

The Efficacy of Warm Needle Moxibustion-Assisted Tongxinluo capsules in Diabetic Peripheral Neuropathy and its effect on patients' nerve function

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Keywords

Tongxinluo capsule, Warm needle moxibustion, Diabetic peripheral neuropathy, Neuromechanism, Nerve conduction velocity

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Abstract:

Background: To analyze the efficacy of warm needle moxibustion-assisted Tongxinluo capsule in treating diabetic peripheral neuropathy (DPN) and its effect on patients' nerve function. **Methods:** 132 DPN patients were randomly divided into a control group (n=66) and an observation group (n=66). Both groups were given conventional Western medicine treatment. The control group was given macaroni capsules on this basis, and patients in the observation group were treated with warm needle moxibustion on the basis of the control group. The patients in both groups were treated for 3 courses with 5 days as a course of treatment. Clinical symptoms, nerve function, nerve conduction velocity and adverse reactions were compared between the two groups. **Results:** After treatment, the scoring levels of the four clinical symptoms including numbness, pain, burning sensation and paresthesia and myelin basic protein (MBP) levels in both groups were markedly lower ($P<0.05$), and those of the observation group were distinctly lower ($P<0.05$). After treatment, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and insulin-like growth factor-1 (IGF-1) levels as well as the motor nerve conduction velocity (MCV) and sensory nerve conduction velocity (SCV) of the left and right tibia nerves were obviously higher ($P<0.05$), and those of the observation group were significantly higher ($P<0.05$). There was no statistically significant difference in the overall incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Warm needle moxibustion-assisted Tongxinluo capsule can effectively alleviate the clinical symptoms of DPN patients, improve their nerve function, and increase the speed of nerve conduction.



1. Introduction

Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes, and the incidence rate of DPN in patients with diabetes is as high as 30%~90% [1]. The pathogenesis of DPN is complex, which is related to a variety of physiology such as disturbance of body metabolism, oxidative stress, neurotrophic disturbance and microvascular disorder [1]. Currently, there is no effective treatment for DPN in Western medicine except for drugs controlling blood pressure, blood sugar and blood fat [2]. However, long-term use of Western medicine suffers from flaws including different individual curative effects and drug tolerance as well as lots of side effects, which restricts its clinical application [2]. Traditional Chinese medicine emphasizes treatment based on syndrome differentiation, which has the unique advantages of less recurrence and side effects [3]. DPN belongs to "diabetes arthralgia" in traditional Chinese medicine, which is caused by insufficient Qi and blood and tight tendons and vessels [3]. Tongxinluo capsule, a traditional Chinese compound prescription to invigorate Qi, promote blood circulation, dredge collaterals and relieve pain, can protect nerves and remove stasis[4]. It has been reported that Tongxinluo capsule is effective in improving clinical overall response rate and hemorheological indexes of patients with transient ischemic attack [5]. In addition, Tongxinluo capsule can reduce nerve cell apoptosis after cerebral ischemia in middle cerebral arterial obstructive model rats [6].

Nevertheless, there is no sufficient evidence-based medicine study supporting the effect of Tongxinluo capsule on DPN. Warm needle moxibustion combines acupuncture and moxibustion, transmits heat to acupoints through needles, and mainly cures diseases with Qi and blood stagnation [7, 8]. Warm needle moxibustion can warm the meridians and promote flow of Qi and blood circulation [7, 8]. The previous study has proved the effectiveness and safety of warm needle acupuncture for the treatment of sciatica [9], but there are few studies on warm needle moxibustion combined with Tongxinluo capsule in patients with DPN. The purpose of this study is to explore the effect of warm needle moxibustion combined with Tongxinluo capsule on the clinical efficacy, neurological function and nerve conduction velocity of patients with DPN, so as to provide reference for clinical treatment. The research results are reported as follows.

2. Materials and methods

2.1 General information

132 DPN patients who were treated in our hospital from January 2019 to December 2021 were selected and randomly divided into an observation group (n=66) and a control group (n=66). There was no significant difference in gender, age, course of diabetes and course of DPN between the two groups ($P>0.05$), as shown in Table 1. This study was approved by Medical Ethics Committee, and patients were informed and agreed.

