Effect of calcium dobesilate combined with irbesartan therapy on proteinuria and serum inflammatory mediator levels in early diabetic nephropathy

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ABSTRACT

Objective: To analyze the effect of calcium dobesilate combined with irbesartan therapy on proteinuria and serum inflammatory mediator levels in early diabetic nephropathy. Methods: A total of 74 patients with early diabetic nephropathy who received inpatient treatment in our hospital from July 2013 to July 2015 were included in the study and divided into observation group and control group (n=37) according to random number table. Control group received routine therapy, observation group received additional calcium dobesilate combined with irbesartan therapy, and then differences in proteinuria, hemorheology, renal blood flow parameters, serum inflammatory mediator levels and so on were compared between two groups. Results: Urine microalbumin, UAER value, whole blood viscosity, plasma viscosity, fibrinogen and Hct levels of observation group after treatment were lower than those of control group; color Doppler Vs max and Vd min values of observation group after treatment were higher than those of control group while PI and RI values were lower than those of control group; sICAM-1, MCP-1 and NLR values of observation group after treatment were lower than those of control group. Conclusion: Calcium dobesilate combined with irbesartan therapy can significantly inhibit the progression of early diabetic nephropathy and improve renal blood supply, and it has positive clinical significance.

1. Introduction

Diabetic nephropathy (DN) is the complication caused by diabetic microvascular damage, and also one of the leading causes of death in patients with diabetes. Early DN is mainly manifested as proteinuria, and along with the increased amount of proteinuria and progressive deterioration of renal function, it will eventually develop into renal failure[1]. For patients with early DN, aggressive treatment is expected to reverse the disease trend and optimize the treatment outcome. Hypertension and hyperglycemia are the two main factors in the occurrence and development of DN, so in addition to conventional hypoglycemic therapy, the vascular endothelial function, blood flow state and son on should be intervened. Calcium dobesilate is capillary protectant, which adjusts the physiological function of capillary wall so as to increase its permeability and reduce vascular resistance[2,3]. Irbesartan is angiotensin II (Ang II) receptor inhibitor, and can specifically dilate renal efferent arteriole, reduce the intraglomerular pressure and improve the renal hemodynamic status. In the study, the effect of calcium dobesilate combined with irbesartan therapy on proteinuria and serum inflammatory mediator levels in early diabetic nephropathy was mainly analyzed, hereby reported as follows.

2. Research subjects and information

2.1. Research subjects

A total of 74 patients with early diabetic nephropathy who received inpatient treatment in our hospital from July 2013 to July 2015 were included in the study and divided into observation group and control group (n=37) according to random number table. Control group included 19 male cases and 18 female cases, they were 43-71 years old, the average age was (58.93±9.51) years, the course of diabetes was 9-15 and the average course was (12.71±1.95) years;
observation group included 20 male cases and 17 female cases, they were 42-73 years old, the average age was (59.76±9.88) years, the course of diabetes was 8-14 and the average course was (12.35±1.86) years. The two groups were not statistically different in gender, age, course of diabetes and other baseline information (P>0.05) and they were comparable.

2.2. Treatment methods

Control group received conventional treatment for early diabetic nephropathy, specifically as follows: diabetic diet was provided, blood glucose was monitored, and aspart 30 was used to control blood glucose.

On the basis of conventional treatment, observation group received calcium dobesilate combined with irbesartan therapy, specifically as follows: calcium dobesilate 0.5 g, oral administration, 3 times/d; irbesartan 0.15 g, oral administration, 1 time/d, 12 weeks as 1 course of treatment.

2.3. Observation indexes

2.3.1. Proteinuria-related indexes

Before treatment and 1 month after treatment, 24 h urine was obtained, immunoturbidimetry was used to determine microalbumin levels and urinary albumin excretion rate (UAER), and the average value of three times was taken as the final value.

2.3.2. Hemorheology

Before treatment and 1 month after treatment, fasting peripheral venous blood was extracted from patients, LBYN68 automatic cleaning rotary viscometer was used to determine patients’ hemorheology indexes, including the whole blood viscosity, plasma viscosity, fibrinogen level and Hct.

