Effects of alprostadil combined with calcium dobesilate in patients with diabetic peripheral neuropathy

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Abstract

OBJECTIVE: To observe the clinical curative effects of alprostadil combined with calcium dobesilate in type 2 diabetes patients with peripheral neuropathy.
METHODS: We randomly divided 120 type 2 diabetes patients with diabetic peripheral neuropathy into two groups. The treatment group was prescribed alprostadil (10 µg, once daily) and oral calcium dobesilate (0.5 g, 3 times daily), and the control group was prescribed alprostadil (10 µg, once daily) for a total treatment duration of 2 weeks. The Michigan Diabetic Neuropathy Score (MDNS) and the Michigan Neuropathy Screening Instrument (MNSI) were used to evaluate differences between the two groups before and after treatment.
RESULTS: Following 2 weeks of treatment, the total effective rate in the treatment group was significantly better than that of the control group ($p<0.05$) and the MDNS and MNSI scores in the treatment group were significantly lower than those in the control group ($p<0.05$ or $p<0.01$).
CONCLUSION: Combined alprostadil and calcium dobesilate treatment for type 2 diabetic peripheral neuropathy showed good clinical efficacy and an improved curative effect than single alprostadil treatment.

INTRODUCTION

Diabetic peripheral neuropathy is one of the most common chronic complications of diabetes, and the prevalence rate is reported to range between 10% and 90%. The main pathological features include degeneration of distal nerves, loss of nerve fiber, and demyelination and degeneration stages. The pathogenesis of diabetic peripheral neuropathy (DPN) remains unclear. However, a number of clinical studies have identified hyperglycemia as the main cause of various physiological and pathological changes, such as high blood glucose due to metabolic disorders, microvascular disease, lack of neurotrophic factors, free radical damage, abnormal gene expression and other pathogenic factors that interact to damage nerve cells and nerve fibers through ischemic demyelination (Tsukahara *et al.* 2003; Head 2006; Srivastava *et al.* 2006; Kandadi *et al.* 2011; Ziegler *et al.* 2014; Ji *et al.* 2012). There is no targeted treatment. Calcium dobesilate is a vaso-protective agent that has been used in the prevention and treatment of diabetic retinopathy (Garay *et*

al. 2005; Leal *et al.* 2010; Zhang *et al.* 2015). It functions to inhibit platelet aggregation through activating adenosine cyclase levels and ascending cyclic adenosine monophosphate. Calcium dobesilate can reduce capillary permeability in patients with diabetes, reducing albumin exudation and improving blood albumin levels. One study (10 found that it has beneficial effects on many microvascular circulatory disorders. Other studies (Vinazzer and Hachen 1987; Szlavy *et al.* 1992; Arceo *et al.* 2002; Kaur *et al.* 2003; Marinello and Videla 2004) have found that this medication has been useful in the treatment of renal disease, chronic venous insufficiency, incomplete thrombotic disease, and specific heart diseases, and has been widely used in diabetes-related nephropathy. These findings suggest that treatment with calcium dobesilate may be beneficial in treating DPN. Alprostadil is a vaso-active drug, which can dilate blood vessels and inhibit platelet aggregation, reduce blood viscosity and erythrocyte aggregation, and improve microcirculation within the brain. To this end, this study aimed to observe the curative effects of calcium dobesilate combined with alprostadil in the treatment of DPN.

MATERIALS AND METHODS

Patients

A total of 120 patients with diabetes, hospitalized in the Department of Endocrinology in 2016, Chengyang District People's Hospital of Qingdao City, aged from 45 years to 80 years, were divided into two groups: treatment group (56 patients) and control group (64 patients). All the patients met the World Health Organization (WHO) diagnostic criteria for type 2 diabetes mellitus (Gabir *et al.* 2000), the American Diabetes Association criteria, and the 2010 European Association for the Study of Diabetes diagnosis expert consensus standards diagnosis for DPN (Tesfaye *et al.* 2010). Patients with a history of alcoholics (that is, alcohol consumption of 100 ml/day, the alcohol content of 40%, more than 10 years) were excluded. Further, patients with the following diseases were excluded: severe acute complications such as diabetic ketoacidosis, hyperosmolar non-ketotic syndrome, low blood sugar, lactic acidosis, and diseases such as cerebrovascular disease, cervical and/or lumbar diseases, infectious polyneuropathy, connective tissue disease, vasculitis, uremia, foot infections, edema, depression, anxiety disorders, and peripheral neuropathy caused by severe hepatorenal dysfunction and other diseases. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Chengyang People's Hospital in Qingdao. Written informed consent was obtained from all participants.