Table 1 Comparison of general information between the two groups

Groups	Number of cases	Gender (cases)		Age (years old)	Course of DM (years)	Course of DPN (months)
		Male	Female			
Observation group	66	36	30	53.44±7.99	6.18±2.17	5.46±1.24
Control group	66	34	32	52.91±8.67	6.29±1.90	5.53±0.84
χ^2/t		0.122		0.365	-0.310	-0.380
P		0.727		0.716	0.757	0.705

2.1.1 Inclusion criteria

(1) People who are diagnosed with DPN according to medical history, clinical manifestations,

electromyography and others, and present clinical syndromes consistent with the diagnostic criteria of Qi-deficiency and Blood-stasis Syndrome DFN from

the Guidelines for Clinical Diagnosis and Management of Patients with Diabetic Peripheral Neuropathy in Traditional Chinese Medicine 2016 outlined by Chinese Diabetes Society, including limb weakness and numbness, more severe pain at night, mental fatigue, shortness of breath and unwillingness to speak, sweating after a little exercise, diarrhea or constipation, slightly dark tongue body or petechiae in tongue with white and thin fur, and thready and uneven pulse; (2) No treatment with anti-DPN drugs within 3 weeks; (3) Those with complete clinical data and without history of allergy to Tongxinluo capsule and acupuncture.

2.1.2 Exclusion criteria

(1) Patients with peripheral neuropathy caused by cerebral infarction, malnutrition, metal poisoning, infection and other reasons; (2) Patients with diabetes retinopathy, diabetic foot, diabetic ketoacidosis and other diabetes complications; (3) Patients with dysfunction of heart, liver, lung and other important organs, as well as disorders of immune system, blood system and cognitive system; (4) Pregnant or menstruating women.

2.2 Treatment methods

The patients in both groups were given routine Western medicine treatment such as hypoglycemic drugs, insulin and diet control. The observation group took Tongxinluo capsule (Shijiazhuang Yiling Pharmaceutical Co., Ltd., SFDA Approval No.: Z19980015, specification: 0.26*90 capsules) orally, 4 capsules each time and 2 times per day. On the basis of the observation group, the control group was treated with warm needle moxibustion, taking bilateral Quchi (LI11), Hegu (LI4), Zusanli (ST36), Sanyinjiao (SP6) and Taichong (LR3) as the main points, and bilateral Pishu (BL20), Shenshu (BL23), Qihai (CV6) and Guanyuan (CV4) as the auxiliary points. Filiform needle of 0.38 mm × 100 mm was used for acupuncture and retained after the arrival of Qi. A set of moxa stick was added to the needle handle and ignited. The needle was removed when the patient felt warm or the local skin turned red, and the

treatment of the observation group was performed once a day. Both groups were treated for 3 courses with 5 days as a course of treatment.

2.3 Observation indexes

(1) Clinical symptoms: With the application of neuropathic subjective symptom questionnaire (TSS) score [10], the clinical symptoms such as numbness, pain, burning sensation and paresthesia in the affected limbs of the two groups were observed before and 15 days after treatment, and scored according to the severity and frequency. The higher the score, the more serious the symptom. (2) Nerve function: 5 ml morning fasting venous blood was collected from patients in the two groups before and 15 days after treatment. The levels of myelin basic protein (MBP, ml060477), brain-derived neurotrophic factor (BDNF, ml900214), nerve growth factor (NGF, ml063385) and insulin-like growth factor-1 (IGF-1, ml022803) were detected by enzyme-linked immunosorbent assay (ELISA, Shanghai Biological Technology Co., Ltd. enzyme research). (3) Nerve conduction velocity: Before and 15 days after treatment, the motor nerve conduction velocity (MCV) and sensory nerve conduction velocity (SCV) of the left tibial nerve and the right tibial nerve of the two groups were measured by electromyogram evoked potential instrument (NcuroCare-D1, Shanghai mechanical note 20192070559). (4) Adverse reactions: The adverse reactions such as abdominal distension, erythra and anorexia in the two groups during treatment were observed.

2.4 Statistical methods

The statistical analysis was conducted using SPSS 20.0, and the enumeration data were compared using χ^2 test. The measurement data were expressed as mean \pm standard deviation ($\bar{x} \pm s$). Comparisons between two groups were performed using the independent sample *t*-test, and the paired sample *t*-test was used for comparison among different time points in the same group. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1 The clinical symptoms of DPN patients were improved after the treatment of warm needle moxibustion-assisted Tongxinluo capsules

Before treatment, there was no significant difference in the scores of numbness, pain, burning sensation and

paresthesia between the two groups ($P>0.05$). After treatment, the scores of the four clinical symptoms in the two groups were obviously lower than those before treatment ($P<0.05$), and the scores in the observation group were significantly lower than those in the control group ($P<0.05$), as shown in Table 2.