2.3.3. Renal blood flow parameters

Color Doppler ultrasonic instrument was used for renal color ultrasonography, the probe frequency was set to 3.5 MHz, blood flow spectrum of renal artery and its branches were recorded, and the following parameters were measured: maximum systolic velocity (Vs max), minimum diastolic velocity (Vd min), pulsatility index (PI) and resistance index (RI).

2.3.4. Inflammation-related mediators

Before treatment and 1 month after treatment, 2 mL of peripheral venous blood was extracted from patients, enzyme-linked immunosorbent assay was used to detect soluble intercellular adhesion molecule-1 (sICAM-1) and monocyte chemoattractant protein-1 (MCP-1), and automatic blood analyzer was used to determine neutrophil-to-lymphocyte ratio (NLR).

2.4 Statistical methods

SPSS 23.0 software was used to input and analyze data, measurement data was by t test, count data was by chi-square test and P<0.05 indicated statistical significance in differences.

3. Results

3.1. Proteinuria–related indexes

Urine microalbumin (53.82±6.01 vs. 56.47±6.12 ng/g•Cr) and UAER value (158.94±20.37 vs. 161.52±19.63 mm/24 h) were not statistically different between two groups before treatment (P>0.05), urine microalbumin and UAER values of both groups after different treatment were lower than those before treatment, and urine microalbumin (23.13±3.05 vs. 41.67±5.09 ng/g•Cr) and UAER value (103.27±11.33 vs 145.34±18.63 mm/24 h) of observation group after treatment were lower than those of control group (P<0.05), shown in Table 1.

3.2. Hemorheology

Before treatment, whole blood viscosity, plasma viscosity, fibrinogen and Hct were not statistically different between two groups (P>0.05), whole blood viscosity, plasma viscosity, fibrinogen and Hct levels of both groups decreased after different, and whole blood viscosity, plasma viscosity, fibrinogen and Hct levels of observation group after treatment were lower than those of control group (P<0.05), shown in Table 2.

3.3. Renal blood flow parameters

Analysis of related parameters in renal color Doppler ultrasound

Table 1.

Comparison of proteinuria-related index values between two groups before and after treatment (n=37).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Urine microalbumin (ng/g•Cr)</th>
<th>UAER (ng/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>Observation</td>
<td>53.82±6.01</td>
<td>23.13±3.05</td>
</tr>
<tr>
<td>Control</td>
<td>56.47±6.12</td>
<td>41.67±5.09</td>
</tr>
<tr>
<td>t</td>
<td>0.182</td>
<td>8.394</td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 2.

Comparison of hemorheology indexes between two groups before and after treatment (n=37).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Whole blood viscosity (mPas)</th>
<th>Plasma viscosity (mPas)</th>
<th>Fibrinogen (g/L)</th>
<th>Hct (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>Observation</td>
<td>7.25±0.81</td>
<td>4.61±0.53</td>
<td>3.21±0.44</td>
<td>1.53±0.18</td>
</tr>
<tr>
<td>Control</td>
<td>7.34±0.83</td>
<td>6.92±0.71</td>
<td>3.18±0.45</td>
<td>2.76±0.31</td>
</tr>
<tr>
<td>t</td>
<td>0.172</td>
<td>6.393</td>
<td>0.216</td>
<td>5.834</td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
images of the typical cases of two groups before and after treatment was as follows: before treatment, renal blood flow parameter values were not statistically different between two groups ($P<0.05$); Vs max and Vd min values of both groups after different treatment were higher than those before treatment while PI and RI values were lower than those before treatment, Vs max and Vd min values of observation group after treatment were higher than those of control group while PI and RI values were lower than those of control group ($P<0.05$), shown in Table 3.

3.4. Inflammation–related mediators

Before treatment, serum sICAM-1 and MCP-1 levels and NLR were not statistically different between two groups ($P<0.05$), serum sICAM-1 and MCP-1 levels and NLR values of both groups after different treatment were significantly lower than those before treatment, and serum sICAM-1 and MCP-1 levels and NLR value of observation group after treatment were significantly lower than those of control group ($P<0.05$), shown in Table 4.

