Diffusion Tensor Imaging Evaluates Effects of Acupoint Injection at Zusanli (ST36) for Type 2 Diabetic Peripheral Neuropathy

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Financial support: Funding came from the scientific research funding of Tianjin Medical University Chu Hisen-I Memorial Hospital (2019ZDKF09)

Conflict of interest: None declared

Background:
Acupoint injection is an therapeutic method that combines acupuncture and Western medicine and shows good curative effects for neuropathies. This study aimed to explore the efficacy of acupoint injection for treating diabetic peripheral neuropathy (DPN) by magnetic resonance neuroimaging (MRN).

Material/Methods:
Forty patients with DPN were randomly divided into an acupoint injection group (AI; n=20) and intramuscular injection group (MI; n=20). The AI group received an acupoint injection of mecobalamin at acupoint Zusanli (ST36); the MI group received intramuscular injection of mecobalamin. The curative effect was evaluated by the Toronto Clinical Neuropathy Score and diffusion tensor imaging (DTI).

Result:
The neuropathy scores of both groups decreased from baseline (AI 9.31±2.36; MI 9.34±2.54) to after the 2-week treatment (AI 7.12±1.87; MI 7.86±2.11); the differences were not significant. The fractional anisotropy (FA) value showed significant differences on the common peroneal nerve (AI 0.36±0.04; MI 0.31±0.05; P<0.05) and tibial nerve (AI 0.38±0.07; MI 0.34±0.06; P<0.05) after treatment. Likewise, apparent diffusion coefficient (ADC) values between groups showed significant differences for the common peroneal nerve (AI 1.44±0.17×10^{-3} mm²/s; MI 1.61±0.20×10^{-3} mm²/s; P<0.05) and tibial nerve (AI 1.54±0.22×10^{-3} mm²/s; MI 1.60±0.17 10^{-3} mm²/s; P<0.05).

Conclusions:
Patients with DPN showed lower nerve FA and higher ADC in DTI-MRN. The acupoint injection of mecobalamin could treat DPN and repair the damaged nerves, which was shown by elevated FA and lowered ADC. Our study provides clinical evidence for the application of acupoint injection therapy and the evaluation of DPN by MRN.

Keywords: Acupuncture Therapy • Diabetic Neuropathies • Diffusion Tensor Imaging

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/935979
Background

Diabetic neuropathy is one of the main chronic complications of diabetes and the most common type is diabetic peripheral neuropathy (DPN). The average prevalence rate of DPN is approximately 60% to 90%. DPN could affect the motor, sensory, and even autonomic nerves [1], resulting in symmetrical numbness, pain, and other paresthesia and movement disorders of the distal extremities. In severe cases, it could lead to ulcers, gangrene, and even amputation, which is the main cause of disability in diabetes. The pathogenesis of DPN is not yet clear but is closely related to disorders of the polyol pathway, glucose metabolism, and reactive oxygen species [2,3]. Hyperglycemia can affect the metabolism of nerve cells and indirectly damage nerves and axons. It can also directly damage nerves and cause pathological changes in nerves. Blood sugar causes excessive mitochondrial superoxide and increased glycosylation end products [4], which activate the expression of cell surface adhesion factors, causing oxidative stress damage and segmental demyelination of peripheral nerve fibers. Therefore, the treatment of DPN by modern medicine is based on blood glucose management.

The application of antihyperglycemic drugs can improve the clinical symptoms of DPN and lower the risk of serious complications. Meanwhile, microcirculation drugs and neurotrophic agents are supplemented according to clinical symptoms [5]. However, there is still a lack of therapeutic drugs that directly target the lesions on the involved limbs of patients with DPN. Therefore, it is necessary to explore a more comprehensive treatment scheme.

Diabetes is called Xiaoke or XiaoDan in traditional Chinese medicine (TCM). As one of the complications of diabetes, DPN belongs to the classifications of numbness, blood Bi syndrome, pain syndrome, and Wei syndrome in TCM theory. Classical TCM says that the method of treating Wei syndrome is solely based on Yangming (spleen and stomach). Patients with diabetes have weak qi in the spleen and stomach, which leads to insufficiency of the essence, blood and body fluid, muscles, and tendons. The Zusanli (ST36) acupoint is located below the knee, on the tibialis anterior muscle, an acupoint of the foot-Yangming-stomach meridian. Stimulation through acupuncture of the Zusanli point can produce the viscera qi and blood. Once the viscera is nourished, the Wei syndrome can be eliminated. Long-term clinical practice has shown that acupuncture therapy, as one of the means to treat DPN, can alleviate the symptoms of diabetic neuropathy and delay the progression of neuropathy. According to the clinical evidence on the treatment of DPN with acupuncture and moxibustion, the current main acupuncture therapies include milli-acupuncture, electroacupuncture, acupoint injection, moxibustion, cupping, scalp acupuncture, and skin acupuncture. Acupoint injection is the method of injecting drugs into relevant acupoints or specific parts under the guidance of TCM theory to achieve treatment through the combination of drugs and acupuncture, which has a higher rate of clinical efficacy than acupuncture alone [6].