Patient Treatment

For glycemic control, the treatment group was administered alprostadil (Beijing Pharmaceutical Co., Ltd. TED) 10 µg, once daily, and oral calcium dobesilate (Jiangsu Wangao Pharmaceutical Co., Ltd.) 0.5 g, 3 times daily, for 2 weeks. The control group was administered alprostadil (Beijing Pharmaceutical Co., Ltd. TED) 10 µg once daily, for 2 weeks. Both groups were requested not to take any other medication for the treatment of DPN. Assessment using the Michigan Diabetic Neuropathy Score (MDNS) and the Michigan Neuropathy Screening Instrument (MNSI) was undertaken before and after treatment (Huang *et al.* 2010).

In order to ensure the data were accurate, complete and reliable, all patient data regarding the duration of diabetes, age, sex, height, weight, waist circumference (WC), hip circumference (HC), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG) and fasting blood glucose at 8-10 hours, total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL-c), and low density lipoprotein (LDL) were measured and recorded. Blood glucose was measured using the glucose oxidase method and an automatic biochemical analyzer was used to measure blood lipid levels.

Clinical efficacy criteria

Clinical efficacy was shown to be effective when paresthesia disappeared, and tendon reflexes either significantly improved or returned to normal. Clinical efficacy was shown to be efficient when paresthesia reduced, and tendon reflexes improved. Clinical efficacy was shown to be ineffective when no improvement was reported or paresthesia worsened. The total efficacy rate was calculated as: (effective + efficient) / total number of patients × 100%.

Statistical analysis

We used SPSS 17.0 statistical software for data processing, measurement of data using $\bar{x} \pm s$, and the t-test for comparison between the groups. A *p* value of $p < 0.05$ was considered statistically significant for differences between the groups. We calculated body mass index (BMI) as BMI = weight / height squared (kg/m²).

RESULTS

Comparison of baseline data survey patients before and after treatment

There was no significant difference in baseline data between the treatment and control groups ($p > 0.05$) (Table 1).

Comparison of clinical efficacy

The total efficacy rate of the control group and the treatment group was 87.50% (56/64) and 96.43% (54/56), respectively. The clinical curative effect of the treatment group was significantly better than that of the control

group and the difference was statistically significant (*p*<0.05) (Table 2).

Comparison of diabetic neuropathy scores

The MDNSs for the control group before and after treatment were 25.26±5.81 and 22.35±4.48, respectively, and the MDNSs for the treatment group before and after treatment were 25.39±5.54 and 18.96±3.62, respectively. The MNSI scores for the control group before and after treatment were 6.11±0.98 and 5.28±0.88, respectively; the MNSI scores for the treatment group before and after treatment were 5.98±1.74 and 2.10±0.90, respectively. The MDNSs and MNSI scores in the two groups after treatment decreased significantly compared with the before-treatment scores, and were lower than the control group, with statistically significant differences in *p*<0.05 (Table 3).

