EFFECTS OF ALPROSTADIL ON OXIDATIVE STRESS, VASCULAR ENDOTHELIAL FUNCTION AND PLASMA ATRIAL NATRIURETIC PEPTIDE, BRAIN NATRIURETIC PEPTIDE AND C-TYPE NATRIURETIC PEPTIDE IN PATIENTS WITH PERIDIABETIC VASCULAR DISEASE

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ABSTRACT

Purpose: To investigate the effects of alprostadil on oxidative stress, vascular endothelial function, and plasma atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) in patients with peripheral diabetic vascular disease.

Methods: From January 2017 to January 2018, 82 patients with peripheral diabetic vascular disease were selected and divided into an observation group (n = 41) and a control group (n = 41). The control group was treated with antihypertensive, lipid-lowering, and hypoglycaemic routine therapy, and the observation group was treated with alprostadil injection on the basis of the control group. The two groups were treated continuously for 2 weeks. In both groups we compared the effects of bed, the ankle-brachial index before and after treatment, and the change of clinical symptom score. We also compared the levels of oxidative stress, serum malondialdehyde (MDA), superoxide dismutase (SOD), advanced protein oxidation product (AOPP), total antioxidant capacity (T-AOC), vascular endothelial function [von Willebrand factor (vWF), plasma endothelin-1 (ET-1), atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) before and after treatment.

Results: After treatment, the total effective rate in the observation group was 95.12%, significantly higher than that in the control group (73.18%). The ankle-brachial index in the observation group was significantly higher than that in the control group, and the clinical symptom score was significantly higher than that in the control group (P<0.05). After treatment, the levels of MDA, AOPP, SOD, and T-AOC in the observation group were significantly lower than those in the control group, and the difference was statistically significant (P<0.05). After treatment, the levels of plasma vWF and ET-1 in the observation group were significantly lower than those in the control group (P<0.05), the levels of ANP and BNP in the observation group were significantly lower than those in the control group, and the levels of CNP were significantly higher than those in the control group (P<0.05). In the control group, the difference was statistically significant (P<0.05).

Conclusion: Alprostadil is effective in the treatment of diabetic peripheral vascular disease. It can significantly improve the clinical symptoms and peripheral blood flow of peripheral vascular disease, alleviate oxidative stress injury in vivo, improve endothelial cell function, and regulate ANP. The levels of BNP and CNP maintain the balance of water and sodium.

Keywords: Alprostadil, peridiabetic angiopathy, oxidative stress, vascular endothelial function, plasma atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide.

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Introduction

Peripheral diabetic vascular disease is one of the complications of diabetic macrovascular disease, with high incidence and poor prognosis. Early patients may have abnormal limb sensation, numbness, pain, and intermittent claudication, which can lead to peripheral ulceration or ischemic gangrene, or even amputation(1). Studies have shown that the basic pathological changes of peridiabetic vascular lesions are mainly thrombosis caused by atherosclerosis, atherosclerosis caused by diabetes, hyperglycaemia, heredity, abnormal fat metabolism, and inflammatory reaction. Oxidative stress disorder and other factors are related(2,3). Alprostadil is an analogue of prostacyclin and can inhibit platelet aggregation, reduce blood viscosity, the effects of long disease duration, rapid dispersion, and less dosage(4). The effects of alprostadil on oxidative stress, vascular endothelial cell function, plasma atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide were observed.
Data and methods

General information
From January 2017 to January 2018, 81 patients with peripheral diabetic angiopathy were treated in the Endocrinology Department of our hospital.

Admission criteria:
- All patients were in accordance with the diagnostic criteria for diabetes mellitus established by the WHO\(^5\);
- All patients were in accordance with the diagnostic criteria for peripheral vascular disease of diabetes;
- The symptoms were not improved after months of treatment and were not suitable for operation. Patients and their families gave informed consent and cooperated with the treatment.

Exclusion criteria:
- Patients with severe heart, liver, and kidney insufficiency, patients with severe mental or nervous system disease, patients with other acute and chronic complications of diabetes, patients with peripheral venous thrombosis with hemorrhagic tendency, and patients treated with anticoagulants or vasodilators within 51 months were excluded. The mean age was (60.21±9.56) years. The course of disease was 1-8 years. All patients were randomly divided into an observation group (n = 41) and a control group (n = 41). There was no significant difference in age, sex, and course of disease between the two groups (P>0.05). See Table 1.