Magnetic resonance neuroimaging (MRN) can obtain high-resolution 3-dimensional images of nerve fibers, which can provide a basis for the diagnosis of peripheral neuropathy [7]. Traditional neuro-electromyography has poor diagnosis efficiency of nerve lesions and is highly subjective. For peripheral neuropathy that is hard to diagnose, MRN can exclude other factors such as drug-induced neuropathy and peripheral soft tissue masses by showing multifocal neurological abnormalities. MR diffusion tensor imaging (DTI) can display peripheral neuropathy more intuitively and is a powerful tool for studying diabetic peripheral neuropathy [8]. The quantitative parameters of DTI include fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values, which reflect the diffusion characteristics of water molecules and are altered with the damage of nerve tissue. Wan et al performed sciatric nerve DTI imaging on a rabbit model of radiation-induced peripheral nerve injury and found that the FA value decreased after nerve injury, and DTI quantitative parameters such as the FA value were more sensitive and accurate than the T2 value [9]. Kabakci combined the measurement of peripheral nerve DTI parameters with fiber bundle tracing technology and proposed a normal range of the peripheral nerve FA value [10]. Some MRN studies of peripheral neuropathy have shown that both the tibial nerve and the common peroneal nerve in patients with type 2 diabetes have a decrease in FA value and an increase in ADC value [11-13]. Another study showed that for type 1 diabetic peripheral neuropathy, the FA value of DTI imaging was lower than that of patients without DPN [14]. Therefore, we aimed to analyze the changes in the FA and ADC values of MRN-DTI sequencing and the Toronto Clinical Scoring System (TCSS) scores after acupoint injection of mecobalamin at Zusanli for the treatment of type 2 DPN and to evaluate the therapeutic effect of acupoint injection therapy.

Material and Methods

The approval of the Ethics Committee of Chu Hisen-I Memorial Hospital of Tianjin Medical University was obtained, and the study was conducted according to the Declaration of Helsinki. All enrolled patients signed informed consent forms. This study was registered with the Chinese Clinical Trial Registry (no. ChiCTR 2100054566).

Study Design

This study was a single-center, case-controlled study. The study was carried out as shown in the flow chart in Figure 1.
Forty patients with type 2 DPN who were admitted to the ward of the Department of Integrated Traditional Chinese and Western Medicine of Chu Hisen-I Memorial Hospital from December 1, 2019, to August 31, 2020 were recruited. Patients were randomly divided into an acupoint injection group (Al group; n=20) and an intramuscular injection group (MI group; n=20).

The inclusion criteria were as follows: type 2 diabetes according to the 1999 WHO Diabetes Diagnosis Criteria; TCSS score >5; HbA1c >7.0%; no exposure to neurotrophic agents ≥2 weeks; 18 to 60 years of age; no history of lower limb or knee joint trauma and surgery; and no exposure to neurotoxins.

The exclusion criteria were as follows: MRN examination contraindications, cochlear implants, cardiac pacemakers and artificial stent implants, claustrophobia, pregnancy and breastfeeding, and the following diseases: (a) cervical and lumbar spine disease, sequelae of cerebrovascular disease, osteoarthritis, peripheral vascular disease, and genetic peripheral neuropathy; (b) foot ulcers, infections, and edema; (c) ALT, AST, and blood creatinine exceeding the normal limit; and (d) diabetic ketosis, ketoacidosis, and severe infection. Individuals were also excluded if our investigator believed they were not suitable to participate in this study.

Clinical Intervention

Both groups were treated with insulin combined with oral drugs for antihyperglycemic treatment. The patients’ blood glucose levels were controlled at levels of fasting <7.0 mmol/L and postprandial <10.0 mmol/L. Both groups were given an intravenous (i.v.) drip of alprostadil injection 10 ug daily for 2 weeks. For the Al group, the bilateral Zusanli acupoints were located and 0.25 mg of mecobalamin was injected into each acupoint daily for 14 days. For the intramuscular injection group, 0.5 mg of mecobalamin was administrated by intramuscular injection on the hip muscle for 14 days.

