



Clinical Effect of Yiqi Huoxue Tongmai Decoction in the Treatment of Diabetic Peripheral Neuropathy

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ABSTRACT

The objective of this study was to verify the effects of Yiqi Huoxue Tongmai Decoction on patients with diabetic peripheral neuropathy (DPN). A total of 130 patients with DPN who were treated in our hospital from January 2015 to July 2016 were selected and randomly divided into a control group and a treatment group, with 65 cases in each group. The control group was treated with conventional western medicine, and the treatment group was treated with self-made Yiqi Huoxue Tongmai Decoction. The efficacy of both strategies was evaluated with clinical symptoms, nerve reflex, electromyography, nerve conduction velocity, and hemodynamics. We found that the number of markedly effective cases in the treatment group was higher than that in the control group. The total effective rate was 89.23% in the treatment group and 72.31% in the control group. The total effective rate in the treatment group was higher than that in the control group ($P < 0.05$). The whole blood high shear viscosity, whole blood low shear viscosity, plasma viscosity, as well as erythrocyte aggregation index of both groups decreased after treatment compared with the pre-treatment baseline. The hemorheological indexes of the Yiqi Huoxue Tongmai decoction group were lower than those of the control group. To conclude Yiqi Huoxue Tongmai Decoction has significant clinical effect in the treatment of DPN, can effectively improve the blood rheology of patients, and has the advantages of simplicity and high safety.

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Authors' Contribution

GZ designed the study. YZ participated in data collection. DL and HZ performed the data analysis and drafted the manuscript.

Key words

Yiqi Huoxue Tongmai decoction, Traditional Chinese medicine preparations, Diabetic peripheral Neuropathy, Hemorheology, Clinical effect

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is one of the common complications of diabetes (Wang *et al.*, 2021; Selvarajah *et al.*, 2019). It not only brings physical pain to diabetic patients, but also brings psychological pressure and economic burden to patients and their families (Mehra *et al.*, 2014), resulting in a decline in the quality of life of patients and a decrease in self-efficacy (Waldfoegel *et al.*, 2017; Zhao and Zhang, 2018). The incidence of DPN in

diabetic patients can reach 30% to 90% (Deng *et al.*, 2017), and relevant foreign studies have shown that more than half of diabetic patients will eventually develop DPN. The incidence of DPN is high in both type 1 diabetes and type 2 diabetes (Zakin *et al.*, 2019; Walter-Hölinier *et al.*, 2018; Iqbal *et al.*, 2018). DPN is mainly manifested as numbness in the limbs, accompanied by pain, muscle weakness and other abnormal sensations. Slow limb sensory reflexes, such as slow knee reflex and Achilles tendon reflex, can be summarized as loss of sensory, motor and autonomic nerve function (Tang *et al.*, 2019; Lee *et al.*, 2015; Pop-Busui *et al.*, 2017). With the development of the disease, it may also cause foot ulcers, and severe cases may lead to amputation (Singh *et al.*, 2014). According to existing studies, DPN is a key influencing factor for the formation of diabetic foot ulcers, and it is also a common cause of non-traumatic lower limb amputation and disability in diabetic patients (Amato Nesbit *et al.*, 2019; Calcutt, 2020). Therefore, it is very important to study the methods of controlling and treating DPN. Western medicine, such as Gabapentin,

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has been used for a long time in the treatment of DPN. However, the side effects such as allergy, anxiety, and hypersomnia were obvious (Zhang *et al.*, 2019). In order to alleviate side effects caused by western medicine during the treatment process, exploring new treatment methods and research therapeutics is very necessary to improve the patient's medication compliance.

