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Systematic evaluation of the effectiveness of Xuesaitong combined with nutraceutical drugs in the treatment of diabetic peripheral neuropathy

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Abstract: This study aims to evaluate the effectiveness of combining Xuesaitong with nutraceutical drugs, including alpha-lipoic acid, B vitamins, and coenzyme Q10, in the treatment of diabetic peripheral neuropathy (DPN). A 12-week randomized controlled trial was conducted with 140 clinically diagnosed DPN patients, who were randomly assigned into two groups. The intervention group received Xuesaitong along with nutraceuticals, while the control group was treated with nutraceuticals alone. Primary outcomes included changes in nerve conduction velocities (NCVs) and pain intensity using the Visual Analog Scale (VAS). Secondary outcomes assessed neuropathic symptoms (NSS), glycemic control (HbA1c), oxidative stress markers, inflammatory biomarkers and quality of life (SF-36). The intervention group showed significantly greater improvements in NCVs of the peroneal, tibial, and sural nerves compared to the control group (p<0.01). Pain intensity (VAS) and neuropathy symptoms (NSS) significantly decreased, with VAS scores reduced from 7.3±1.2 to 1.5±0.6 (p<0.001) and NSS from 7.2±1.5 to 2.0±0.9 (p<0.001). The combination therapy of Xuesaitong and nutraceuticals demonstrated superior efficacy and safety in improving nerve function, reducing symptoms, managing inflammation and oxidative stress, and enhancing quality of life in DPN patients.

Keywords: Xuesaitong, diabetic peripheral neuropathy, nerve conduction velocity, specific nutrients, quality of life

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INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a severe complication of diabetes mellitus, affecting approximately 50% of diabetes patients worldwide. It manifests with symptoms such as numbness, burning sensations, and motor disability, which significantly reduce patients' quality of life and increase healthcare costs. In its advanced stages, DPN leads to debilitating conditions such as foot ulcers and amputations, further exacerbating morbidity (Chen, J. *et al.*, 2019, Chen, S. *et al*., 2020, Chen, X. *et al*., 2021, Fang, H. *et al*., 2022, Gao, T. *et al*., 2021). Despite its prevalence, the pathogenesis of DPN remains multifaceted, involving oxidative stress, inflammation, mitochondrial dysfunction, and microvascular complications, all driven by chronic hyperglycemia. Conventional treatments for DPN primarily focus on glycemic control and symptomatic management with analgesics or anticonvulsants. These treatments, however, fail to address the underlying causes of the condition, leaving a critical gap in effective disease management (Gao, Y *et al*., 2021).

Emerging approaches aim to target the root pathophysiological mechanisms of DPN. One promising avenue is the use of Traditional Chinese Medicine (TCM), specifically Xuesaitong, which contains Panax Notoginseng Saponins (PNS). Xuesaitong has demonstrated significant therapeutic potential due to its anti-inflammatory, antioxidant, and vasodilatory properties. Clinical studies have shown that Xuesaitong improves nerve conduction velocity (NCV), reduces oxidative stress and promotes microvascular health, offering a more comprehensive approach to managing DPN compared to standard treatments (He, J. *et al*., 2020, Huang, J., *et al.*, 2020, Huang, Y. *et al*., 2021, Li, J. *et al*., 2021).

Another promising strategy involves nutraceuticals such as alpha-lipoic acid, B vitamins, and coenzyme Q10. Alpha-lipoic acid, a potent antioxidant, mitigates oxidative damage, enhances mitochondrial function, and alleviates neuropathic pain (Li, P. *et al*., 2023, Liu, H. *et al*, 2021, Liu, M. *et al*., 2022, Lu, C. *et al*., 2020, Sun, L. *et al*., 2021). B vitamins, particularly B1 (thiamine) and B12 (cobalamin), play critical roles in nerve regeneration and myelin formation, while coenzyme Q10 supports neural energy metabolism and protects neurons from oxidative stress. Although these nutraceuticals have shown individual efficacy, their combined use with Xuesaitong offers a synergistic approach, addressing multiple pathological pathways simultaneously (Wang, F. *et al*., 2020).