TCSS Scoring

TCSS scores were recorded in both groups before and after treatment.

MRN Examination

All patients underwent MRN examination in the Radiology Department of Tianjin First Central Hospital before and after treatment. MRN was performed using a 1.5-channel knee coil on a 3T magnetic resonance machine (Prisma, Siemens Healthineers, Germany). The scan ranged from the middle of the femur to the middle of the tibia, including the tibial nerve and the common peroneal nerve. The scanning sequence included axial SPAIR T2 weighted images (WI) and DTI. The detailed MR protocols were as follows:

1) The parameters of 2D axial T2W with fat suppression: TR/TE=8330/31 ms, FOV=160×160 mm², matrix size=384×269, slice thickness=2 mm, slice gap=1 mm, and 73 slices. The scan time was 2 min 56 s.

2) Axial DTI scanning parameters: TR/TE=8100/71 ms, FOV=250×250 mm², matrix size=128×128, gradient directions=30, slice thickness=2 mm, slice gap=1 mm, b=0, 1000 s/mm², and 73 slices. The scan time was 4 min 37 s.

DTI Post-Processing

The original image was transferred to a Siemens workstation. Images of the DTI sequence were processed and analyzed by the MR neural 3D post-processing software Syngo.via. The T2WI were used to determine the anatomical location of the tibial nerve and common peroneal nerve. The regions of interest (ROI) of the tibial nerve and common peroneal nerve were placed manually on the T2WI axial image and copied to the same region of the DTI. The first layer was the central plane of the knee joint cavity. The second and third layer were 10 mm above and below the first layer, respectively. The ROI covered the maximum diameter of the target nerve fiber and avoided tissues with high FA values, such as fat and muscle. The average FA and ADC values of each ROI of the tibial and common peroneal nerves were measured by 2 experienced radiologists with 3 years of experience in neuroimaging diagnosis, using a double-blind method.

Statistical Analysis

Statistical analysis was done with SPSS 17.0 software. Data are reported as mean±standard deviation, and the t test was...
used for comparison between groups. A value of $P<0.05$ was considered statistically significant.

### Results

#### Cohort Characteristics

The proportion of men was 49% in the AI group and 38% in the MI group, and patient age ranged from 43 to 60 years old. There were no significant differences in sex, age, body mass index, fasting plasma glucose, HbA1c, diabetic retinopathy, and urine albumin-creatinine ratio between the 2 groups at baseline ($P>0.05$) (Table 1).

#### TCSS Score

The TCSS neuropathy score of both groups decreased from baseline (AI 9.31±2.36; MI 9.34±2.54) to after the 2-week treatment (AI 7.12±1.87; MI 7.86±2.11). The difference between groups was not significant ($P>0.05$) (Table 2).

#### FA and ADC Values

The ROIs of the tibial nerve and common peroneal nerve were manually placed on T2WI (Figure 2A) and copied on DTI. At the popliteal fossa level, the FA (Figure 2B) and ADC (Figure 2C) were mapped out and FA, ADC values of the 2 nerves were measured. The FA values showed significant differences on both the common peroneal nerve (AI group 0.36±0.04; MI group 0.31±0.05; $P<0.05$) and the tibial nerve (AI group 0.38±0.07; MI group 0.34±0.06; $P<0.05$) after treatment (Table 3). After treatment, ADC values between the groups also showed significant differences for the common peroneal nerve (AI group 1.44±0.17×10^{-3} mm^2/s; MI group 1.61±0.20×10^{-3} mm^2/s; $P<0.05$) and tibial nerve (AI group 1.54±0.22×10^{-3} mm^2/s; MI group 1.60±0.17×10^{-3} mm^2/s; $P<0.05$) (Table 4).

### Discussion

DPN is one of the common microvascular complications of diabetes, which is often accompanied by other refractory microvascular complications such as diabetic retinopathy and diabetic nephropathy [15]. In this study, 18 patients of 40 were diagnosed with diabetic retinopathy. The 18 patients had a higher urine albumin-creatinine ratio (>3 mg/mmol), which is an indicator of diabetic nephropathy, and the average FBG and HbA1c levels were not ideal (FBG <7 mmol/L and HbA1c <7%) (Table 1).

In Western medicine, it is necessary to control blood glucose levels and apply vasoactive drug alprostadil and neurotrophic agent mecobalamin for DPN [16].