Table 2 Comparison of clinical symptom improvement between the two groups ($\bar{x}\pm s$, points)

Observation indexes		Observation group (n=66)	Control group (n=66)	t	P
Numbness	Before treatment	3.20±0.49	3.16±0.53	0.450	0.653
	After treatment	0.74±0.12*	1.86±0.25*	-32.812	0.000
Pain	Before treatment	2.82±0.51	2.81±0.55	0.108	0.914
	After treatment	0.86±0.23*	1.03±0.22*	-4.339	0.000
Burning sensation	Before treatment	2.78±0.22	2.82±0.21	-1.068	0.287
	After treatment	1.22±0.26*	1.97±0.40*	-12.772	0.000
Paresthesia	Before treatment	2.72±0.50	2.77±0.42	-0.622	0.535
	After treatment	1.09±0.32*	1.79±0.40*	-11.102	0.000

Note: compared with before treatment: * $P<0.05$

3.2 The nerve function of DPN patients were improved after the treatment of warm needle moxibustion-assisted Tongxinluo capsules

Before treatment, difference in the levels of MBP, BDNF, NGF and IGF-1 between the two groups was not statistically significant ($P>0.05$). After treatment, the MBP level in the two groups was markedly lower than that before treatment ($P<0.05$), and MBP level in the observation group was obviously lower than that in the control group ($P<0.05$). After treatment, the levels of BDNF, NGF and IGF-1 in the two groups were significantly higher than those before treatment ($P<0.05$), and these levels in the observation group were distinctly higher than those in the control group ($P<0.05$), as exhibited in Table 3.

3.3 Warm needle moxibustion-assisted Tongxinluo capsules accelerated the nerve conduction velocity

of DPN patients

Prior to treatment, there was no significant difference in left tibial nerve MCV, left tibial nerve SCV, right tibial nerve MCV and right tibial nerve SCV between the two groups ($P>0.05$). After treatment, MCV of left tibial nerve, SCV of left tibial nerve, MCV of right tibial nerve and SCV of right tibial nerve in the two groups were evidently higher than those before treatment ($P<0.05$), and those in the observation group were obviously higher than those in the control group ($P<0.05$), as shown in Table 4.

3.4 Warm needle moxibustion-assisted Tongxinluo capsules did not cause adverse reactions

There was no significant difference in the total incidence of adverse reactions between the two groups ($P>0.05$), as presented in Table 5.

Table 3 Comparison of nerve function between the two groups before and after treatment ($\bar{x}\pm s$)

Observation indexes		Observation group (n=66)	Control group (n=66)	t	P
MBP (μg/L)	Before treatment	5.75±0.65	5.69±0.72	0.503	0.616
	After treatment	2.96±0.42*	4.34±0.48*	-17.578	0.000
BDNF (ng/mL)	Before treatment	1.47±0.43	1.48±0.50	-0.123	0.902
	After treatment	3.90±0.58*	2.03±0.55*	19.006	0.000

NGF (ng/L)	Before treatment	1.57±0.32	1.60±0.33	-0.530	0.597
	After treatment	4.61±0.55*	3.26±0.52*	14.490	0.000
IGF-1 (ng/L)	Before treatment	148.65±15.65	149.05±15.19	-0.149	0.882
	After treatment	239.71±32.70*	207.09±24.73*	6.464	0.000

Note: compared with before treatment: *P<0.05

Table 4 Comparison of nerve conduction velocity between the two groups before and after treatment ($\bar{x}\pm s$, m/s)

Observation indexes		Observation group (n=66)	Control group (n=66)	t	P
MCV of left tibial nerve	Before treatment	38.72±5.18	37.88±4.99	0.949	0.344
	After treatment	46.10±6.34*	41.29±5.11*	4.799	0.000
SCV of left tibial nerve	Before treatment	34.59±4.24	35.12±4.76	-0.675	0.501
	After treatment	41.73±4.43*	38.62±4.27*	4.106	0.000
MCV of right tibial nerve	Before treatment	40.06±4.64	40.93±5.20	-1.014	0.312
	After treatment	45.89±4.11*	42.34±4.67*	4.636	0.000
SCV of right tibial nerve	Before treatment	35.70±3.61	35.98±3.08	-0.479	0.632
	After treatment	40.79±4.20*	38.87±3.57*	2.830	0.005

Note: compared with before treatment: *P<0.05

Table 5 Comparison of adverse reactions between the two groups [cases (%)]

Groups	Number of cases	Abdominal distension	Erythra	Anorexia	Total incidence
Observation group	66	3 (4.55)	2 (3.03)	2 (3.03)	7 (10.61)
Control group	66	3 (4.55)	3 (4.55)	2 (3.03)	8 (12.13)
χ^2					0.075
P					0.784

4. Discussion

Tongxinluo capsule is a Chinese patent medicine for supplementing Qi and activating blood circulation [11]. It can eliminate collateral stasis, replenish Qi and blood, and go to the pathogenesis of DPN [12]. Warm needle moxibustion was developed from moxibustion and acupuncture. It is recorded in the Compendium of Acupuncture and Moxibustion that "After needling at acupuncture points, Angelica dahurica is used as a medicinal cake and put on the needles, and moxibustion is used... It may be effective for people

catching a cold.". Warm needle moxibustion has the effect of dredging the meridians and activating blood circulation, and warming the meridians and promoting Qi circulation, and has a good effect on arthralgia syndrome caused by wind [13, 14]. This study investigated the role of warm needle moxibustion combined with Tongxinluo capsule in the clinical efficacy and neurological function of patients with DPN. The results showed that the combined treatment had a better effect.

