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Effect analysis of tanshinone IIA sulfonate sodium combined with α-lipoic acid in patients with diabetes peripheral neuropathy

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Abstract: To investigate the effect of tanshinone IIA sulfonate sodium combined with α-Lipoic acid on fasting blood sugar (FPG), 2h postprandial blood glucose (2hPG), total cholesterol (TG), triacylglycerol (TC) and therapeutic effect in patients with diabetes peripheral neuropathy (DPN). The control group (n=52) was treated with tanshinone IIA sodium sulfonate alone. The study group was treated with α-Lipoic acid and tanshinone IIA sodium sulfonate. The changes in blood glucose, blood lipid levels, oxidative stress indicators and the improvement of nerve function conduction of both two groups were compared. After treatment, study group's FPG, 2hPG, TG and TC were found to be lower than the control group (P<0.05). The levels of Super oxide dismutase (SOD) and nitric oxide (NO) in the study group were higher than those in the control group. The study group had lower Malondialdehyde (MDA) (P<0.05). The study group had higher nerve motor conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) (P<0.05). Tanshinone IIA sulfonate sodium combined with α-Lipoic acid can improve DPN patients' blood glucose and lipid levels, alleviate the oxidative stress reaction of the body, promote the recovery of nerve conduction function and enhance the therapeutic effect.

Keywords: DPN; Sodium tanshinone IIA sulfonate; α-Lipoic acid; FPG, 2hPG, TG, TC

INTRODUCTION

Global data survey shows that (Levinstein *et al.,* 2023) the range of DPN incidence rate can reach 27.4%~81.6%. Moreover, the occurrence of diseases can seriously affect patients' sensory and motor tissue nerves, reduce their quality of life and endanger their life safety. Currently, drugs are an important means of clinical treatment for DPN. However, the pathogenesis of DPN is still unclear and has complex, diverse and multi-link pathological characteristics. Therefore, using medication alone to improve the condition still cannot achieve the desired therapeutic effect. Research and discussion need to be conduct on the optimal medication plan for multiple pathological stages of treatment to enhance treating effect of diseases and improve prognosis. Tanshinone IIA is an important monomer extracted from *Salvia miltiorrhiza*, with strong lipid solubility, while sodium tanshinone IIA sulfonate is a drug formed after sulfonation of tanshinone IIA. It enhances the affinity of tanshinone IIA to water. When the drug acts on the body, it can effectively expand blood vessels, improve microcirculation, increase local blood volume and achieve the purpose of relieving vasospasm (Li *et al.,* 2021). α-Lipoic acid is a kind of strong anti-oxidant containing sulfur in the clinic, which can be converted into reduced dihydrolipoic acid to eliminate reactive oxygen species and free radicals in the body, and has significant effect on controlling tissue damage caused by oxidative stress. α-Lipoic acid can activate the metabolism and circulation of a variety of antioxidants in the body of patients, make them form regenerative circulation connections, continuously reduce oxidative stress reaction, restore and maintain the normal level of antioxidants, and have significant anti oxidative therapeutic effect. Turkyilmaz *et al*. (2021) used α-Lipoic acid in DPN patients to improve the disease treatment effect. Kong *et al*. (2020) applied sodium tanshinone IIA sulfonate to effectively improve the patient's condition in DPN patients. However, few clinical studies are available on the combination treatment of both drugs. Therefore, the aim of this study was to use tanshinone α A sulfonate sodium and α-Lipoic acid in combination to treat DPN patients and analyze the treatment effect.

MATERIALS AND METHODS

Research materials

A survey was conducted on 104 DPN patients admitted to the hospital from February 2022 to February 2023. In the study, 104 DPN patients hospitalized from February 2022 to February 2023 were selected and divided into groups by random number table. The control group (n=52) was treated with tanshinone IIA sodium sulfonate alone. The study group was treated with α-Lipoic acid and tanshinone IIA sodium sulfonate. Age, gender, Body Mass Index (BMI), DM course, DPN course and blood pressure data were compared between the two groups (P>0.05) in table 1.