Acupuncture is an in vitro method with neurological effects and has unique advantages to treat neuropathy. Clinical studies have confirmed that acupuncture significantly improves painful symptoms of patients with DPN. Acupoint injection was established under the guidance of Chinese acupuncture and Western medicine. A number of clinical studies have confirmed that the acupoint injection method of drug administration combining

### Table 1. Demographic and baseline characteristics.

| Group                  | Acupoint injection | Intramuscular injection | $P$ value |
|------------------------|--------------------|-------------------------|-----------|
| Age (years)            | 49.2±5.24          | 51.5±5.66               | 0.13      |
| Male, n (%)            | 49%                | 38%                     | 0.14      |
| BMI index (kg/m$^2$)   | 23.1±3.19          | 24.1±2.69               | 1.01      |
| FBG (mmol/L)           | 7.8±2.11           | 8.2±2.14                | 0.63      |
| HbA1c (%)              | 8.1±2.22           | 8.5±2.41                | 0.52      |
| DR, n (%)              | 8 (20)             |                         | 0.46      |
| UACR (mg/g)            | 16.1±2.15          | 14.4±2.88               | 0.21      |

BMI – body max index; FBG – fasting blood glucose; HbA1c – glycated hemoglobin; DR – diabetic retinopathy; UACR – urine albumin-creatinine ratio.

### Table 2. Toronto Clinical Scoring System scores of both groups.

| Group | Baseline | 14th day | Baseline | 14th day |
|-------|----------|----------|----------|----------|
| TCSS score | 9.31±2.36 | 7.12±1.87* | 9.34±2.54 | 7.86±2.11* |

*Comparison before and after treatment within groups, $P<0.05$. 

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Western medicine and the meridian theory of TCM is more effective than acupuncture or intramuscular injection of drugs alone. Studies have shown that acupoint injection can effectively improve pain thresholds and nerve conduction velocities in DPN [17-19].

Chen et al [17] randomly divided 78 patients with DPN into 2 groups. The control group was treated with acupuncture alone, and the acupoints were taken from the bilateral sides of Zusanli. The treatment group was treated with mecobalamin acupoint injection, and the acupoint selection was consistent with the control group. The results showed that the total effective rate of the treatment group was 77.5% and that of the control group was 57.89% (P<0.05). Wang [18] randomly divided 60 patients with DPN into 2 groups. The treatment group was treated with an acupoint injection of vitamin B1 and vitamin B12 injection in Zusanli. A single acupuncture therapy was applied to the control group. The results showed that the total effective rate of the treatment group was 95% and that of the control group was 45% (P<0.05). Compared with acupuncture, acupoint injection not only stimulates acupoints, dredges the meridians, and relieves pain through acupuncture, but also has the pharmacological effects of the injected drugs, which can improve clinical efficacy and is more effective than acupuncture. Another clinical study confirmed that in terms of the administration method, acupoint injection of mecobalamin is better than intravenous injection for patients with DPN [19]. The treatment group was given mecobalamin injection in Zusanli, while the control group was treated with i.v. mecobalamin. There was an improvement of 91.67% in nerve conduction velocity and neurological symptoms in the treatment group and of 77.78% in the control group (P<0.05).

In our study, the Zusanli (ST36) acupoint was selected, which is a He acupoint of the foot-Yangming-stomach meridian and...
is located on the lower limbs, where the DPN usually occurred. We chose Zusanli to replenish qi, nourish blood, balance yin and yang and use mecobalamin to repair the damaged nerves. In contrast to the classic acupuncture method of manual twirling, acupoint injection of Zusanli is safer and more effective in providing pain relief. The combination of muscle injection and Chinese acupuncture can achieve the effects of regulating Zang-fu organs, nourishing meridians, regulating qi, and relieving pain.

The clinical diagnosis of DPN mainly relies on medical history, clinical symptoms, and neuro-electrophysiological examination. Clinical symptom assessment methods include quantitative sensory testing and scoring scales such as the TCSS. Other methods include sural nerve biopsy and skin biopsy [20]. Quantitative sensory testing can quantitatively detect sensory nerve function and evaluate the function of nerve fibers, which is time-consuming, laborious, and subjective, and has poor reproducibility. A sural nerve biopsy can directly manifest the pathological changes of nerve fibers, but it is invasive. Electro-neurophysiological examination is currently the criterion standard to diagnose DPN, but it is time-consuming and susceptible to the proficiency and subjectivity of the operator. The TCSS was used to sample and evaluate patients with DPN in our study. It has been reported that TCSS has good diagnostic efficacy in the screening and diagnosis of DPN and is highly consistent with the results of neuro-electrophysiological examination and sural nerve morphology examination [21].