Treatment methods
Both groups were given diabetes education, diet control, and proper exercise. The patients in the control group were given hypoglycaemic therapy (fasting blood glucose was controlled at 6.0~8.5 mmol/L, 2 h postprandial blood glucose was controlled at 8.0~12.0mmol/L), lowering blood fat, lowering blood pressure, etc. The observation group was treated with alprostadil injection (specification: 10g / Zhiha Pharmaceutical Group Bioengineering Co., Ltd.), where 10 g alprostadil injection was injected intravenously into 0.9% normal saline 100ml once a day for 2 weeks in both groups.

Observation indicators
Clinical efficacy:
There are 6 clinical efficacy criteria.

Remarkable effect:
- After treatment, the clinical symptoms such as pain, cold, numbness, and intermittent claudication had basically disappeared, and the painless walking distance of the patients was more than 2 times longer than that before treatment. The colour Doppler ultrasound score of peripheral blood vessels decreased by more than 70%.

Ineffective:
- Patients with peripheral pain, cold, numbness, intermittent claudication, and other clinical symptoms have not improved. The colour Doppler ultrasound score of peripheral blood vessels was not decreased. Total effective rate = (effective) / total number of cases x 100%.

Ankle-brachial ratio:
- The systolic blood pressure of the bilateral brachial artery was measured with Doppler probe, and the systolic blood pressure of the ipsilateral ankle artery and dorsalis pedis artery was measured. The middle and high values of the systolic blood pressure of ankle and brachial artery were obtained. The ratio of ankle brachial artery to brachial artery was equal to that of ankle systolic blood pressure / brachial systolic pressure.

Clinical symptom score:
This score mainly included the maximum distance of walking speed of intermittent claudication 70~80m/min, pain, numbness and cold feeling. Each item was 4 points, the total score was 1-16 points, and the higher the score, the more serious the condition.

Oxidative stress index:
Before and after treatment, 2 ml of fasting elbow venous blood was extracted from the patients in the morning and then the supernatant was collected by centrifugation. Serum malondialdehyde (Malondialdehyde, MDA) and superoxide dismutase (SOD) were detected by automatic biochemical analyzer. The total antioxidant capacity of a late protein oxidation product (advanced oxidation protein products, AOPP, Total antioxidant cap Acity, T-AOC) level was obtained.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Sex (M / F)</th>
<th>Age (years)</th>
<th>Course of Disease (years)</th>
<th>BMI (kg/m(^2))</th>
<th>Fasting Blood-Glucose (mmol/L)</th>
<th>Glycosylated Hemoglobin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>41</td>
<td>22/19</td>
<td>60 (20±10)</td>
<td>4.52±3.24</td>
<td>22.95±1.43</td>
<td>8.35±3.26</td>
<td>7.56±1.05</td>
</tr>
<tr>
<td>Control</td>
<td>41</td>
<td>23/18</td>
<td>61 (20±9.8)</td>
<td>4.33±3.25</td>
<td>23.06±1.39</td>
<td>8.26±3.01</td>
<td>7.26±0.99</td>
</tr>
</tbody>
</table>

\[ t/\chi^2 \]

\[ P \]

Table 1: Comparison of general data between two groups of patients.
**Endothelial function:**

- The level of plasma endothelin-1 (ET-1) of von Willebrand factor (vWF) was measured by enzyme-linked immunosorbent assay (ELISA).

- Enzyme-linked immunosorbent assay (ELISA) was used to detect the changes of plasma atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-natriuretic peptide (CNP).

**Statistical methods**

SPSS19.0 software package was used for statistical analysis of the research data, and the data were measured according to the standard deviation (T test was used for comparison among groups, [n (%)] for counting data and χ~2 test for comparison between groups (P<0.05).

**Results**

**Comparison of clinical efficacy between the two groups**

After treatment, the total effective rate in the observation group was 95.12 and in the control group it was 73.18. The difference between the two groups was statistically significant (P<0.05). See Table 2.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Excellence</th>
<th>Effective</th>
<th>Of no avail</th>
<th>Total effective rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>41</td>
<td>23(56.10%)</td>
<td>16(39.02%)</td>
<td>2(4.88%)</td>
<td>39(95.12%)</td>
</tr>
<tr>
<td>Control</td>
<td>41</td>
<td>15(36.59%)</td>
<td>15(36.59%)</td>
<td>11(26.83%)</td>
<td>30(73.18%)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 7.405 \]

\[ P = 0.006 \]

Table. 2: Comparison of clinical efficacy between two groups after treatment [n (%)].

