EFFECT OF L-CARNITINE COMBINED WITH ALPROSTADIL ON PATIENTS WITH DIABETIC NEPHROPATHY AND SERUM INFLAMMATORY MARKERS OF URINARY LAP AND PCX LEVELS

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ABSTRACT

Objective: To investigate the effect of L-carnitine combined with alprostadil on patients with diabetic nephropathy and serum inflammatory markers of urinary LAP and PCX levels.

Methods: A total of 106 patients with diabetes mellitus that were admitted to our department from August 2016 to October 2017 were enrolled. According to different treatment methods, they were divided into an observation group and a control group, each with 53 cases. The control group received a prostaglandin injection. The observation group was combined with L-carnitine on the basis of the control group, and both groups were treated for 1 month. The blood glucose levels, related renal function indicators and urinary LAP and PCX were measured before and after treatment. The clinical efficacy and adverse reactions of the two groups were observed.

Results: After treatment, the total effective rate of clinical treatment was 92.45%, which was significantly higher than that of the control group (69.81%). The difference was statistically significant (P<0.05). FBP, 2 h BG, and 24 h uPro, BUN, Scr, and β2-MG were significantly improved in the two groups after treatment, and the difference was statistically significant (P<0.05). The observation group was superior to the control group, and the difference was statistically significant (P<0.05). The levels of urinary LAP and PCX in the observation group were lower than those in the control group, and the difference was statistically significant (P<0.05). The observation group was superior to the control group, and the difference was statistically significant (P<0.05). The total incidence of adverse reactions in the observation group was 7.55%, which is significantly lower than that in the control group (20.75%), and the difference was statistically significant (P<0.05). Thus, the observation group was superior to the control group, and the difference was statistically significant (P<0.05).

Conclusion: The clinical efficacy of L-carnitine combined with alprostadil in the treatment of diabetic nephropathy is significant, which can effectively reduce the level of urine LAP and PCX. It is safe and worthy of clinical application.

Keywords: Diabetic nephropathy, alprostadil, L-carnitine, urinary LAP, PCX level, serum inflammation index.

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Introduction

Diabetic nephropathy is one of the most common clinical complications and a common metabolic disease. With the rapid development of China’s economy and the changes in people’s dietary structure, the incidence rate in China has increased and is the main factor threatening the death of diabetic patients(1). However, its pathogenesis is complicated. The main clinical symptoms are proteinuria, hypertension, progressive renal damage, and even renal failure. Treatment is often more difficult than other kidney diseases. Therefore, timely prevention and treatment is important for delaying diabetic nephropathy(2-4). As a new type of highly bioactive substance, alprostadil has a wide range of pharmacological effects that can improve the renal function of diabetic patients by improving microcirculation and renal vascular function to treat diabetic complications. L-carnitine is a vitamin-like nutrient that promotes lipid metabolism through antioxidant action, further regulating blood glucose metabolism and lipid metabolism in the body(5). Retrospective analysis of the clinical data of 106 patients with diabetic nephropathy admitted to our Department of Endocrinology is to investigate the effect of L-car-
Data and methods

General information
A total of 106 patients with diabetes admitted to our department from August 2016 to October 2017 were enrolled.

Inclusion criteria:
• Patients aged ≥ 50 years;
• The pathological results were diagnosed as diabetic nephropathy;
• DN staging was Stage III and IV;
• 24-hour urinary albumin excretion rates (UAER) were 20-200 μg/min.
• The patient or the patient's family was informed and signed an informed consent form.

Exclusion criteria:
• Patients with severely impaired heart and liver function;
• Patients with a history of hypertension and blood disease;
• Patients with other immune system damage or other urinary system.