In this study, the TCSS was selected to evaluate the efficacy of acupoint injection therapy and conventional intramuscular injection in the treatment of DPN. The TCSS neuropathy score of both groups decreased from baseline (AI 9.31±2.36; MI 9.34±2.54) to after the 2-week treatment (AI 7.12±1.87; MI 7.86±2.11). The TCSS scores of the 2 groups showed no significant differences after treatment, which might be due to the short length of treatment and the small sample size. To further detect the changes of nerve fibers after treatment, DTI imaging was applied to map the changes in the tibial and peroneal nerves.

MRN technology can evaluate peripheral nerves with a diameter of 2 mm and above and identify the fine structure of peripheral nerves [7]. Among the sequences, DTI is a noninvasive functional MR technology developed on the basis of diffusion-weighted imaging to display the fine structure of tissues [23]. In the human body, the tissue of the peripheral nerves has a strong structure. Water molecules are easy to diffuse along the direction of the nerve fiber bundles but not in the direction perpendicular to the fiber. DTI analyzes the free diffusion direction and the rate of water molecules in each tissue structure in 3-dimensional space, which could evaluate the integrity of tissue structure and the relationship between tissue structure and function at the cellular level. The FA and ADC values of a DTI sequence are related parameters describing the anisotropy and average diffusion degree of water molecules in nerve fibers, respectively. When neuropathy occurs by the blockage of axoplasmic flow, venous congestion, and Waller’s degeneration, it could widen the potential gap between the axon and the surrounding covering, speed up the diffusion of water molecules, and thus decrease the FA value and increasing the ADC value [10]. Once the microstructure of nerve tissue is damaged, disintegration of axons or demyelination and nerve edema could occur and the FA value decrease. The ADC value reflects the degree of diffusion of water molecules in each voxel, which is an average value of the diffusion size of water molecules in all directions. It is an indicator to evaluate the size of diffusion barriers such as cell membranes or myelin. Damage such as inflammation and edema could increase the ADC value. In this study, the DTI sequence diagnosis

| Table 3. Fractional anisotropy values of both groups. |
|-------------------------------------------------------|
| **Group** | **Acupoint injection** | **Intramuscular injection** |
|           | **Baseline** | **14th day** | **Baseline** | **14th day** |
| Common peroneal nerve | 0.22±0.05 | 0.36±0.04** | 0.22±0.04 | 0.31±0.05* |
| Tibial nerve | 0.25±0.06 | 0.38±0.07** | 0.26±0.08 | 0.34±0.06* |

* Comparison between groups, P<0.05; ** comparison before and after treatment within groups, P<0.05.

| Table 4. Apparent diffusion coefficient (ADC) values of both groups. |
|-------------------------------------------------------|
| **Group** | **Acupoint injection** | **Intramuscular injection** |
|           | **Baseline** | **14th day** | **Baseline** | **14th day** |
| Common peroneal nerve | 1.64±0.21 | 1.44±0.17** | 1.69±0.19 | 1.61±0.20* |
| Tibial nerve | 1.82±0.18 | 1.54±0.22** | 1.81±0.18 | 1.60±0.17* |

ADC value (10^-3 mm²/s). * Comparison between groups, P<0.05; ** comparison before and after treatment within groups, P<0.05.
of DPN showed characteristics of good repeatability, noninvasiveness, and accuracy, and the ADC and FA values were sensitive indicators for evaluating nerve tissue damage. The FA values of the common peroneal nerve (AI group 0.36±0.04; MI group 0.31±0.05) and the tibial nerve (AI group 0.38±0.07; MI group 0.34±0.06) were higher than the baseline (all P<0.05). After treatment, the FA value of the AI group was significantly increased compared with that of the MI group (P<0.05). The ADC values of the tibial and peroneal nerves in both groups after treatment were lower than the baseline values, while the ADC value of the AI group was significantly decreased compared with the MI group (P<0.05). The data alteration of the DTI parameters indicated that the acupoint injection with mecobalamin had better therapeutic effects on DPN than intramuscular injection alone. The mechanism of acupoint injection involved the regulation of nerve conduction, neuron signal pathways, protein expression, and oxidative stress levels, and injection with mecobalamin at Zusanli was demonstrated to increase the expression of nerve growth factor and superoxide dismutase expression [6].

There are some limitations of this study. The sample size was small and the length of treatment was short. Also, patients did not undergo a neuro-electromyography examination owing to a lack of research funding.

Conclusions

The results of this study showed that acupoint injection of mecobalamin at the Zusanli acupoint could ameliorate DPN, which was confirmed by the changes in TCSS scores and the MRI-DTI sequence-related parameters of FA and ADC values. This study provides clinical data for the application of acupoint injection therapy.

Acknowledgements

The authors express their appreciation to all the patients who participated in this study.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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