Inclusion and exclusion criteria

Inclusion criteria: (A) Confirmed as DPN and the criteria in reference (Nkonge K M *et al.* 2023).
(B) The Toronto clinical scoring system (TCSS) score greater than 5 points. (C) Hemoglobin A1C (HbA1c)>7%.

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(D) Electromyography showed that the patient had motor Sensory nerve conduction disorder. (E) Normal mental state, cognition, and reading and writing abilities.

Exclusion criteria: (A) DPN caused by genetic, vascular, or immune diseases. (B) History of severe allergies in previous clinical medication. (C) Diabetic ketoacidosis. (D) Other diabetic complications such as glaucoma and nephropathy. (E) Concomitant systemic infection or malignant tumor. The experiment was approved by the hospital ethics committee. All patients had signed informed consent forms.

Research methods

Both groups of patients underwent routine treatment and blood glucose control. The patients took orally hypoglycemic drugs or used insulin to control the blood sugar level strictly and regularly according to the doctor's instructions and assisted diabetes diet and regular exercise.

Control group: Patients were treated with pure tanshinone IIA sulfonic acid sodium medication, and tanshinone IIA sulfonic acid sodium was taken (Manufacturer: Haiyi Biochemical Pharmaceutical Co., Ltd., national drug approval No.H31022558, specification: 10mg/2mL). For this treatment, 40mg of medication was mixed with 0.9% sodium chloride for intravenous drip once a day.

Study group: Patients were treated with α-Lipoic acid on the basis of drug treatment in the control group. The dosage and method of administration of sodium tanshinone IIA sulfonate were the same as those of the control group. α-Lipoic acid (obtained was manufactured by: Shanghai Hyundai Hasen (Shangqiu) Pharmaceutical Co., Ltd. National Drug Approval Number: H20056403. Specification: 20ml: 0.6g). This time, 20mL of medication was taken and mixed with 0.9% sodium chloride. After thorough mixing, intravenous drip was administered once a day. The treatment lasted for 4 weeks and lasted for a total of 3 courses.

Observation indicators and evaluation

General information: A self-made survey questionnaire was used for evaluation in the experiment. The content included in patient age, gender, DM course, DPN course, BMI, SBP, DBP.

Blood glucose and blood lipids: The evaluation items included FPG, 2hPG, TG and TC. The above indicators were evaluated by the responsible nurse and attending physician before treatment (first day of admission) and after treatment (before discharge). The levels of FPG and 2hPG were measured by blood glucose instrument on an empty stomach and 2h after meal, respectively. The patient kept fasting in the morning, 4mL of fasting blood was taken, centrifuged at a speed of 3000r/min for 10 minutes and the supernatant was taken. The levels of TG and TC were measured using radioimmunoassay.

Oxidative stress indicators: The assessment items included super oxide dismutase (SOD), nitric oxide (NO), malondialdehyde (MDA). The attending physician tested the above indicators in the laboratory before and after treating. 3mL of venous blood was taken on an empty stomach in the early morning and centrifuged at a speed of 3000r/min. The serum samples were obtained and tested using enzyme-linked immunosorbent assay (Krittanai *et al.* 2023).

Nerve conduction: The evaluation indexes were sensory nerve conduction velocity (SNCV) and motor nerve conduction velocity (MNCV) of median/common peroneal nerve. The attending physician used Neurocare-C Electromyography instrument to detect the above indexes before and after treatment. The collection of the above indicators was conducted by the investigators after consulting medical records and collecting information.

Ethical approval

Ethics Committee approval was obtained from the Institutional Ethics Committee of Changzhou Cancer Hospital (No.024015) to the commencement of the study.

STATISTICAL ANALYSIS

SPSS26.0 was used to analyze the data, and the counting data were represented by the number of cases (n) and rate, with χ^2 inspection between groups. The mean ± standard deviation (x±s) was used to represent the metrological data that completely conform to the normal distribution, and the independent sample *t* was applied for testing. $P<0.05$ indicated a statistically significant difference.

