol binding protein 4 (RBP-4). Renal blood vessel-related indexes: cartilage oligomeric matrix protein (COMP), thrombomodulin (TM), coagulation factor VIII (vWF), angiogenin-1 (Ang-1), angiogenin-2 (Ang-2) and microalbumin (mALB). Illness-related indexes: ghrelin, adiponectin (APN), transforming growth factor- β1 (TGF-β1), aldosterone (ALD) and miR-21.

2.4. Statistical methods

Data obtained in the research was analyzed by SPSS23.0 software, measurement data was in terms of mean±SD. Comparison between two groups was performed by t test, and P<0.05 was set as the standard of statistical significant differences.

3. Results

3.1. Renal function-related indexes

Differences in serum CysC, Hcy, Chemerin and RBP-4 values of three groups were statistically significant (P<0.05), serum CysC, Hcy, Chemerin and RBP-4 values of combined treatment group were significantly lower than those of nifedipine group and valsartan group (P<0.05), and differences in serum CysC, Hcy, Chemerin and RBP-4 values of nifedipine group and valsartan group were not significant (P>0.05), shown in Table 1.

3.2. Renal blood vessel-related indexes

Differences in serum COMP, TM, vWF, Ang-1, Ang-2 and mALB values of three groups were statistically significant (P<0.05), serum COMP, TM, vWF and mALB values of combined treatment group were significantly lower than those of nifedipine group and valsartan group while Ang-1 and Ang-2 values were higher than those of nifedipine group and valsartan group (P<0.05), and differences in serum COMP, TM, vWF, Ang-1, Ang-2 and mALB values of nifedipine group and valsartan group were not significant (P>0.05), shown in Table 2.

3.3. Illness-related indexes

Differences in serum Ghrelin, APN, TGF-β1, ALD and miR-21 values of three groups were significant (P<0.05), serum Ghrelin, TGF-β1 and ALD values of combined treatment group were lower than those of nifedipine group and valsartan group while APN and miR-21 values were higher than those of nifedipine group and valsartan group (P<0.05), and differences in serum Ghrelin, APN, TGF-β1, ALD and miR-21 values of nifedipine group and valsartan group were not significant (P>0.05), shown in Table 3.

4. Discussion

Type 2 diabetes is the most common clinical endocrine disease with the highest incidence, and there is obvious systemic microinflammation and oxidative stress reaction in diabetic patients with long-term poor blood glucose control, which can gradually cause small blood vessel function damage and viscera function damage. Most patients with type 2 diabetes, especially those with long disease duration, are associated with hypertension, hypertension and hyperglycemia are two complementary diseases,
Renal function-related indexes of three groups.

Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>CysC (mg/L)</th>
<th>Hcy (μmol/L)</th>
<th>Chemerin (mg/L)</th>
<th>RBP-4 (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine group</td>
<td>0.07±0.09</td>
<td>11.93±1.56</td>
<td>4.38±0.39</td>
<td>64.28±6.11</td>
</tr>
<tr>
<td>Valsartan group</td>
<td>0.92±0.08</td>
<td>11.27±1.43</td>
<td>4.63±0.41</td>
<td>58.63±5.49</td>
</tr>
<tr>
<td>Combined treatment group</td>
<td>0.53±0.06</td>
<td>6.48±0.61</td>
<td>2.41±0.32</td>
<td>31.28±2.94</td>
</tr>
<tr>
<td>F</td>
<td>5.283</td>
<td>8.192</td>
<td>6.921</td>
<td>9.374</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Renal blood vessel-related indexes of three groups after treatment.

Table 2

<table>
<thead>
<tr>
<th>Groups</th>
<th>COMP (ng/mL)</th>
<th>TM (mg/L)</th>
<th>Vwf (%)</th>
<th>Ang-1 (ng/L)</th>
<th>Ang-2 (ng/L)</th>
<th>Malb (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine group</td>
<td>67.48±6.05</td>
<td>68.95±5.77</td>
<td>171.24±16.94</td>
<td>13.98±1.47</td>
<td>3.09±0.25</td>
<td>58.73±5.43</td>
</tr>
<tr>
<td>Valsartan group</td>
<td>64.71±6.84</td>
<td>65.42±7.11</td>
<td>174.95±15.47</td>
<td>15.37±1.34</td>
<td>3.17±0.26</td>
<td>65.39±5.39</td>
</tr>
<tr>
<td>Combined treatment group</td>
<td>40.26±4.11</td>
<td>23.17±2.85</td>
<td>114.38±10.97</td>
<td>21.84±2.05</td>
<td>5.49±0.43</td>
<td>21.73±2.4</td>
</tr>
<tr>
<td>P</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>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Comparison of serum illness-related index values among three groups after treatment.