4. Discussion

Kidney is the most common target organ in patients with long-term diabetes, and clinical data shows that the probability of diabetic nephropathy is more than 40% in patients with diabetes for more than a decade. Diabetic nephropathy (DN) belongs to progressive disease, it will inevitably progress to end-stage renal disease when obvious proteinuria appears, and therefore, active intervening measures should be taken for patients with early diabetic nephropathy in order to reverse the disease progression and the ultimate outcome[4,5]. Both calcium dobesilate and irbesartan are common drugs for the treatment of DN, calcium dobesilate inhibits high permeability effect caused by vaso-active substances to improve the biosynthesis of basement membrane collagen, and it can alleviate microvascular circulatory disturbance. Irbesartan is angiotensin II (Ang II) receptor inhibitor that can selectively block the combination of Ang II and AT1 receptor to inhibit vasoconstriction and aldosterone release and produce antihypertensive effect, and it has been confirmed that irbesartan plays a positive role in the treatment of early DN[6,7].

Based on routine hypoglycemic treatment, calcium dobesilate and irbesartan were used in the study for the treatment of patients with early DN, and at first, the curative effect was observed from the aspect of urine protein. Microalbuminuria is the main performance in patients with early DN and reflects the extensive endothelial dysfunction and vascular injury in diabetes, and the occurrence of persistent microalbuminuria is closely related to early renal hemodynamic abnormalities and various metabolic disorders[8]. Further glomerular and interstitial damage can cause increased urinary albumin excretion rate (UAER), aggravated DN and its progression to the substantial renal function damage[9]. Urine microalbuminuria and UAER values are the reliable indexes to reflect the severity early DN in patients, and the study results showed that urine trace albumin and UAER levels of observation group were lower after treatment, indicating that calcium dobesilate combined with irbesartan therapy could significantly reverse the albuminuria in patients and prevent further disease progression as a whole.

DM is a severe microvascular complication of diabetes and one of the leading causes of death in patients with diabetes. Hypertension and hyperglycemia are the basic factors of the DN, and blood viscosity increase is an important factor causing the occurrence of microvascular lesions[10]. There are vascular endothelial injury and dysfunction, platelet dysfunction and coagulation/anticoagulation system dysfunction in patients with DN, which will eventually lead to abnormal hemorheology. The study found that there were hypercoagulability, high viscosity, high agglutination, decreased erythrocyte deformation ability and other phenomena in two groups of patients before treatment, and blood viscosity increase will directly aggravate renal ischemia and hypoxia, increase the glomerular basement membrane permeability, lead to massive proteinuria and accelerate renal impairment[11,12]. It was found that hemorheology parameters such as whole blood viscosity, plasma viscosity, fibrinogen and Hct values of observation group decreased after treatment, showing that calcium dobesilate combined with irbesartan therapy could effectively improve the high blood viscosity state, reduce the formation of blood stasis, microvascular thrombus, etc., and protect renal function[13]. In addition to the change of systemic hemorheology, there is the change of renal blood flow parameters in patients with DN, which is mainly manifested as decreased renal blood flow and increased renal vascular resistance. In the study, color Doppler ultrasound was further used to determine

### Table 3.
Comparison of renal blood flow parameter values between two groups before and after treatment ($n=37$).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Vs max (cm/s) Before treatment</th>
<th>Vs max (cm/s) After treatment</th>
<th>Vd min (cm/s) Before treatment</th>
<th>Vd min (cm/s) After treatment</th>
<th>PI Before treatment</th>
<th>PI After treatment</th>
<th>RI Before treatment</th>
<th>RI After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>28.16±3.05</td>
<td>33.04±4.13</td>
<td>9.56±0.97</td>
<td>12.51±1.74</td>
<td>1.12±0.15</td>
<td>0.91±0.09</td>
<td>0.72±0.08</td>
<td>0.63±0.07</td>
</tr>
<tr>
<td>Control</td>
<td>28.52±3.12</td>
<td>30.17±3.84</td>
<td>9.43±0.96</td>
<td>10.23±1.13</td>
<td>1.09±0.17</td>
<td>0.98±0.12</td>
<td>0.71±0.09</td>
<td>0.70±0.08</td>
</tr>
<tr>
<td>$t$</td>
<td>0.217</td>
<td>5.838</td>
<td>0.154</td>
<td>6.094</td>
<td>0.253</td>
<td>6.182</td>
<td>0.152</td>
<td>5.283</td>
</tr>
<tr>
<td>$P$</td>
<td>$&gt;$0.05</td>
<td>$&lt;$0.05</td>
<td>$&gt;$0.05</td>
<td>$&lt;$0.05</td>
<td>$&gt;$0.05</td>
<td>$&lt;$0.05</td>
<td>$&gt;$0.05</td>
<td>$&lt;$0.05</td>
</tr>
</tbody>
</table>

### Table 4.
Comparison of serum sICAM-1 and MCP-1 levels and NLR between two groups before and after treatment ($n=37$).