RESULTS

Comparison of general data between the two groups

Comparison of age, gender, duration of DM, duration of DPN, BMI, SBP, and DBP between the two groups were not different ($P>0.05$), as shown in table 1.

Comparison of FPG, 2hPG, TG and TC indicators

Before treating, blood glucose levels between the two groups were not different ($P>0.05$). After treatment, two groups' FPG, 2hPG, TG and TC decreased and the study group was found to be lower ($P<0.05$) in table 2.

Comparison of SOD, MDA and NO levels

Oxidative stress levels between the two groups were not significantly different before treatment ($P>0.05$). The SOD and NO levels in both groups increased and the study group had higher SOD and NO levels than those of the control group, with a statistically significant difference ($P>0.05$).

Table 1: Two sets of general information (x±s, %)

Group	n	Age (year)	Sex		DM course (year)	DPN course (year)
			Male	Female		
Control group	52	61.18±5.16	28	24	13.59±2.68	8.67±1.67
Research group	52	61.37±5.02	31	21	13.87±2.36	8.92±1.46
t		0.190	1.891		0.565	0.813
P		0.849	0.169		0.573	0.418
Group	n	BMI (kg/m^2)	SBP (mmHg)		DBP (mmHg)	
Control group	52	24.26±2.06	118.67±7.29		72.49±5.29	
Research group	52	24.81±2.01	119.48±7.05		72.63±5.17	
t		1.378	0.576		0.136	
P		0.172	0.566		0.892	

Comparison of FPG, 2hPG, TG and TC indicators

Table 2: Levels of FPG, 2hPG, TG and TC (x±s)

Group	n	FPG (mmol/L)		2hPG (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	52	8.46±1.67	7.02±1.16*	12.86±0.86	9.26±0.53*
Study group	52	8.51±1.59	5.93±0.86*	12.93±0.75	7.19±0.51*
t		0.156	5.443	0.442	13.431
P		0.876	0.000	0.659	0.000
Group	n	TG (mmol/L)		TC (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	52	3.86±0.62	2.71±0.42*	7.86±1.64	6.21±0.98*
Study group	52	3.94±0.57	1.95±0.28*	7.95±1.56	5.76±0.64*
t		0.685	10.857	0.287	2.772
P		0.495	0.000	0.775	0.007

Note: * Compared with before treatment in this group, $P<0.05$.

Table 3: Levels of SOD, MDA and NO (x±s)

Group	n	SOD (U/mL)		MDA (U/mL)		NO (μmol/L)	
		Before treating	After treating	Before treating	After treating	Before treating	After treating
Control group	52	31.28±4.16	35.69±4.95*	4.96±0.86	3.63±0.72*	50.59±10.12	54.39±11.68*
Research group	52	31.52±4.69	41.27±5.03*	4.85±0.91	3.10±0.44*	50.67±10.39	59.98±12.42*
t		0.276	5.702	0.634	4.529	0.040	2.364
P		0.783	0.000	0.528	0.000	0.968	0.020

Note: * Compared with before treatment in this group, $P<0.05$.

Table 4: Neuroconductive function indicators before and after treatment in two groups (x±s, m/s)

Group	n	Median nerve			
		MNCV		SNCV	
		Before treating	After treating	Before treating	After treating
Control group	52	38.49±4.19	49.26±4.55*	33.97±2.67	43.17±3.24*
Research group	52	38.62±4.03	51.83±4.83*	33.75±2.49	45.05±3.85*
t		0.161	2.793	0.434	2.694
P		0.872	0.006	0.665	0.008
		Common peroneal nerve			
Group	n	MNCV		SNCV	
		Before treating	After treating	Before treating	After treating
Control group	52	35.48±4.16	45.59±5.26*	32.09±2.49	41.47±2.85*
Research group	52	35.62±4.09	48.72±6.13*	32.41±2.18	43.06±3.11*
t		0.173	2.794	0.697	2.718
P		0.863	0.006	0.487	0.008

The MDA levels in both groups decreased and the study group h lower MDA levels than those of the control group, with a statistically significant difference (P<0.05) as shown in table 3.

