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Effects of Xueshuantong combined with antioxidant drugs on nerve conduction function and oxidative stress in patients with diabetic peripheral neuropathy

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ABSTRACT

Objective: To study the effect of Xueshuantong combined with antioxidant drugs on nerve conduction function and oxidative stress in patients with diabetic peripheral neuropathy. **Methods:** 138 cases of patients with diabetic peripheral neuropathy who were treated in endocrinology department of our hospital between June 2014 and October 2016 were enrolled and randomly divided into two groups. The combination group received Xueshuantong combined with antioxidant drug therapy, and the control group received antioxidant drug therapy. Before and after treatment, the nerve conduction velocity as well as serum content of oxidative stress indexes and nerve cytokines was measured. **Results:** 4 weeks and 8 weeks after treatment, common peroneal nerve and median nerve MNCV and SNCV as well as serum SOD, GSH-Px, HO-1, CAT, CNTF, BDNF and SDF-1 levels of both groups were significantly higher than those before treatment while serum MDA, AOPP and 8-OHdG levels were significantly lower than those before treatment, and common peroneal nerve and median nerve MNCV and SNCV as well as serum SOD, GSH-Px, HO-1, CAT, CNTF, BDNF and SDF-1 levels of combination group were significantly higher than those of control group while serum MDA, AOPP and 8-OHdG levels were significantly lower than those of control group. **Conclusion:** Xueshuantong combined with antioxidant drugs can improve the nerve conduction function, inhibit oxidative stress response and improve neurotrophy status in patients with diabetic peripheral neuropathy.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a common disease of endocrinology, the incidence is rising year by year, elevated blood sugar levels and insulin resistance are the important characteristics of T2DM patients, and substandard blood glucose control will increase the risk of macrovascular complications and microvascular complications. Diabetic peripheral neuropathy is a microvascular complication common in T2DM patients, symmetry limb sensory dysfunction is the characteristic change, and severe cases will evolve into diabetic foot[1,2]. Oxidative stress is considered to be the important pathological factor for high glucose environment to cause neural function damage, and antioxidant drugs are widely used in the treatment of diabetic peripheral neuropathy. In the progression of diabetic peripheral neuropathy, local hypoxia caused by microvascular lesions is an important reason to activate the oxidative stress, and the blood-promoting therapy to improve circulation for local oxygen has important mechanism[3,4]. Xueshuantong is a Chinese patent drug that promotes blood circulation to remove blood stasis, improves microcirculation and scavenges oxygen free radicals[5], and the effect of Xueshuantong combined with antioxidant drugs on nerve conduction function and oxidative stress in patients with diabetic peripheral neuropathy was analyzed in the following research.

2. Case information and research methods

2.1 Case information

Case information of 138 patients with diabetic peripheral neuropathy who were treated in endocrinology department of Pidu District People's Hospital between June 2014 and October 2016

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were selected, all patients were diagnosed with type 2 diabetes by OGTT, the EMG examination confirmed the existence of peripheral neuropathy, and the trauma and organic disease as well as nervous system disease and mental illness-induced peripheral neuropathy were eliminated. Random number table was used to divide the 138 patients into two groups, each with 69 cases. Combination group received Xueshuantong combined with antioxidant drug therapy, including 42 male cases and 27 female cases that were 42-58 years old; control group received antioxidant drug therapy, including 39 male cases and 30 female cases that were 41-61 years old. There was no significant difference in general information between the two groups of patients (P>0.05).

2.2 Therapy

Both groups received regular diet, exercise intervention and hypoglycemic therapy, hypoglycemic goal was glycosylated hemoglobin < 7%, fasting glucose < 6.0 mmol/L and 2 h postprandial h plasma glucose < 8.0 mmol/L. The control group received regular antioxidant therapy, and the method was as follows: the α-thioctic acid injection 0.6 g in saline 250 mL, by intravenous drip, one time per day; methylamine injection 1 mg in saline 100 mL, by intravenous drip, 1 time per day. Combination group of patients received Xueshuantong combined with antioxidant therapy, and methods were as follows: same α-thioctic acid injection and methylamine injection therapy as those of control group, and Xueshuantong injection 450 mg in 250 mL saline, by intravenous drip, 1 time a day.