<table>
<thead>
<tr>
<th>Groups</th>
<th>sICAM-1 (μg/L) Before treatment</th>
<th>sICAM-1 (μg/L) After treatment</th>
<th>MCP-1 (ng/L) Before treatment</th>
<th>MCP-1 (ng/L) After treatment</th>
<th>NLR Before treatment</th>
<th>NLR After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>512.48±63.19</td>
<td>153.28±19.47</td>
<td>173.28±21.27</td>
<td>173.28±21.27</td>
<td>2.53±0.31</td>
<td>2.09±0.24</td>
</tr>
<tr>
<td>Control</td>
<td>509.47±59.84</td>
<td>341.26±45.83</td>
<td>176.41±20.46</td>
<td>125.05±15.74</td>
<td>2.55±0.30</td>
<td>2.41±0.29</td>
</tr>
<tr>
<td>$t$</td>
<td>0.217</td>
<td>13.264</td>
<td>0.192</td>
<td>9.823</td>
<td>0.112</td>
<td>5.738</td>
</tr>
<tr>
<td>$P$</td>
<td>$&gt;$0.05</td>
<td>$&lt;$0.05</td>
<td>$&gt;$0.05</td>
<td>$&lt;$0.05</td>
<td>$&gt;$0.05</td>
<td>$&lt;$0.05</td>
</tr>
</tbody>
</table>
the values of renal blood flow parameters in patients, and it was found that Vs max and Vd min values of observation group were higher after treatment while PI and RI values were lower, indicating that calcium dobesilate combined with irbesartan therapy could optimize renal blood flow state and reduce the substantial damage and declined renal function caused by renal ischemia hypoxia.

Many clinical studies have confirmed that there are inflammatory cell infiltration and high inflammatory mediator state in patients with diabetic nephropathy, so the chronic persistent inflammation plays an important role in the occurrence and development of DN. Testing serum levels of inflammatory mediators in patients with early DN can not only judge the disease severity, but can also be used as the objective standard of treatment effectiveness[14]. Interleukin-6 (IL-6), tumor necrosis factor- (TNF-), etc. can promote the massive expression of lymphocyte-related ligand ICAM-1 by vascular endothelial cells, help to enhance the adhesive force between T lymphocytes and endothelial cells, and accelerate the vascular endothelial inflammatory injury and DN illness. Soluble constituent of ICAM-1, soluble intercellular adhesion molecule-1 (sICAM-1) levels in serum can indirectly reflect the ICAM-1 expression levels on endothelial cell surface and further reflect the degree of local and systemic inflammation[15]. Human mesangial cells can express and synthesize monocyte chemotactic protein-1 (MCP-1), and both hyperglycemia and HbA1c can increase its expression. Excessive expression of MCP-1 can mediate massive macrophage chemotaxis and activation, participate in inflammation and increase renal tissue damage. Research shows that the total number and differential count of white blood cells are related to DN illness, neutrophils are the most important inflammatory cells in inflammatory response, and neutrophil levels increase in patients with DN[16]. There is significant lymphocyte change in patients with DN, which is specifically characterized by decreased total number of lymphocytes and CD4/CD8 ratio, so monitoring neutrophil-to-lymphocyte ratio (NLR) can macroscopically reflect the extent of systemic inflammation in patients. The research results showed that sICAM-1, MCP-1 and NLR values of observation group were lower after treatment, indicating that the calcium dobesilate combined with irbesartan therapy could effectively reduce the systemic inflammation state in patients with DN and prevent inflammatory factors from further aggravating the DN illness.

To sum up, it is concluded as follows: calcium dobesilate combined with irbesartan therapy can significantly inhibit the progression of early diabetic nephropathy and improve renal blood supply, and it’s worth popularization and application in clinical practice in the future.

References