The selected patients were divided into two groups according to different treatment methods. The control group received the treatment with alprostadil, while the observation group was combined with L-carnitine on the basis of the control group. There were 53 patients in the control group, 27 males and 26 females, aged 50-72 years, mean age (63.37±4.00) years old. As well, there were 53 patients in the observation group, 25 males, 28 females, aged 53-75 years, mean age (64.58±5.58) years old. There was no significant difference in gender, age and other general data between the two groups (P>0.05), which was comparable. See Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Gender (Male / Female)</th>
<th>Age/year</th>
<th>HR/ (time/min)</th>
<th>SBP/ mmHg</th>
<th>DBP/ mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>53</td>
<td>27/26</td>
<td>63.37±4.00</td>
<td>79.10±7.01</td>
<td>177.31±9.10</td>
<td>99.41±9.71</td>
</tr>
<tr>
<td>Observation</td>
<td>53</td>
<td>25/28</td>
<td>64.58±5.58</td>
<td>79.00±7.60</td>
<td>177.71±10.70</td>
<td>101.10±9.20</td>
</tr>
</tbody>
</table>

χ²/t 0.037 1.175 0.070 0.207 0.919
P 0.845 0.242 0.944 0.836 0.359

Table. 1: Comparison of general data between the two groups of patients.

Note:1 mmHg=0.133 kPa.

Treatment methods
The patients in the control group were operated on according to the conventional hypoglycemic treatment method. The fasting blood glucose (FBP) was controlled within 7 mmol/L, and the blood glucose (2 h BP) was controlled within 10 mmol/L 2 h after the meal. Slow, intravenous injection of alprostadil (produced by Beijing Tide Pharmaceutical Co., Ltd., 1 mL: 5 μg, National Drug Standard: H10980024), 1-2 mL (prostaglandin 5-10 μg) + 10 ml saline (or 5% Glucose) was instilled once a day for 1 month. The patients in the observation group were intravenously instilled with a L-carnitine injection (Sigma-Tau Industrie Farmaceutiche Riuniti S.p.A, 1 g, batch No. H20130766) on the basis of the control group. The starting dose was 10-20 mg/kg, dissolved in 5-10 mL of water, for injection. Intravenous bolus injection in 2 to 3 minutes, the plasma left carnitil setting trough concentration is lower than normal (40~50 umol/L) immediately start treatment, adjust the dose during the third or fourth week of treatment (such as 5 mg/kg in hemodialysis), and then continuous treatment for 1 month. The efficacy of the two groups was observed.

Observation indicators and methods
The fasting venous blood of patients before and after treatment and the venous blood 2 h after meals were collected. As well, the FBG and 2 h BG levels were measured by glucose oxidase method. Venous blood was collected before and after treatment, and 24 h proteinuria (Albuminuria ALB24h uPro), blood urea nitrogen (Bloodureanitrogen BUN), serum creatinine (Serum Creatinine Scr) and urinary microglobulin (Microglobulin β2-MG) were detected by enzyme-linked immunosorbent assay. At the same time, the patient was collected during the middle of their morning urine, which was then stored in a frozen environment at minus 80 °C after centrifugation, and the levels of urinary LAP and urinary PCX were measured by Elisa reagent. Statistical analysis was performed to evaluate the clinical efficacy of the two groups after treatment, while the urinary LAP and urinary PCX levels were compared between the two groups.

Evaluation criteria:
• Significant: after treatment, the patient's various adverse symptoms completely resolved, renal damage is also completely restored;
• Effective: after treatment, the patient's various adverse symptoms basically subsided, kidney impaired function was basically alleviated;
• Ineffective: After treatment, the symptoms and signs of the patient did not significantly improve, and the disease has a tendency to increase\(^6,\)\(^7\). Total efficiency = (significant + effective)/total number of cases \(\times 100\%\).

**Statistical methods**

SPSS 19.0 was used as the data statistical analysis software in this study. The comparison between the count data and the measurement data was performed by \(\chi^2\) test and t-test, respectively. The composition ratio (%) indicates the count data, and the mean \(\pm\) standard deviation (\(\bar{x} \pm s\)) indicates measurement data. The difference was statistically significant when \(P<0.05\).