2.3 Nerve conduction function evaluation methods

Before treatment as well as 4 weeks and 8 weeks after treatment, EMG instrument was used to determine the motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) of common peroneal nerve and median nerve of two groups of patients.

2.4 Serum index detection methods

Before treatment as well as 4 weeks and 8 weeks after treatment, 3-5 mL cubital venous blood was collected from two groups of patients and centrifuged to separate serum, radioimmunoprecipitation kits were used to determine the content of MDA, AOPP, 8-OHdG, SOD, GSH-Px, HO-1 and CAT, and enzyme-linked immunosorbent assay kits were used to determine the content of CNTF, BDNF and SDF-1 .

2.5 Statistical methods

SPSS 20.0 software was used to input the nerve conduction velocity and serum indexes, above data between two groups were by t test and P<0.05 indicated statistical significance in differences.

3. Results

3.1 Nerve conduction velocity before and after treatment

Before treatment as well as 4 weeks and 8 weeks after treatment, analysis of common peroneal nerve and median nerve MNCV and SNCV between two groups of patients was as follows: before treatment, differences in common peroneal nerve and median nerve MNCV and SNCV were not statistically significant between two groups of patients (P>0.05); 4 weeks and 8 weeks after treatment, common peroneal nerve and median nerve MNCV and SNCV of both groups were significantly higher than those before treatment (P<0.05), and common peroneal nerve and median nerve MNCV and SNCV of combination group were significantly higher than those of control group (P<0.05).

3.2 Serum oxidative stress index levels

Before treatment as well as 4 weeks and 8 weeks after treatment, analysis of serum oxidative stress products MDA (nmol/L), AOPP (μmol/L) and 8-OHdG (pg/ml) levels between two groups of patients was as follows: before treatment, differences in serum MDA, AOPP and 8-OHdG levels were not statistically significant

Table 1.
Comparison of nerve conduction velocity between two groups of patients before and after treatment (m/s).

Groups	n	Time	Common peroneal nerve		Median nerve	
			MNCV	SNCV	MNCV	SNCV
Combination group	69	Before treatment	34.41±5.92	30.24±4.95	33.26±5.64	36.29±5.62
		4 weeks after treatment	51.94±7.26[ab]	45.61±7.14[ab]	49.51±6.28[ab]	52.11±7.12[ab]
		8 weeks after treatment	63.21±9.35[ab]	54.20±8.25[ab]	56.22±7.51[ab]	61.94±7.88[ab]
Control group	69	Before treatment	34.29±5.26	30.95±5.25	32.89±4.95	35.69±5.28
		4 weeks after treatment	43.23±6.25[a]	38.52±7.21[a]	40.26±6.21[a]	45.21±6.25[a]
		8 weeks after treatment	49.05±7.14[a]	44.21±6.29[a]	47.52±7.29[a]	50.26±7.92[a]

[a]: comparison between after treatment and before treatment, P<0.05; [b]: comparison between combination group and control group, P<0.05.

Table 2.
Comparison of serum oxidative stress products between two groups of patients before and after treatment.

Groups	n	Time	MDA	AOPP	8-OHdG
Combination group	69	Before treatment	13.47±1.94	49.51±7.41	642.59±77.86
		4 weeks after treatment	6.47±0.94[ab]	27.64±3.95[ab]	357.31±52.93[ab]
		8 weeks after treatment	4.26±0.73[ab]	20.31±2.89[ab]	221.36±32.94[ab]
Control group	69	Before treatment	13.84±2.03	49.93±7.25	648.42±89.25
		4 weeks after treatment	8.79±1.02[a]	38.19±5.62[a]	497.65±61.25[a]
		8 weeks after treatment	6.42±0.77[a]	26.41±3.95[a]	373.41±49.75[a]

[a]: comparison between after treatment and before treatment, P<0.05; [b]: comparison between combination group and control group, P<0.05.

Table 3.
Comparison of serum anti-oxidative stress enzymes between two groups of patients before and after treatment.