Comparison of nerve conduction function indicators

Before treatment, the nerve conduction velocity was not different significantly (P>0.05) between the two groups. After treating, the MNCV and SNCV of the median/common peroneal nerve increased in the two groups and the study group had higher MNCV and SNCV (P<0.05) as shown in table 4.

DISCUSSION

At present, the mechanism that leads to the onset of DPN is not fully understood, but the confirmed occurrence of the disease is due to the development of multifactorial related factors. The pathogenesis of the disease can include oxidative stress, neural ischemia and hypoxia, metabolic and genetic factors, etc. (Elafros *et al.,* 2022). Oxidative stress: DM patients are in a long-term high state of blood sugar, leading to disordered metabolism of proteins, sugars and fats in the body, producing more free radicals and increasing oxides. These excess substances exceed the normal antioxidant capacity of the body, resulting in oxidative stress, damage to nerve fiber membranes and cells, damage to neurons and ultimately leading to impaired axonal signaling and transportation (Koutsaliaris *et al.,* 2022). Nerve ischemia and hypoxia: Long-term high blood glucose leads to endothelial cell proliferation and continuous thickening of micro vascular basement membrane. This causes narrowing of the vascular lumen, slowing down of circulating blood flow, causing hypoxia and hypoperfusion of nerve fibers, ultimately leading to abnormal pathological changes and necrosis of nerve fibers. Metabolic disorders: Persistent high blood sugar levels lead to disturbances in various metabolic cycles within the body. This leads to abnormal changes in the structure and function of normal nerves, affects the normal capacity metabolism of nervous tissue and triggers DPN. For genetic factors: Wang *et al*. (2022) showed that some patients had long-term high blood sugar levels, but their neurological symptoms were not obvious. However, for another group of patients, their blood sugar levels were relatively stable, but they were prone to neurovascular diseases. This indicates that the occurrence of the disease may also be due to the patient's own genetic susceptibility. Through the analysis of the pathogenesis of the above-mentioned diseases in DPN patients, it is found that single medication can alleviate clinical symptoms and signs of the disease, and delay the course of the disease. But its therapeutic effect on diseases is not significant, and there is still a possibility of recurrence. Therefore, relying solely on medication alone to control the occurrence and development of DPN has limitations (Lopez-Garzon *et al*., 2022). In this study, the combination of tanshinone IIA sulfonate sodium and α-Lipoic acid was used to treat DPN and the results showed that the combined use of tanshinone IIA sulfonate sodium and α-Lipoic acid alone had significant effects in improving FPG, 2hPG, TG, TC and therapeutic effect of DPN patients.

FPG and 2hPG are important indicators for evaluating and diagnosing the occurrence of DM, and their levels can reflect the patient's condition and recovery from the disease. TG and TC are both lipid serum indicators. When TG and TC are at abnormally high levels, they are more likely to lead to oxidative stress reactions in pancreatic islet cells and gradually exacerbate insulin resistance. Moreover, under high blood sugar levels, the toxic effects of the above indicators on pancreatic islet cells are enhanced. In addition, the increase in TG and TC levels leads to the excessive production of free fatty acids in the body, which increases blood viscosity, leads to microcirculation disorders, and damages peripheral nerves (Khanam *et al*., 2022). The study group receiving combination drug therapy showed more significant improvements in FPG, 2hPG, TG and TC levels compared to the control group receiving only medication, consistent with the study by Najafi *et al*. (2022). Reason analysis: After acting on the body, sodium tanshinone IIA sulfonate can have dual drug effects on blood vessels and blood flow, which is important to improve cell metabolism and blood circulation in DPN patients. Firstly, this drug can improve the endothelial function of blood vessels, alleviate vasospasm and maintain normal vascular balance. In terms of improving blood flow, it could effectively anticoagulate, lower blood lipids, strengthen tissue fiber activity and dilute hypercoagulable blood. α-Lipoic acid can eliminate free radicals, alleviate oxidative stress and promote the circulation of glucose and lipid metabolism. The combination of two drugs achieves the goal of maintaining blood glucose balance and promoting lipid metabolism, thereby improving the levels of FPG, 2hPG, TG and TC (Zhao *et al*. 2022).