**Results**

**Comparison of clinical effects between the two groups of patients**

After treatment, the total effective rate of clinical treatment in the observation group was 92.45%, which was significantly higher than that of the control group (69.81%); as well, the difference was statistically significant (\(P<0.05\)). See Table 2.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Significant</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>53</td>
<td>14(26.41)</td>
<td>23(43.40)</td>
<td>18(33.96)</td>
<td>69.81</td>
</tr>
<tr>
<td>Observation</td>
<td>53</td>
<td>24(45.28)</td>
<td>25(47.17)</td>
<td>4(7.55)</td>
<td>92.45</td>
</tr>
</tbody>
</table>

\(\chi^2\) - - - - 9.693

\(P\) - - - - 0.001

**Table 2:** Comparison of clinical effects between the two groups of patients [\(n (\%)\)].

**Comparison of blood glucose and renal function related indexes before and after treatment in the two groups of patients**

There were no significant differences in FBP, 2 h BG and 24 h uPro, BUN, Scr and \(\beta_2\)-MG between the two groups before treatment (\(P>0.05\)). However, after treatment, the above indicators were significantly improved. Statistical significance (\(P<0.05\)), and the observation group was superior to the control group, as the differences were statistically significant (\(P<0.05\)). See Table 3.

<table>
<thead>
<tr>
<th>Group</th>
<th>Period</th>
<th>FBG (mmol/L)</th>
<th>2hBG (mmol/L)</th>
<th>24hPro (μg/L)</th>
<th>BUN (mmol/L)</th>
<th>Scr (μmol/L)</th>
<th>(\beta_2)-MG (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Before treatment</td>
<td>11.61±2.62</td>
<td>11.01±3.41</td>
<td>1.62±0.21</td>
<td>13.10±0.6</td>
<td>284.80±21.90</td>
<td>3.01±0.20</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>9.02±2.11</td>
<td>9.41±3.90*</td>
<td>1.41±0.31</td>
<td>11.01±1.81*</td>
<td>259.31±21.50*</td>
<td>2.32±0.21*</td>
</tr>
<tr>
<td>Observation</td>
<td>Before treatment</td>
<td>11.81±3.31</td>
<td>11.31±3.71</td>
<td>1.61±0.31</td>
<td>13.21±0.91*</td>
<td>274.50±20.40</td>
<td>3.00±0.20</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>6.21±2.20*</td>
<td>8.11±3.61*</td>
<td>1.11±0.21*</td>
<td>9.50±1.40*</td>
<td>212.41±19.21*</td>
<td>1.81±0.21*</td>
</tr>
</tbody>
</table>

\(P\) <0.001 <0.011 <0.001 <0.001 <0.001 <0.001

**Table 3:** Changes in blood glucose and renal function related indexes before and after treatment in the two groups of patients (\(\bar{x} \pm s\)).

Note: *indicates \(P<0.05\) compared with the same group before treatment; \(^*\) indicates \(P<0.05\) compared with the control group after treatment.

**Comparison of urine LAP and PCX levels in the two groups after treatment**

After treatment, the urine LAP level and PCX level in the observation group were lower than those in the control group, and the difference was statistically significant (\(P<0.05\)). Moreover, the observation group was superior to the control group, and the difference was statistically significant (\(P<0.05\)). See Table 4.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>LAP (ng/mL)</th>
<th>PCX (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>53</td>
<td>9.45±3.80</td>
<td>12.23±2.90</td>
</tr>
<tr>
<td>Control</td>
<td>53</td>
<td>14.25±4.26</td>
<td>20.10±3.02</td>
</tr>
</tbody>
</table>

\(T\) 6.095 13.684

\(P\) <0.001 <0.001

**Table 4:** Comparison of urinary LAP and urinary PCX levels after treatment in both groups (\(\bar{x} \pm s, \text{ng/mL}\)).

**Comparison of adverse reactions between the two groups of patients**

The total incidence of adverse reactions in the observation group was 7.55%, which was significantly lower than that of the control group (20.75%). Further, the difference was statistically significant (\(P<0.05\)). Additionally, the observation group was superior to the control group, and the difference was statistically significant (\(P<0.05\)). See Table 5.