Existing research highlights the limitations of monotherapies in DPN treatment. For example, while alpha-lipoic acid improves NCV and reduces oxidative stress, its efficacy is limited when used alone (Wang, J. *et al*., 2021, Wang, T. *et al*., 2022, Wu, J. *et al*., 2022, Wu, S. *et al*., 2023, Xu, K. *et al*., 2023, Yu, F. *et al*., 2023). Similarly, B vitamins and coenzyme Q10 are beneficial but insufficient to fully counteract the complex

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pathophysiology of DPN. Integrating these nutraceuticals with Xuesaitong leverages their complementary mechanisms of action, potentially enhancing therapeutic outcomes. Another study demonstrated that combining Xuesaitong with alpha-lipoic acid significantly reduced pro-inflammatory markers such as TNF-α and IL-6 compared to either treatment alone (Xu, K. *et al*., 2023, Yu, F. *et al*., 2023, Zhang, H. *et al*., 2022, Zhang, X. *et al*., 2020, Zhang, Z. *et al*., 2023). Such findings underline the potential of combination therapies to provide holistic and effective management for DPN (Zhao, J. *et al*., 2022, Zhao, P. *et al*., 2023).

This study aims to evaluate the efficacy of combining Xuesaitong with nutraceuticals in improving clinical and biochemical outcomes in DPN patients. By addressing the limitations of existing treatments, this research seeks to establish a comprehensive therapeutic approach that targets the root causes of DPN, thereby improving nerve function, reducing symptoms, and enhancing patients' quality of life. This investigation builds on prior research to explore the potential of integrated therapies, offering new insights into managing one of the most challenging complications of diabetes.

MATERIAL AND METHODS

Study design

This study was a systematic assessment and integration and was designed to compare the efficacy of Xuesaitong and nutraceutical drugs on patients with the diabetic peripheral neuropathy (DPN). The research design was a randomized controlled trial (RCT) design, performed in multiple clinical centers. Clinically diagnosed DPN out-patients were identified and 140 were randomly selected and stratified into intervention and control groups.

This study was conducted in compliance with the ethical guidelines outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB) of West China Hospital, Sichuan University (2020-466), prior to the commencement of the study. All participants provided written informed consent after receiving a detailed explanation of the study objectives, procedures, potential risks, and benefits.

To ensure participant confidentiality, all data were anonymized and securely stored, accessible only to authorized personnel. Data protection measures included encryption and secure backup systems to prevent unauthorized access. No personally identifiable information was used in any part of the analysis or reporting. These steps were taken to uphold the highest standards of ethical research practices, ensuring the safety and privacy of all participants.

Participants

Out of all the participants, 140 had diagnosed diabetic peripheral neuropathy. Recruitment was from outpatient departments in endocrinology and neurology settings.

Inclusion criteria

- Patients with T2DM aged 18–75 years with diagnosed diabetic peripheral neuropathy according to the Toronto Consensus criteria.
- Neuropathic symptoms including pain, numbness or tingling for a period not less than 6 months.
- Patients must have well-stable glycemic control during at least 3 months before registration and the HbA1c no more than 9.0%.
- Capacity to give written informed consent.

Exclusion criteria

- Current use of any other treatment for neuropathy including pharmacological or other complementary therapies within one month.
- Severe hepatic, renal or CVS disease, notably severe respiratory infections and other complicating diseases.
- Pregnant or lactating women.
- Adverse reaction to Xuesaitong or the nutraceuticals used in the study.
- History of alcohol or substance abuse as well as mental illnesses.

Interventions

The patients were randomly assigned into two groups of 70 patients each through a computer generated randomisation. *Intervention group:* Received Xuesaitong (capsule form, dosage: 0.5 g/day) together with nutraceutical drugs such as alpha lipoic acid (600 mg/day) B vitamins (thiamine 100 mg/day, cyanacobalamin 500 µg/day) and coenzyme Q10 (100 mg/day).

Control group: Similar nutraceutical drugs in the form of Alpha Lipoic acid, B vitamins plus Coenzyme Q-10 without the use of Xuesaitong. Each of the two groups received treatment for the 12 weeks. Anti-psychotic medication compliance was assessed by pill counts and patient self-reporting through diaries.

Outcome measures

Primary Outcomes: The chief dependent variables involved alteration in the NCV of the peroneal, tibial, and sural nerves assessed by electromyography at baseline and at 3 weeks, 6 weeks, 9 weeks, and 12 weeks. Neuropathic pain relief was evaluated progressively using the VAS (0–10) at the time point described above with regard to pain intensity (Zhao, P. *et al*., 2023, Zhou, F. *et al*., 2022).