Groups	*n*	Time	SOD	GSH-Px	HO-1	CAT
Combination group	69	Before treatment	94.21±11.42	102.35±16.48	62.39±8.23	75.95±9.35
		4 weeks after treatment	135.48±17.76[ab]	148.69±19.24[ab]	97.84±11.25[ab]	110.32±15.62[ab]
		8 weeks after treatment	158.52±11.25[ab]	192.32±24.57[ab]	126.29±15.62[ab]	152.39±20.24[ab]
Control group	69	Before treatment	96.02±11.82	104.02±15.61	63.41±8.93	76.61±9.62
		4 weeks after treatment	118.25±17.27[a]	120.25±16.29[a]	78.69±9.24[a]	92.31±10.25[a]
		8 weeks after treatment	128.31±19.24[a]	139.48±20.32[a]	90.31±11.29[a]	127.52±16.82[a]

[a]: comparison between after treatment and before treatment, $P<0.05$; [b]: comparison between combination group and control group, $P<0.05$.

Table 4.
Comparison of serum neurotrophic cytokines between two groups of patients before and after treatment.

Groups	*n*	Time	CNTF	BDNF	SDF-1
Combination group	69	Before treatment	1.85±0.25	6.29±0.93	42.95±7.62
		4 weeks after treatment	3.77±0.51[ab]	9.51±1.14[ab]	78.42±9.35[ab]
		8 weeks after treatment	5.08±0.77[ab]	14.27±1.86[ab]	97.28±11.27[ab]
Control group	69	Before treatment	1.90±0.24	6.41±0.87	43.41±7.83
		4 weeks after treatment	2.78±0.36[a]	7.96±0.93[a]	60.32±8.94[a]
		8 weeks after treatment	3.59±0.52a	11.25±1.85[a]	74.12±9.35[a]

[a]: comparison between after treatment and before treatment, $P<0.05$; [b]: comparison between combination group and control group, $P<0.05$.

between two groups of patients ($P>0.05$); 4 weeks and 8 weeks after treatment, serum MDA, AOPP and 8-OHdG levels of both groups were significantly lower than those before treatment ($P<0.05$), and serum MDA, AOPP and 8-OHdG levels of combination group were significantly lower than those of control group ($P<0.05$).

Before treatment as well as 4 weeks and 8 weeks after treatment, analysis of serum anti-oxidative stress enzymes SOD, GSH-Px, HO-1 and CAT levels between two groups of patients was as follows: before treatment, differences in serum SOD, GSH-Px, HO-1 and CAT levels were not statistically significant between two groups of patients ($P>0.05$); 4 weeks and 8 weeks after treatment, serum SOD, GSH-Px, HO-1 and CAT levels of both groups were significantly higher than those before treatment ($P<0.05$), and serum SOD, GSH-Px, HO-1 and CAT levels of combination group were significantly higher than those of control group ($P<0.05$).

3.3 Serum neurotrophic cytokine levels

Before treatment as well as 4 weeks and 8 weeks after treatment, analysis of serum neurotrophic cytokines CNTF (pg/mL), BDNF (ng/mL) and SDF-1 (ng/mL) levels between two groups of patients was as follows: before treatment, differences in serum CNTF, BDNF and SDF-1 levels were not statistically significant between two groups of patients ($P>0.05$); 4 weeks and 8 weeks after treatment, serum CNTF, BDNF and SDF-1 levels of both groups were significantly higher than those before treatment ($P<0.05$), and serum CNTF, BDNF and SDF-1 levels of combination group were significantly higher than those of control group ($P<0.05$).

4. Discussion

Diabetic peripheral neuropathy is a diabetic microvascular complication, and the local hypoxia caused by microvascular lesions can lead to mitochondrial dysfunction and increased formation of oxygen free radicals, and thus cause oxidative stress injury to nerve function. Methylamine and thioctic acid are the drugs that have neurotrophic and antioxidant properties, and are widely used in the treatment of diabetic peripheral neuropathy[6]. However, the recovery of nerve function is not ideal due to the failure of patients to improve the microvascular disease[7,8]. Xueshuantong is a common Chinese patent drug to treat cardiovascular and cerebrovascular diseases, and the salvia miltiorrhiza, radix astragali, notoginseng and other pharmaceutical ingredients have the effects of dilating blood vessels, improving circulation and increasing blood capillary permeability, and can also remove oxygen free radicals and reduce oxidative stress damage[9,10]. Lowered nerve conduction velocity in extremities is the main pathological change of diabetic peripheral neuropathy, and in order to define the value of Xueshuantong combined with antioxidant drugs for the treatment of diabetic peripheral neuropathy, common peroneal nerve and median nerve conduction velocity were compared between two groups of patients before and after treatment, and the results showed that common peroneal nerve and median nerve MNCV and SNCV of both groups increased significantly after treatment, and common peroneal nerve and median nerve MNCV and SNCV of combination group were significantly higher than those of control group after treatment. This means that both routine antioxidant drug therapy and Xueshuantong combined with antioxidant drug therapy can improve nerve conduction function in patients with diabetic peripheral neuropathy, and Xueshuantong combined with antioxidant drugs can better improve the nerve conduction function than conventional antioxidant drug therapy.