**Comparison of Ankle-Brachial Ratio and Clinical Symptom Score between the two groups**

After treatment, the ankle-brachial ratio in the observation group was significantly higher than that before treatment and in the control group, and the clinical symptom score was significantly lower than before treatment or in the control group (P<0.05). There was no significant difference in ankle-brachial ratio and clinical symptom score between the control group and pre-treatment group (P>0.05). See Table 3.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>MDA (nmol/L)</th>
<th>AOPP (µmol/L)</th>
<th>SOD (U/L)</th>
<th>T-AOC (U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>41</td>
<td>Pre-therapy</td>
<td>5.83±0.62</td>
<td>58.36±6.13</td>
<td>61.25±6.87</td>
<td>7.83±0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-treatment</td>
<td>3.75±0.48*</td>
<td>38.56±4.09*</td>
<td>89.74±9.12*</td>
<td>13.82±1.67*</td>
</tr>
<tr>
<td>Control</td>
<td>41</td>
<td>Pre-therapy</td>
<td>5.93±0.65</td>
<td>59.26±6.75</td>
<td>60.17±7.03</td>
<td>7.75±0.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-treatment</td>
<td>4.96±0.53</td>
<td>45.69±5.23</td>
<td>76.66±8.93</td>
<td>10.53±1.29</td>
</tr>
</tbody>
</table>

Table. 3: Comparison of ankle-brachial ratio and clinical symptom score between two groups (X±s).

**Comparison of oxidative stress indexes between two groups**

After treatment, the serum MDA, AOPP level of the observation group was significantly lower than that of the control group, and the SOD, T-AOC level of the antioxidant index was significantly higher than that of the control group (P<0.05). See Table 4.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>time</th>
<th>vWF (%)</th>
<th>ET-1(ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>41</td>
<td>Pre-therapy</td>
<td>190.25±21.20</td>
<td>116.75±30.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-treatment</td>
<td>161.11±28.30*</td>
<td>84.26±19.47*</td>
</tr>
<tr>
<td>Control</td>
<td>41</td>
<td>Pre-therapy</td>
<td>188.26±23.15</td>
<td>114.56±33.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-treatment</td>
<td>184.57±27.01</td>
<td>10.95±24.63</td>
</tr>
</tbody>
</table>

Table. 4: Comparative analysis of oxidative stress indexes between the two groups (X±s).

Note: *compared with the control group after treatment, P<0.05.

**Comparison of vascular endothelial cell function between two groups**

After treatment, the levels of plasma vWF and ET-1 in the observation group were significantly lower than those in the control group (P<0.05), and the difference was statistically significant (P<0.05) and was significantly better than that in the control group (P<0.05). See Table 5.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>time</th>
<th>vWF (%)</th>
<th>ET-1(ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>41</td>
<td>Pre-therapy</td>
<td>190.25±21.20</td>
<td>116.75±30.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-treatment</td>
<td>161.11±28.30*</td>
<td>84.26±19.47*</td>
</tr>
<tr>
<td>Control</td>
<td>41</td>
<td>Pre-therapy</td>
<td>188.26±23.15</td>
<td>114.56±33.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-treatment</td>
<td>184.57±27.01</td>
<td>10.95±24.63</td>
</tr>
</tbody>
</table>

Table. 5: Comparison of plasma vWF and ET-1 levels before and after treatment between the two groups (X±s).

Note: *compared with the same group before treatment, P<0.05, compared with the control group after treatment, P<0.05.
Comparison of ANP, BNP, and CNP between two groups

After treatment, the levels of ANP and BNP in the observation group were significantly lower than those in the control group (P<0.05). The level of CNP in the observation group was significantly higher than that in the control group (P<0.05). See Table 6.

Discussion

The main pathological changes of peridabetic vascular lesions are thickening of the wall of peripheral arteries, multiple atherosclerotic plaques in the lumen, stenosis of vascular lumen, and ischemia of extremities. The disease is serious, progress is fast, and the amputation rate is high. These changes can seriously affect the patient's quality of life(7). At present, the main treatment for clinical patients with peripheral diabetic vascular disease is drug therapy. As a vasoactive drug, alprostadil has a wide range of biological effects, including anti-platelet aggregation, dilatation of vascular smooth muscle, and cell protection. The application of alprostadil in vascular diseases has been confirmed by many studies. In this study, alprostadil was used to treat peridabetic vascular disease patients with good clinical efficacy, and the results are as follows.