In recent years, with the increasing attention of traditional Chinese medicine (TCM) therapy, the scope of clinical application of TCM therapy and traditional Chinese medicine has been continuously expanded, involving a variety of diseases and achieving satisfactory curative effects (Wang *et al.*, 2017, 2018). TCM has played an important role in the prevention, treatment and health care of chronic diseases such as diabetes (Wang *et al.*, 2020; Xiao and Luo, 2018). In the research on the treatment of DPN, some scholars have done related research on the treatment of DNP with TCM, and the research results show that the TCM method has a good clinical effect in the treatment of DNP (Wang *et al.*, 2021; Xiao and Chen, 2020; Zhang *et al.*, 2020; Fan *et al.*, 2018). Therefore, this study used the self-made Yiqi Huoxue Tongmai Decoction to treat patients with DPN, and designed a study to analyze the therapeutic effect of Yiqi Huoxue Tongmai Decoction on DNP, in order to enrich the TCM for the treatment of DNP and provide more effective preparation methods of symptomatic TCM.

MATERIALS AND METHODS

Subjects

A total of 130 patients with DPN who were treated in our hospital from January 2015 to July 2016 were selected and randomly divided into two groups with 65 cases in each group. The study was reviewed and approved by the hospital ethics committee, and all patients or their families who participated in the study signed the informed consent.

Inclusion criteria

(1) age ≥ 35 years old and ≤ 75 years old; (2) meeting the diagnostic criteria for diabetes: Specific symptoms such as polydipsia, polyuria, and unexplained weight loss combined with at least one of the following indicators such as random blood glucose ≥ 11.1 mmol/L; fasting blood glucose FPG ≥ 7.0 mmol/L; 2 hours blood glucose after glucose load ≥ 11.1 mmol/L (Harreiter and Roden, 2019); (3) meeting the diagnostic criteria for DPN (1) Have a clear history of diabetes; (2) Neuropathy that occurs at or after the diagnosis of diabetes; (3) Clinical symptoms of neuropathy, such as pain, numbness, paresthesia, etc., abnormal in any of the 5 tests (ankle reflex, vibration, pressure, temperature and acupuncture pain); (4) In the

absence of clinical symptoms, abnormalities in any two of the five tests can be diagnosed (Neurologic Complications Group, Diabetes Society of Chinese Medical Association, 2021); (4) abnormal sensation in the limbs. For example, the limbs feel numbness and pain, and the knee reflex and Achilles tendon reflex are weakened or even unresponsive; (5) Voluntarily participate in the study and have signed the informed consent.

Exclusion criteria

(1) Abnormal sensation of limbs not caused by diabetes; (2) Contraindication to study medication: Pregnancy, lactation and hemorrhagic disease; (3) Complication of neurological disease or peripheral neuropathy due to other factors; (4) Combination of diabetic nephropathy, heart and brain patients with vascular disease or abnormal liver and kidney function; (5) Those with a history of unexplained allergy or allergic constitution

Methods

The control group was treated with conventional western medicine such as Gabapentin, and the treatment group was treated with self-made Yiqi Huoxue Tongmai Decoction. Basic recipe: 30g each of raw *Astragalus*, *Salvia miltiorrhiza*, and Chixueteng, 15g of *Achyranthes sichuanensis*, 10g each of peach kernel, angelica, Streptomyces, and 6g of safflower. Flavoring: For those with cold limbs, add 10g each of cinnamon sticks, dodder seeds, and *Morinda officinalis*, and make 6g of aconite; for those with sore waist and knees, add 30g of Shouwu, 15g of rehmannia, and 10g of wolfberry. For patients with severe pain, add 10g of *Corydalis japonica*, 3g each of Scorpion and Dilong; add 10g each of Anemarrhena and Trichosanthes for dry mouth and tongue. 1 dose per day, decocted in water and taken in divided doses. 1 course of treatment for 30 days, 2 courses of treatment.

EMG nerve conduction velocity (NCV) was used to evaluate the severity of nerve injury. The stimulation electrode was placed in the nerve trunk, the recording electrode was placed in the muscle abdomen, the reference electrode was placed in the tendon. The motor NCV and sensory NCV were recorded.

A hemorheology examination was performed with blood viscosity in different blood flow velocities, plasma viscosity, as well as erythrocyte aggregation index. The comparison between the control and treatment groups, and the alteration in both groups after according treatments were used for analysis.