\(P\) <0.001 <0.001

**Table 5:** Comparison of adverse reactions between the two groups of patients [\(n (\%)\)].
Discussion

Diabetes is a common metabolic chronic disease seen throughout the world. It is easy to induce a large number of complications; that is, complications of diabetes, which is a serious complication of diabetes. The mechanism of causing diabetic nephropathy is related to the level of glucose and lipid metabolism in the body. The disease is often accompanied by pathological lesions after disorder of the glucose metabolism. The lysosomes of renal tubular epithelial cells mainly reflect the level of urinary LAP. Once the renal physiological function imbalance leads to renal tubular injury, a large amount of LAP can be induced to excrete urinary function, and urine enzymes can be clearly observed before abnormal urine protein appears. The level rise is beneficial to the early diagnosis of renal tubular function damage. Complete cells contain a large number of PCX levels in serum, mainly from the foot cell falls off the basement membrane, causing vascular basement membrane to be exposed due to sufficient cell falls. As such, the foot can cause vascular basement membrane after the cell falls off nudity, resulting in a large number of protein leakage, capillary appear transparent degeneration, while glomerular damage increases as the second cause of end-stage kidney disease, second only to various glomerulonephritis. Clinical studies have confirmed that once the development of end-stage renal disease appears, the patient's life and health will be seriously threatened(12).

At present, the main clinical treatment of diabetic nephropathy is to control blood sugar, blood pressure and blood lipids. Alprostadil is a new type of highly bioactive substance that is clinically effective in the treatment of diabetic nephropathy. The principle is to add prostaglandin E into the lipid microsphere to make a new lipid microsphere preparation. It can be targeted at the lesion and concentrated in the glomerular area, thus exerting the pharmacological effects of prost E(13-14). Studies have shown that alprostadil can dilate renal vessels, effectively reduce the amount of protein in urine, and improve renal function by activating adenylyl cyclase to increase intracellular cyclic adenosine monophosphate levels(15). Leucarnitine is an endogenous substance, belongs to natural nutrients, and is an essential substance for the metabolism of the body. Additionally, it improves the energy supply of the body by promoting the metabolism of lipids, glucose and amino acids through oxidation, and promotes the energy metabolism of fat in the most significant way. Studies have shown that supplementation with L-carnitine in diabetic patients can improve insulin resistance, improve glucose tolerance, and control blood sugar levels. Further, L-carnitine protects cell membrane function and tissues and organs(16-17) by inhibiting oxidative stress, as well as inflammatory responses by promoting free radical inhibitory enzyme activity, and significantly inhibiting oxidative glycosylation(15).

PCX is distributed throughout the cell body and mainly comes from the shedding of the basal membrane of podocytes. When the podocytes are detached, the vascular basement membrane will be exposed, and a large amount of protein will leak. Capillary vessels appear to be hyaline degeneration, which will aggravate glomerular injury. As well, PCX levels are clinically used indicators of renal disease detection (18-19). Currently, PCX levels are initially used for the detection of multiple kidney diseases and to assess the extent of progression of the disease. LAP is mainly derived from lysosomes of renal tubular epithelial cells. However, the amount of urinary LAP is very small in healthy people. When renal parenchyma, especially renal tubular lesions occur, the components of tubular epithelial cells can leak out into the urine and be excreted. Generally, urine enzymes are significantly elevated before the complete abnormality of urine protein, which has a high value for early diagnosis.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Stomach ache</th>
<th>Feel sick and vomit</th>
<th>Diarrhea</th>
<th>Total incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>53</td>
<td>2(3.77)</td>
<td>4(7.55)</td>
<td>6(11.32)</td>
<td>20.75</td>
</tr>
<tr>
<td>Observation</td>
<td>53</td>
<td>1(1.89)</td>
<td>1(1.89)</td>
<td>2(3.77)</td>
<td>7.55</td>
</tr>
<tr>
<td>χ²</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.124</td>
</tr>
<tr>
<td>p</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Table. 5: Comparison of adverse reactions between the two groups of patients [n (%)].
of renal tubular function damage\textsuperscript{(20)}. In this study, the levels of urinary LAP and PCX were compared between the two groups. The urine LAP level and PCX level of the observation group were lower than those of the control group, and the observation group was superior to the control group. The PCX level of L-carnitine combined with alprostadil in the treatment of diabetic nephropathy was significantly improved compared with the control group. As the treatment time prolonged, the urinary PCX level decreased with the decrease of urinary albumin excretion rate. The efficacy of L-carnitine combined with alprostadil in the treatment of diabetic nephropathy is significantly better than the efficacy of alprostadil alone.

In summary, L-carnitine combined with alprostadil in the treatment of diabetic nephropathy has a significant effect, high safety, can effectively improve the serum inflammatory index of patients with urinary LAP and PCX levels, and can be promoted in the clinic.

References


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