The results showed that the total effective rate of the observation group was 95.12% significantly higher than that of the control group (73.18%), the ankle-brachial ratio of the observation group was significantly higher than that of the control group, and the clinical symptom score of the observation group was significantly higher than that of the control group. The results showed that alprostadil was effective in the treatment of diabetic peripheral vascular disease and could effectively improve the clinical symptoms of the patients. Its main mechanism includes(10): increasing the level of intracellular cyclic adenosine monophosphate and reducing the peripheral vascular resistance, inhibition of platelet aggregation and synthesis of thromboxane A2, improvement of erythrocyte deformability and prevention of atherosclerotic lipid plaque formation, and the inhibition of free Ca in vascular smooth muscle in order to inhibit the release of nor-epinephrine from vascular sympathetic nerve endings and improve the peripheral circulation.

Studies have shown that hyperglycemia can cause oxidative and antioxidant disorders in the body, resulting in cell damage, cell membrane lipid peroxidation, and the rise of free radicals thereby promoting cell proliferation and accelerating atherosclerosis. MDA, as a product of lipid peroxidation, can reflect the level of lipid peroxide in vivo. SOD is a superoxide radical scavenger(11). In this study, the levels of oxidative stress in two groups of patients were measured after treatment. It was found that the serum MDA, AOPP level of patients in the observation group was significantly lower than that of the control group, and the level of SOD, T-AOC was significantly lower than that of the control group. It is concluded that alprostadil can effectively regulate the oxidative stress level and increase the activity of antioxidants while inhibiting the release of oxidation products, thus reducing the damage of oxidative stress to the peripheral vascular lesions of diabetes mellitus. The results are consistent with those of Gaozhi et al(12).

Plasma vWF is a glycoprotein synthesized and secreted by vascular endothelial cells. It can reflect the functional state of endothelial cells by measuring its content in blood. As a coagulant factor, it also plays a certain role in thrombosis and blood coagulation. ET-1 is a vasoactive peptide synthesized and secreted by vascular endothelial cells. It reduces glomerular filtration rate. When vascular endothelial cells are in pathological conditions, the secretion of ET increases with blood vessels in a state of contraction, leading to hemodynamic disorders and aggravating the progress of the disease(13). The results showed that the levels of plasma vWF and ET-1 in the observation group were significantly lower than those in the control group after treatment, which confirmed that alprostadil could effectively protect vascular endothelial cells in patients with peridabetic vascular disease. The reduction of peripheral vascular resistance is consistent with that of Fu Rao, et al(14).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>ANP (ng/L)</th>
<th>BNP (ng/L)</th>
<th>CNP (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>41</td>
<td>Pre-therapy</td>
<td>213.93±12.98</td>
<td>56.56±4.38</td>
<td>1.60±0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-treatment</td>
<td>179.68±17.34*</td>
<td>38.07±3.47#</td>
<td>2.28±0.24*</td>
</tr>
<tr>
<td>Control</td>
<td>41</td>
<td>Pre-therapy</td>
<td>214.82±10.41</td>
<td>55.34±4.26</td>
<td>1.69±0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-treatment</td>
<td>195.68±16.26</td>
<td>51.17±8.09</td>
<td>1.98±0.26</td>
</tr>
</tbody>
</table>

Table. 6: Comparison of ANP, BNP, and CNP levels between two groups (X±s).

Note: *compared with the same group before treatment, P<0.05, compared with the control group after treatment, P<0.05.
Natriuretic peptide is a peptide hormone synthesized by amino acid residues. ANP, BNP, and CNP are members of natriuretic peptide family. ANP is synthesized and secreted by atrial myocytes. When blood pressure, heart rate, and blood volume increase, the content of ANP in plasma increases. BNP is secreted by ventricular cells. When cardiomyocytes are in an overload state, the content of BNP is increased. CNP mainly exists in the central nervous system. When vascular endothelial cells are damaged, the secretion of CNP decreases significantly. The results of this study showed that the levels of ANP and BNP in the observation group were significantly lower than those in the control group, and the CNP level was significantly decreased after treatment. We proved that alprostadil could prevent and treat peridiabetic vascular lesions, and its mechanism might be related to the improvement of the secretion of natriuretic peptide.

In conclusion, alprostadil is effective in treating peridiabetic vascular disease which can effectively improve oxidative stress, protect endothelial cell function, regulate the secretion of natriuretic peptide, and slow down the development of the disease. This is worthy of clinical application.

References


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