The occurrence of oxidative stress is mainly due to the excessive production of reactive oxygen species/nitrogen free radicals by the body after being subjected to harmful stimuli. When these substances aggregate and exhibit high activity, they use free radical reaction chains as mediators to promote per oxidation reactions in enzymes, phospholipids, nucleic acids and cell proteins on the nerve cell membrane, leading to abnormal nerve conduction signals. SOD, MDA, NO, etc. are indicators of oxidative stress. SOD is a kind of metalloenzyme, which can eliminate oxygen free radicals through the body's disproportion to avoid the damage of oxygen free radicals to cells. Based on the reaction chain, MDA is the product formed by the peroxide reaction of unsaturated phosphatidic acid and other enzymes, proteins, phospholipids and nucleic acids in phospholipids. The

level of MDA can reflect the degree of cell free radical damage. NO is an important anti-inflammatory mediator in the body and can regulate intercellular information transmission. It is produced in endothelial cell nuclei and macrophages, which can regulate vascular tension and resist inflammation in the body (Avianggi *et al.*, 2022). Compared to the control group, the study group's SOD, MDA, and NO levels had significantly improved. Analysis of reasons: *Salvia miltiorrhiza* has the effects of cooling blood, eliminating carbuncle, promoting blood circulation, and unblocking collaterals.

The main component of sodium tanshinone II A sulfonate is *Salvia miltiorrhiza* extract. After sulfonation, the drug's effect is significantly improved. When applied to DPN patients, it can expand blood vessels, improve microcirculation, reduce blood viscosity and also clear intracellular free radicals, improve inflammatory reactions, repair tissues and protect neural function (Ma *et al.*, 2022). α-Lipoic acid, one of the strongest antioxidants in the clinic, can not only inhibit the inflammatory reaction of the body, but also improve the oxidative stress reaction of the body to the maximum extent. The combination of two drugs can improve the condition while maintaining stable levels of SOD, MDA and NO (Luo *et al.*, 2022).

Long-term high blood sugar levels can damage and destroy vascular epithelial cells, leading to micro vascular occlusion and the inability of nutrients to be transported through the blood to the peripheral nerves. This leads to long-term lack of nutrient supply to the nerves, leading to dysfunction and thus affecting nerve conduction function (Jiménez-Del-Barrio *et al.*, 2022). This study showed that the study group has higher MNCV and SNCV after treatment, similar to Ma *et al*. (2022) and Hu *et al*. (2021). The reason for this is that Danshen IIA sodium sulfonate is a water-soluble substance, with important components separated from Danshen. When drugs are used in DPN patients, they can relieve vasospasm, expand arteriole, and improve microcirculation. At the same time, drugs can regulate the flow pattern of microcirculation, accelerate blood flow velocity, increase red blood cell deformation and oxygen carrying capacity, and stabilize the structural state of cell membranes (Zhao *et al.*, 2022). α-Lipoic acid has a strong reducing ability, which can eliminate excessive oxygen free radicals in the body, antagonize antioxidants, form a unique biological antioxidant regeneration cycle system, and reduce cell apoptosis. Moreover, drugs have a strong repair and resistance effect on cell oxidative damage in DPN patients, which can significantly improve cell survival rate and ensure energy supply to blood vessels and nerves. The two drugs act on the body based on different mechanisms of action, maximizing the synergistic effect between drugs and promoting the recovery of nerve conduction velocity (Jin *et al.* 2022).

CONCLUSION

In conclusion, tanshinone IIA sulfonate sodium combined with α-Lipoic acid has a significant therapeutic effect in patients with DPN. This can improve patients' FPG, 2hPG, TG and TC, alleviate the body's oxidative stress state, reduce the degree of cell damage and promote the recovery of neural function.

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