Oxidative stress is an important pathological link for high glucose environment in diabetic patients to cause peripheral nerve injury, and the massive generation of oxy gen free radicals in the process of oxidative stress reaction will not only directly cause nerve structure and function damage[11,12], but will also generate a variety of oxidation products in the process of oxidation reaction. MDA, AOPP and 8-OHdG are the oxidation products of lipids, proteins and nucleic acids[13]. In order to define the effect of Xueshuantong combined with antioxidant drug treatment on oxidative stress damage degree in patients with diabetic peripheral neuropathy, serum levels of above oxidative stress products were compared in the study, and the results showed that serum MDA, AOPP and 8-OHdG levels of both groups significantly decreased after treatment, and serum MDA, AOPP and 8-OHdG levels of combination group were significantly lower than those of control group after treatment. The large production of oxygen free radicals will not only increase the production of oxidative stress products, but also massively consume a variety of antioxidant enzymes such as SOD, GSH-Px, HO-1 and CAT. SOD and GSH-Px are able to reduce reactive oxygen directly

to hydrogen peroxide, which is reduced to water by CAT and discharged; HO-1 is involved in several processes for antioxidant activity[14,15]. In the study, analysis of the changes in serum levels of above antioxidant enzymes before and after treatment showed that serum SOD, GSH-Px, HO-1 and CAT levels of both groups significantly increased after treatment, and serum SOD, GSH-Px, HO-1 and CAT levels of combination group were significantly higher than those of control group after treatment. This means that both routine antioxidant drug therapy and Xueshuantong combined with antioxidant drug therapy can improve the oxidative stress reaction and enhance antioxidant capacity in patients with diabetic peripheral neuropathy, and Xueshuantong combined with antioxidant drugs can better inhibit oxidative stress reaction than conventional antioxidant drug therapy.

During neural functional recovery in diabetic peripheral neuropathy, various cytokines with neurotrophic functions are involved in the repair of nerve function. Oxidative stress reaction damage to peripheral nerve is not only characterized by neuron and glial cell structure and conduction function destruction, but can also affect the endocrine function of nerve cells and reduce the neurotrophic factor secretion, which is not conducive to the body's self compensatory repair of nerve injury. CNTF, BDNF and SDF-1 are the neurotrophic cytokines that play an important role in the process of peripheral nerve damage and repair. CNTF is a member of gp130 receptor cytokine family, it is secreted by the schwann cells in the peripheral nervous system, and the cytokine can enhance mitochondrial oxidative respiratory energy supply function to promote regeneration of axons in peripheral nerve tissue, which is beneficial to the recovery of neural function[16]; BDNF is a neurotrophic factor derived from the neurons and glial cells, and its combination with the receptor P75 can promote the neuron regeneration and myelination, and thus improve the nerve conduction function[17,18]; SDF-1 can promote the nerve progenitor cell migration to the local damaged nerve and promote the repair of the nerve function[19]. In the study, analysis of the changes in serum levels of neurotrophic cytokines between two groups of patients before and after treatment showed that serum CNTF, BDNF and SDF-1 levels of both groups significantly increased treatment, and serum CNTF, BDNF and SDF-1 levels of combination group were significantly higher than those of control group after treatment. This means that both routine antioxidant drug therapy and Xueshuantong combined with antioxidant drug therapy can improve neurotrophic status in patients with diabetic peripheral neuropathy, and Xueshuantong combined with antioxidant drugs can better improve the neurotrophic status than conventional antioxidant drug treatment.

Based on above discussion, it can be concluded that Xueshuantong combined with antioxidant drug therapy can better improve the nerve conduction function of patients with diabetic peripheral neuropathy than routine antioxidant drug therapy, and to inhibit oxidative stress reaction, improve the antioxidant capacity and improve neurotrophic status are the mechanisms for Xueshuantong to exert therapeutic value.

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