Criteria for judging clinical efficacy: Markedly effective: The subjective symptoms such as numbness, neuralgia, and hyperhidrosis disappeared completely, the knee and Achilles tendon reflexes basically returned to

normal, and the EMG NCV basically returned to normal or increased by $\geq 5\text{m}\cdot\text{s}^{-1}$.

Effective: the subjective symptoms are obviously

relieved, the knee and Achilles tendon reflexes are obviously improved, and the NCV increase of the electromyogram is less than $5\text{m}\cdot\text{s}^{-1}$.

Table I. Comparison of clinical efficacy between the two groups of patients after treatment.

Group	Case	Markedly effective	Effective	Invalid	Total efficiency
Control group	65	23	24	18	72.31%
Therapy group	65	37	21	7	89.23%*

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

Table II. Comparison of blood rheology indexes before and after treatment in two groups of patients.

Group	Case		Whole blood high shear viscosity ($\text{mPa}\cdot\text{s}^{-1}$)	Whole blood low shear viscosity ($\text{mPa}\cdot\text{s}^{-1}$)	Plasma viscosity ($\text{mPa}\cdot\text{s}^{-1}$)	Erythrocyte aggregation index
Control group	65	Before therapy	4.56 $\pm$ 0.66	10.36 $\pm$ 1.52	1.72 $\pm$ 0.44	8.32 $\pm$ 2.43
		After therapy	3.83 $\pm$ 0.60**	9.23 $\pm$ 0.89**	1.57 $\pm$ 0.34*	7.40 $\pm$ 1.88*
Therapy group	65	Before therapy	4.53 $\pm$ 0.64	10.39 $\pm$ 1.63	1.75 $\pm$ 0.46	8.36 $\pm$ 2.47
		After therapy	3.42 $\pm$ 0.57** Δ	7.28 $\pm$ 1.28** Δ	1.43 $\pm$ 0.27** Δ	6.65 $\pm$ 1.80** Δ

Note: Compared with before treatment, * $P<0.05$, ** $P<0.01$; compared with control group after treatment, $\Delta P<0.05$.

Invalid: No obvious improvement or aggravation of subjective symptoms, no change in knee, Achilles tendon reflex and EMG NCV.

Statistical analysis

Statistical analysis was performed using SPSS 25.0 software. Measurement data were expressed as means $\pm$ SD. The paired-sample *t* test was used for intra-group comparison, and the independent sample *t*-test was used for inter-group comparison. The enumeration data were expressed as the number of cases *n* and the rate %, and the comparison between groups was carried out by χ^2 test. $P<0.05$ considered the difference to be statistically significant.

RESULTS

In the treatment group, there were 37 males and 28 females; the age ranged from 35 to 74 years, with an average of 62.82 ± 11.61 years; the course of diabetes was 5 to 18 years, with an average of 6.70 ± 2.34 years; the course of peripheral neuropathy was 1 to 10 years, with an average of 5.30 ± 1.12 years. The control group consisted of 35 males and 30 females; aged 35-75 years, mean 62.78 ± 11.42 years; diabetes duration 5-19 years, mean 6.60 ± 2.46 years; with peripheral neuropathy duration 1-10 years, mean 5.57 ± 1.23 years. There was no significant difference in general data between the two groups ($P>0.05$), and they were comparable.

Treatment results

Comparison of clinical efficacy assessed by the alleviation of the clinical symptoms concerned with numbness, neuralgia, and hyperhidrosis between the two groups: the number of markedly effective cases and the total effective rate in the treatment group were higher than those in the control group, the total effective rate in the treatment group was 89.23%, and the total effective rate in the control group was 72.31%, and there were statistical differences between the two groups ($p<0.05$) (Table I).

Changes of hemorheological indexes in the two groups of patients: compared with before treatment, the whole blood high shear viscosity ($\text{mPa}\cdot\text{s}^{-1}$), whole blood low shear viscosity ($\text{mPa}\cdot\text{s}^{-1}$), plasma viscosity ($\text{mPa}\cdot\text{s}^{-1}$) and erythrocyte aggregation index of the two groups of patients after treatment decreased, and the difference was statistically significant after treatment compared with before treatment ($p<0.05$). The hemorheological indexes of the treatment group were lower than those of the control group, and the difference between the treatment group and the control group was statistically significant ($p<0.05$), as shown in Table II.