Nerve conduction velocity is the generally accepted

standard for the diagnosis of DPN [15]. The research shows that with the continuous aggravation of DPN, the nerve of patients' lower limbs is damaged, which will lead to the decrease of nerve conduction velocity [16]. MBP is a unique basic membrane protein in the myelin sheath of axons of nerve cells, which plays an important role in the formation of myelin sheath and is a specific marker of nervous system damage [17]. The higher its content in the serum, the higher the degree of nerve damage [17]. BDNF is a neurotrophic factor, and NGF and IGF-1 are nerve growth factors, which can maintain the differentiation and growth of neurons and promote the repair of neurological function [18]. Besides, NGF and BDNF were determined to be risk factors for DPN, which are associated with the occurrence and development of DPN [19]. The results of this study exhibited that after treatment, the scores of four clinical symptoms, including numbness, pain, burning sensation and paresthesia, and MBP level in the two groups were distinctly lower than those before treatment, and the scores and level in the observation group were obviously lower than those in the control group; After treatment, the levels of BDNF, NGF and IGF-1 as well as MCV and SCV of left tibial nerve and right tibial nerve in the two groups were significantly higher than those before treatment, and those in the observation group were evidently higher than those in the control group. There was no significant difference in the total incidence of adverse reactions between the two groups. A previous study by Qinwei Fu et al. showed that traditional Chinese medicine foot bath combined with acupoint massage could increase the total effective rate, sensory nerve conduction velocity, motor nerve conduction velocity, and neuropathic syndrome score of DPN patients [20]. As for this study, we firstly found that that warm needle moxibustion combined with Tongxinluo capsule has a good effect on DPN patients, which facilitates the improvement of nerve function and nerve conduction velocity, and its therapeutic effect is safe and reliable. Tongxinluo capsule consists of 12 medicines, including *ginseng*, *leech*, *scorpion*, *cockroach*, *centipede*, *cicada slough*, *radix paeoniae rubrathe*

root of common peon, *sandalwood*, *Dalbergia odorifera*, *mastix*, *semen ziziphi spinosa* and *borneol*. Among them, *scorpion*, *centipede*, *leech*, *cicada slough* and other insect drugs expel wind and dredge collaterals, attack virus and resolve masses, and promote blood circulation and remove blood stasis. *Ginseng* strengthens the spleen and lungs, and invigorates Qi for relieving desertion [21]. *Radix paeoniae rubrathe root of common peon* clears away heat evil and eliminates stasis, and *Borneol* can relieve pain and induce resuscitation [22]. Modern pharmacological studies have indicated that Tongxinluo capsule can inhibit oxidative stress and inflammatory reaction, and increase pain threshold, so as to reduce pain [11]. In addition, Tongxinluo capsule contains many effective ingredients such as panaxacetyl alcohol and panaxacetyl oxide, which have neuroprotective and neurotrophic functions and facilitate the improvement of the function of nervous system and nerve conduction velocity [4]. Meanwhile, Tongxinluo capsule can improve lipid metabolism and insulin resistance to play anti-hyperglycemic and anti-hyperlipidemic roles [23]. Warm needle moxibustion acts on points including bilateral Quchi (LI11), Hegu (LI4), Zusanli (ST36), Sanyinjiao (SP6), Taichong (LR3), Pishu (BL20), Shenshu (BL23), Qihai (CV6) and Guanyuan (CV4), and has the effect of dredging meridians, regulating Qi and replenishing essence [14]. Modern research shows that warm needle moxibustion can transfer heat into the acupoints to increase local temperature, promote local blood circulation, ameliorate the ischemia and hypoxia of peripheral nerve tissue, decrease the degree of oxidative stress response and inflammatory reaction, then reduce nerve damage, improve nerve conduction velocity and sensitivity, and alleviate clinical symptoms such as numbness and pain [24, 25].

5. Conclusions

To sum up, warm needle moxibustion combined with Tongxinluo capsule can effectively alleviate the clinical symptoms of DPN patients, improve their nerve function and increase nerve conduction velocity,

and its effect is safe and reliable.

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Not applicable

Conflict-of-Interest

The authors declare no conflicts of interest.

Authors' contributions

Conceptualization: Y.D; Data curation: Y.Z.X; Formal analysis: Y.Z.X; Methodology: Y.D; Writing – original draft: Y.D; Writing – review and editing: Y.D; All authors have read and agreed to the published version of manuscript.

Ethics approval and consent to participate

This study was approved by Medical Ethics Committee, and patients were informed and agreed.

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Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Supplementary Material

Not applicable.

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