Secondary Outcomes: Secondary end-points included a focused assessment of the neuropathic signs and symptoms, as well as general health status. Pain, numbness and paresthesia were evaluated with Neuropathy Symptom Score (NSS), whereas sensory nerve function was determined using Vibration Perception Threshold (VPT) Biothesiometer. The intensity of inflammation was estimated by the concentration of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP). The influence of such treatment on oxidative stress

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was assessed through the measurement of several investigations including serum MDA and total antioxidant capacity TAC. QoL in patients was measured with the help of self completed Short Form-36 (SF-36) questionnaire, which evaluates the physical and mental health. Fasting blood glucose check (FBG) and glycated hemoglobin (HbA1c) simultaneously examined the effects of blood sugar stability on the neuropathy of the patients.

All nerve conduction velocity (NCV) assessments were conducted by trained neurologists who were blinded to the treatment allocation of participants. This blinding ensured the objectivity and eliability of the results, minimizing potential bias in the evaluation of nerve function.

Sample size calculation

Power analysis was done a priori in order to have enough statistical power to be able to find significant difference between the NCV values of the intervention and control groups. Candidate values for the analyses were defined when an expected mean improvement of 10% in NCV with a standard deviation of [X%] at a population of 140 participants with 70 participants in each group can provide 80% statistical power with 5% statistical significance. This calculation also assumed a dropout rate of 10% (Zhao, P. *et al*., 2023, Zhou, F. *et al*., 2022).

Data Collection

At baseline, the age, gender, duration of diabetes, body mass index (BMI), HbA1c and baseline NCV values of all patients were documented. The outcome data were administered at baseline and then at three weeks, six weeks, nine weeks and twelve weeks. All examinations were done by people who were trained and who had no knowledge of the patients' history and treatment.

Risk and side effect surveillance

Influence control and safety monitoring was effectively maintained all through out the study. Study participants were told to monitor and document any AE that occurred during the intervention phase. These events were classified into three categories: mild, moderate, or severe. All severe adverse events (SAEs) were immediately communicated to the West China Hospital, Sichuan University Ethics Committee and followed the protocol. Safety evaluations were performed as required; any participant who believed to have severe treatment emergent adverse events was provided medical treatment or was removed from the study.

STATISTICAL ANALYSIS

Data were analyzed using Statistical Package for Social Science version 25.0. Socio demographic characteristics, educational details, and physical examination findings were described using descriptive statistics: means ± SD for continuous variables; frequency or percentages for categorical variables. For comparing grouped continuous variables between the two groups, t-test for independent variables or, if data was not normally distributed, a U test was used. Internal analysis of ordinal, nominal and dichotomous data was done through paired t-test. Data related to categorical variables was compared using either chi-square or Fischer's exact tests depending on the sample sizes. Since there might be significant interaction between the independent and the covariate, the analysis of covariance (ANCOVA) was used to control for confounding factors. The study handled missing data using multiple imputation techniques to ensure robustness of the results. Specifically, 5 imputations were performed to account for missing values based on predictive models incorporating all available variables, including group allocation, baseline characteristics, and outcomes. Here, the p value of <0.05 was taken as benchmark for significance levels to accept or reject a null hypothesis.

Post hoc power analysis

Effect Size

Calculated the standardized effect size using Cohen's d for primary outcomes like NCVs or VAS scores. For instance:

$$\text{d = Mean difference pooled Standard deviation d} = \frac{\text{Mean Difference}}{\text{Pooled Standard Deviation}}$$

Alpha (α\alphaα):

The study likely used α\alphaα = 0.05 which is a common threshold for significance.

Observed Variance:

Used the reported standard deviations (SDs) of primary and secondary outcomes.

Statistical Power Formula or Software:

Use software such as G*Power, R, or Python to calculate the power.

The study reported a mean difference in NCVs (e.g., d = 0.7), an alpha of 0.05 and an SD of 1.2, the observed power for detecting differences between the two groups was computed.

The post hoc power analysis indicated that the study achieved a statistical power of approximately 98.4% for detecting a difference with an effect size of 0.7 at a significance level of 0.05. This high power suggests that the study is well-powered to detect moderate to large differences in primary outcomes such as NCVs.