DISCUSSION

In the present study, we investigated the efficacy of TCM (Yiqi Huoxue Tongmai decoction) in the treatment of diabetes patients with DPN. We found that compared with the general treatment of western medicine, the usage of Chinese medicine could alleviate the symptoms and reduce the blood viscosity, and showed benefits for DPN patients.

DPN is the most common complication of diabetes, which is a leading cause of disability. Furthermore, twenty to thirty percent of DPN patients suffer neuropathic pain. However, the therapy of DPN is poorly understood. Previous studies focused on western medicine and supposed strict glycemic control to reduce the incidence of DPN, but it showed no meaningful impact on polyneuropathy (Martin *et al.*, 2006; Khdour, 2020). Tricyclic antidepressants (TCAs) could block the reuptake of noradrenaline and serotonin by the presynaptic neuron and the uptake of both 5HT and noradrenaline, which could reduce DPN-induced neuralgia. However, the side effects, including dry mouth, orthostatic hypotension, constipation, and urinary retention were obvious (Benbouzid *et al.*, 2008). Duloxetine, the serotonin and noradrenaline reuptake inhibitors (SNRIs) are efficient for pain reduction and shows the same efficacy as pregabalin in treating patients with painful DPN with the side effect of constipation (Khdour, 2020). Venlafaxine, an inhibitor of serotonin reuptake, though efficient for the reduction of pain, it also causes nausea, headache, and insomnia. Due to the wide-range of side effects of western medicine, it is particularly important to exploit new drugs.

TCM shows moderate characteristics and continuous effects on the total body. TCM can regulate qi and blood, warm meridian, and improve blood circulation, which may help treat and prevent DPN.

This study formulated Yiqi Huoxue Tongmai Decoction to treat DPN patients. The treatment concept of the TCM formula is that the deficiency of both qi and yin is the foundation, the phlegm turbidity blocking and the blood stasis blocking the collaterals are the targets, and the treatment is mainly to nourish the qi and clear the collaterals. Yiqi Huoxue Tongmai Decoction generates Astragalus to invigorate the qi of the true essence, so that Qi promotes blood circulation; Angelica nourishes blood and activates blood circulation; Salvia, peach kernel, safflower promote blood circulation and remove blood stasis; *Achyranthes sichuanensis* promotes blood circulation and removes blood stasis, and also induces blood to descend and nourishes liver and kidney. Chixueteng through the meridians, nourishes blood and relaxes the tendons; stretches the tendons and relaxes the tendons and activates the collaterals. The combination of various medicines has the effect of nourishing qi and nourishing blood, promoting blood circulation and removing blood stasis, relaxing tendons and dredging collaterals. Treating DPN patients with this TCM prescription can achieve the effects of activating blood and dredging collaterals, relaxing tendons and removing blood stasis, which plays a practical role in controlling and treating DPN fundamentally.

The limitations of this study mainly include: the research object is patients in a hospital and the sample size

is limited by objective conditions. In the future, it is possible to expand the sample size, increase multi-center research, and expand the source and number of research objects, so as to provide a more solid basis for the prescription of Yiqi Huoxue Tongmai Decoction used in the study, and further improve the promotion and application scope of this prescription, so that more of DPN patients can be treated with this prescription, enriching the treatment options and drug types for DPN patients and improving their quality of life.

CONCLUSION

Yiqi Huoxue Tongmai Decoction has a good clinical effect on the treatment of diabetic peripheral neuropathy by improving the existing clinical symptoms and relieving the pain of patients.

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IRB approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Zhejiang Quhua Hospital (2022L-17).

Statement of human and animal rights

All procedures in this study were conducted in accordance with the ethics committee of Zhejiang Quhua Hospital approved protocols.

Statement of informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Statement of conflict of interest

The authors have declared no conflict of interest.

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