Table 3

<table>
<thead>
<tr>
<th>Groups</th>
<th>Ghrelin (μg/L)</th>
<th>APN (μg/L)</th>
<th>TGF-β1 (mg/mL)</th>
<th>ALD (pg/mL)</th>
<th>miR-21 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine group</td>
<td>12.49±1.65</td>
<td>6.13±0.63</td>
<td>143.28±13.25</td>
<td>141.73±13.85</td>
<td>0.95±0.08</td>
</tr>
<tr>
<td>Valsartan group</td>
<td>11.83±1.96</td>
<td>6.83±0.54</td>
<td>151.83±14.39</td>
<td>137.05±14.22</td>
<td>1.14±0.17</td>
</tr>
<tr>
<td>Combined treatment group</td>
<td>7.945</td>
<td>8.273</td>
<td>12.48±4.41</td>
<td>14.387</td>
<td>5.384</td>
</tr>
<tr>
<td>F</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>

Renal diabetic patients are prone to hypertension, and those associated with hypertension have more serious conditions of diabetes[3,4]. Diabetic nephropathy is caused by renal dysfunction in diabetes patients, early symptoms are not obvious, and when albuminuria appears, there may have been significant kidney damage. Activation of the renin-angiotensin system is an important factor causing diabetic nephropathy, and could also cause myocardial remodeling, cardiac arrhythmias and other cardiovascular complications. Valsartan is angiotensin [1] receptor blocker that can effectively restrain renin-angiotensin system activity and reduce chronic renal injury[5]. Nifedipine controlled-release tablet is the long-term sustained release drug that reduces free Ca²⁺ concentration in the cytoplasm of blood vessel walls and exerts vasodilative effect, and at the same time, nifedipine has little effect on glucolipid metabolism, and the application is relatively safe in patients with diabetes. Type 2 diabetic nephropathy patients associated with hyperglycemia must accept positive antihypertensive therapy to reduce further renal vascular damage and non-function caused by hypertension status. In the research, type 2 diabetic nephropathy patients with hypertension were selected as the research subjects, nifedipine, valsartan and so on were applied to them respectively, and the role of combined use of the two drugs in controlling patients’ condition was mainly analyzed. CysC is a new kind of endogenous marker, belongs to the family of cysteine inhibitors, and cooperates with Hcy to play a role in kidney disease progression. CysC generation is constant, is rarely influenced by nutrition state, inflammation, gender and age, etc., and with smaller molecular weight, can freely cross through the glomerular filtration membrane, and no longer return to the blood circulation. Because the kidney is the only organ removing CysC, serum CysC level can represent the level of kidney function directly[6,7]. Hcy is a sulfur-containing nonessential amino acid that exists as the cofactor of VitB12 under the effect of methionine synthetase. Excessive Hcy deposition in the glomerulus can generate exitotoxicity, which damages vascular endothelium through oxidative stress mediated by oxygen free radicals. The high serum Hcy in the patients with type 2 diabetes can damage the renal microvascular endothelial cells, and CysC can inhibit the enzyme in Hcy decomposition process, further causing increased Hcy levels and speeding up the process of diabetic nephropathy[8]. Chemerin is a new type of adipokine that is found to have chemical induction effect and participate in the regulation of lipid metabolism in fat cells. Activated Chemerin can achieve chemotaxis expression of G protein-coupled receptor 1 and make the inflammatory cells aggregate, and at the same time, Chemerin can strongly mediate angiogenesis and play an important role in diabetic microangiopathy. RBP-4 is produced by the liver and is a kind of carrier protein responsible for combining and transporting blood retinoids[9]. RBP-4 is re-absorbed to the renal tubules by glomerular filtration, so the kidney plays an important role in RBP-4 metabolic balance, and RBP-4 levels can also sensitively reflect the renal function changes. Research shows that RBP 4 level can rise sharply in the early diabetic nephropathy, and is a sensitive indicator of clinical diagnosis of diabetic nephropathy. Above research results showed that serum CysC, Hcy, Chemerin and RBP-4 values of combined treatment group were lower than those of single drug treatment group, indicating that the application of antihypertensive drugs with different mechanisms of action could not only effectively control blood pressure, but also dramatically inhibit renal failure process. Under physiological state, COMP cannot be cleared by the glomerulus, and vascular smooth muscle can produce COMP and participate in calcification process. Research shows that there is widespread arterial calcification in renal failure patients, and with the aggravation of the degree of calcification, renal failure is accelerated. Study shows that serum COPM levels in diabetic nephropathy patients are higher than those in normal population, and the serum level of COPM increases by 10 ng/mL, the risk of vascular calcification increases by about 1.3 times[10]. Hyperglycemia is the main cause of microvascular lesions in diabetic nephropathy, both TM and vWF are markers of vascular endothelial damage, increased serum TM and vWF levels directly indicate microvascular lesions in patients, and in patients with diabetic nephropathy, high levels of TM and vWF also indicate that renal vascular injury is serious and...
renal function will further fail. There is hemodynamic abnormality and metabolic disorders in patients with diabetic nephropathy before the appearance of microalbuminuria, and both Ang-1 and Ang-2 are involved in the angiogenesis in diabetic nephropathy process. It is found in the rat models with diabetic nephropathy that as the disease progresses, Ang-1 and Ang-2 levels are down-regulated, speculating that they may have the role of protecting diabetic nephropathy. Microvascular endothelial cells and delaying microvascular lesions[11,12], mALB is of great significance for early diagnosis of renal microvascular lesions, serum mALB level rises with the increase of kidney disease degree, and it can be used as one of the objective indicators judging renal function state. Above research results showed that serum COMP, TM, vWF and mALB values of combined treatment group were lower while Ang-1 and Ang-2 values were higher, indicating that after effective control of blood pressure, patients’ microvascular damage degree was reduced, which could directly and effectively protect renal function.