DISCUSSION

The mechanism of diabetic neuropathy is not completely clear, but in combination with generally reduced sensation and vascular disorders, metabolic disorders, and neurotrophic factors, it leads to the stage of nerve fiber demyelination, degeneration, and necrosis (Premkumar and Pabbidi 2013). DPN has an imbalance between endothelin derived dilated vascular substances, nitric oxide and vasoconstrictor substances, and the main manifestation was elevated ET level, and ET further inhibits the production of nitric oxide, it leads to a decrease in the levels of nitric oxide, and destroys the balance of the internal environment, and thereby an endothelial dysfunction. Vascular endothelial dysfunction aggravated the degree of ischemia and hypoxia of nerve tissue, resulting in axonal degeneration of nerve fibers and affecting the nerve conduction velocity (Ahanchi *et al.* 2007; Matsumoto *et al.* 2010; Kawanabe and Nauli 2011; Volpe *et al.* 2014). It has been found that the plasma ET level in type 2 diabetic patients is positively correlated with diabetic microangiopathy (Kalani 2008). Prostaglandin E1 (PGE1) is the main component of alprostadil, and biologically active substances with vasodilation. The mechanism of action increases inositol content in nerve cells by regulating adenylate cyclase and activity of two phosphate esterase. In addition, by inhibiting the free Ca^{2+} of vascular smooth muscle cells, the vascular smooth muscle cells relax and dilate the blood vessels. It also inhibits

Tab. 1. Comparison of baseline data survey subjects before and after treatment (x̄±s).

Group	(n)	Duration (y)	Age (y)	BMI (kg/m²)	WC (cm)	SBP (mmHg)	DBP (mmHg)
Control	64	8.35±4.86	53.82±11.9	23.92±4.75	82.10±5.51	120.76±18.32	69.82±10.96
Treatment	56	8.45±5.46	54.02±11.9	24.00±5.43	81.62±5.34	119.02±20.98	69.94±11.37

Tab. 1. Comparison of clinical indicators before and after treatment (continous, x̄±s).

Group	FBG (mmol/l)	TG (mmol/l)	TC (mmol/l)	UA (mmol/l)	HDL (mmol/l)	LDL (mmol/l)
Control	5.85±1.79	1.22±0.78	4.97±1.30	265.01±68.24	1.42±0.25	2.78±1.06
Treatment	6.01±1.79	1.21±0.55	4.86±1.30	254.26±53.95	1.41±0.23	2.71±1.07

Tab. 2. Comparison of clinical efficacy between the two groups

Group	n	Effect	Efficient	Invalid	Total effective rate (%)
Control	64	20	36	8	87.50
Treatment	56	34	20	5	96.43*

Note: Compared with the control group, *P<0.05.

Tab. 3. Comparison of diabetic neuropathy score.

Group		MDNS	MNSI
Treatment	Before	25.39±5.54	5.98±1.74
	After	18.96±3.62*&	2.10±0.90*&
Control	Before	25.26±5.81	6.11±0.98
	After	22.35±4.48*	5.28±0.88*

Note: Compared with control group, *p*<0.01; compared with before treatment, *p*<0.05.

smooth muscle cell proliferation, and improves platelet function, and inhibits platelet aggregation, and reduces ET, thromboxane A2 and formation of immune complex, improves tissue blood supply, so as to improve the microcirculation, enhances blood flow and improves nerve conduction velocity (Akahori *et al.* 2004). Therefore, this study using alprostadil found that the MDNSs and the MNSI scores were superior to those in the control group after treatment and that the difference was statistically significant ($p<0.05$).

Calcium dobesilate is a neuroprotective agent that acts to reduce antioxidant stress, reducing apoptosis and delaying the local proliferation of vascular cells (Zhang *et al.* 2015). To improve vascular function and delay the inflammatory process (Garay *et al.* 2005; Yang and Wang 2012), it is commonly used in the treatment of diabetic retinopathy and chronic venous insufficiency, vascular disease, and the treatment of DPN. This study showed that when calcium dobesilate and alprostadil treatment was applied in combination in a treatment group and compared with alprostadil treatment alone in a control group, the MDNS and MNSI scores were better in the treatment group than in the control group, with a difference that was statistically significant ($p<0.05$).

CONCLUSION

The results of this study demonstrate that calcium dobesilate combined with alprostadil can reduce DPN for patients with limb pain, numbness and other neuropathic symptoms, and improve the therapeutic effect, and that this combination is worth of consideration for clinical use.

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CONFLICT OF INTEREST

The authors have a competing interest to declare.

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