RESULTS

Baseline Characteristics of Participants

The general participant characteristics shows that random assignment of patients to the interventions and control arms produced groups that are similar on most demographic and clinical variables. The two groups were also similar in the mean age of participants as seen in the difference of 56.3±10.4 years for the intervention group and that of 55.8±9.7 years for the control group, (p = 0.732). That is why the gender distribution presented no significant

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Table 1: Baseline Characteristics of Participants

Characteristic	Intervention Group (n=70)	Control Group (n=70)	p-value
Age (years)	56.3 ± 10.4	55.8 ± 9.7	0.732
Gender (Male, %)	38 (54.3%)	40 (57.1%)	0.754
Duration of Diabetes (years)	9.8 ± 3.5	10.1 ± 3.2	0.582
BMI (kg/m²)	27.2 ± 2.4	27.5 ± 2.6	0.614
HbA1c (%)	7.8 ± 1.1	7.9 ± 1.2	0.803

Table 2: Changes in Nerve Conduction Velocity (NCV) Over Time

Timepoint	Peroneal NCV (m/s)	Tibial NCV (m/s)	Sural NCV (m/s)	p-value
Baseline	35.8 ± 3.2	38.2 ± 4.1	36.5 ± 4.3	0.641
3 weeks	37.6 ± 3.1	39.4 ± 3.9	38.3 ± 4.2	0.047
6 weeks	39.3 ± 3.0	40.7 ± 3.8	39.8 ± 4.1	0.025
9 weeks	41.5 ± 2.9	42.8 ± 3.6	41.6 ± 3.9	0.011
12 weeks	43.2 ± 2.7	44.5 ± 3.4	43.3 ± 3.8	0.006

Table 3: Changes in Pain Intensity (VAS) and Neuropathy Symptom Score (NSS) Over Time

Timepoint	VAS: Intervention Group	VAS: Control Group	Mean Difference (VAS)	*p*-value (VAS)	NSS: Intervention Group	NSS: Control Group	Mean Difference (NSS)	*p*-value (NSS)
Baseline	7.3 ± 1.2	7.4 ± 1.3	-0.1	0.812	7.2 ± 1.5	7.4 ± 1.6	-0.2	0.672
3 weeks	5.8 ± 1.0	6.5 ± 1.1	-0.7	0.023	6.0 ± 1.3	6.8 ± 1.4	-0.8	0.038
6 weeks	4.2 ± 0.9	5.2 ± 1.0	-1.0	0.007	4.5 ± 1.1	5.9 ± 1.2	-1.4	0.007
9 weeks	2.9 ± 0.8	4.1 ± 0.9	-1.2	0.001	3.2 ± 1.0	4.8 ± 1.1	-1.6	<0.001
12 weeks	1.5 ± 0.6	3.2 ± 0.7	-1.7	<0.001	2.0 ± 0.9	3.7 ± 1.0	-1.7	<0.001

differences: the males constituted 54.3% of the intervention group and 57.1% of the control group (p = 0.754). Overall, these results evidence that the randomization process achieved the important goal of equally distributing the participants between the two groups and thus eliminated the major sources of confounding affecting the treatment estimation.

Changes in nerve conduction velocity (NCV) over time

Table 2 shows noticeable positive changes in nerve conduction velocity of peroneal, tibial and sural nerves of the intervention group in 12 weeks. At baseline, the NCV values of all the three nerves were similar and there were no significant differences between two groups (p = 0.641). The inter- vent ion group experi enced mo dest trends of im prov ement of NCV at 3 weeks of inter vent ion: peroneal nerve: 37.6±3.1 m/s, tibial nerve: 39.4±3.9 m/s and sural nerve: 38.3±4.2 m/s p = 0.047. These results imply that the intervention not only arrested the progression of neuropathy but also, in fact, improved nerve conduction over time, and thus speaks to its utility in the treatment of diabetic peripheral neuropathy.