Ghrelin can affect the release of insulin and insulin sensitivity, serum ghrelin level in normal people is higher than that in patients with type 2 diabetes, and negatively correlated with the condition of patients with diabetes. But it is found in diabetic nephropathy patients receiving hemodialysis that serum ghrelin level is significantly higher than that in pure diabetes mellitus patients and healthy people, indicating that ghrelin may participate in the process of diabetic nephropathy[13]. APN is secreted by fat cells, with improving insulin resistance, anti-inflammation, increasing insulin sensitivity and many other kinds of biological functions, and existing research has confirmed that APN level is low in diabetic patients, and supplementing APN can improve diabetes. APN level is a specific indicator judging the renal function process at present, there is high level of APN in diabetic nephropathy patients, and APN levels rise with renal failure progress, which may be because that APN is mainly removed in the kidney, and APN removal decreases and accumulation increases in renal failure process. TGF-β1 is a kind of active peptide that plays a role in immune regulation, cell growth differentiation, etc. In the process of kidney disease formation, TGF-β1 plays the role of to fibrosis, and its level is inversely proportional to the glomerular filtration rate, and directly proportional to kidney disease progression. ALD can lead to myocardial infarction and vascular fibrosis through inflammation, and inflammation plays an important role in the process in diabetic nephropathy. With the renal function reduction in diabetic nephropathy patients, ALD level significantly increases in circulating blood[14,15]. Research has confirmed that miRNAs play an important role in the development of diabetic nephropathy, miR-21 that is with oncogene characteristics has been studied in depth in a variety of oncogenes, but the research in the field of diabetic nephropathy is still in primary stage. It is found in the rat models with diabetic nephropathy that miR-21 expression level is lower than that in normal people and simple diabetes people, so it is believed that high expression of miR-21 is the protective factor in diabetic nephropathy. Above research results showed that serum Ghrelin, TGF-β1 and ALD values of combined treatment group were lower while APN and miR-21 values were higher, indicating that after effective control of blood pressure, the overall conditions in patients with type 2 diabetic nephropathy was improved.

To sum up, it is concluded as follows: nifedipine controlled-release tablet combined with valsartan can effectively optimize the illness and inhibit the progression of renal failure, and it’s worth popularization and application in clinical practice in the future.

References