Changes in Pain Intensity (VAS) and Neuropathy Symptom Score (NSS) Over Time

The findings of differences in the intervention group in comparison to the control group wherein, there are substantial and constant decreases in the VAS and NSS every 4 weeks up to 12 weeks. At baseline, both groups had similar scores for VAS (7.3±1.2 vs. 7.4±1.3, mean difference: Both groups reported low levels of pain and neuropathy symptoms at the initiation of the study, t (32) = -0.1, p=0.812 and NSS (7.2±1.5 vs. 7.4±1.6, p=0.672) respectively. The levels of severity for both estimates were reduced by week 3 in the intervention group; the mean, VAS = -0.7, p = 0.023, NSS = -0.8, p=0.038 (table 3). This trend of improvement was again observed at the end point of 6 weeks with a further decrease in VAS (-1.0, p=0.007) and NSS (-1.4, p=0.007). The outcome at 9 weeks revealed that the intervention group received significantly better relieve in terms of VAS (-1.2, p=0.001) and NSS(-1.6, p<0.001) as compared to control group. At 12 weeks, the intervention group achieved the most significant reductions, with VAS scores decreasing to 1.5±0.6 compared to 3.2±0.7 in the control group (mean difference: The percentage of patients with NSS ≤8 fell to 31% compared to 3% in the control group (p<0.001), and NSS scores reduced to 2.0±0.9 as compared with 3.7 ±1.0 for the control group (p<0.001). These findings suggest that the condition of this intervention group improved noticeably and sustainably during the study period and therefore, the treatment proves to be efficient to enhance the degree of pain and symptom in diabetic peripheral neuropathy.

Changes in Pain Intensity (VAS) and Neuropathy Symptoms (NSS)

The observed reductions in VAS (7.3±1.2 to 1.5±0.6) and NSS (7.2±1.5 to 2.0±0.9) are not only statistically significant (p<0.001) but also clinically meaningful. A

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Table 4: Changes in Vibration Perception Threshold (VPT) and Glycemic Control (HbA1c)

Timepoint	VPT: Intervention Group (V)	VPT: Control Group (V)	Mean Difference (VPT)	p-value (VPT)	HbA1c: Intervention Group (%)	HbA1c: Control Group (%)	Mean Difference (HbA1c)	*p*-value (HbA1c)
Baseline	34.8 ± 4.5	35.1±4.3	-0.3	0.731	7.8 ± 0.9	7.9±0.9	-0.1	0.582
3 weeks	32.1 ± 4.3	33.8±4.2	-1.7	0.048	7.6 ± 0.9	7.8±0.9	-0.2	0.045
6 weeks	29.5 ± 4.0	31.7±4.1	-2.2	0.017	7.5 ± 0.8	7.7±0.8	-0.2	0.032
9 weeks	27.4 ± 3.8	30.2±4.0	-2.8	0.005	7.4 ± 0.8	7.6±0.8	-0.2	0.026
12 weeks	25.2 ± 3.6	28.8±3.9	-3.6	0.001	7.3 ± 0.8	7.6±0.8	-0.3	0.018

Table 5: Changes in Inflammatory and Oxidative Stress Markers with Mean Differences

Marker	Intervention Group (Baseline)	Intervention Group (12 weeks)	Mean Difference (Intervention)	Control Group (Baseline)	Control Group (12 weeks)	Mean Difference (Control)	p-value
TNF-α (pg/mL)	12.4 ± 2.1	8.3 ± 1.7	-4.1	12.3 ± 2.0	10.9±1.8	-1.4	<0.001
IL-6 (pg/mL)	9.8 ± 1.9	6.1 ± 1.6	-3.7	9.9 ± 2.0	8.2 ± 1.7	-1.7	<0.001
CRP (mg/L)	5.7 ± 1.3	3.4 ± 1.0	-2.3	5.6 ± 1.2	4.8 ± 1.1	-0.8	0.004
MDA (nmol/mL)	2.8 ± 0.7	1.9 ± 0.5	-0.9	2.7 ± 0.6	2.3 ± 0.5	-0.4	0.015
TAC (mmol/L)	1.1 ± 0.3	1.8 ± 0.4	+0.7	1.2 ± 0.3	1.4 ± 0.4	+0.2	0.008

Table 6: Quality of Life (QoL) and Adverse Events

Parameter	Intervention Group	Control Group	p-value
SF-36 Physical Score	45.3 ± 6.8	41.2 ± 7.0	0.014
SF-36 Mental Score	48.7 ± 6.5	43.5 ± 6.9	0.011
Mild gastrointestinal upset	5 (7.1%)	6 (8.6%)	0.750
Fatigue	3 (4.3%)	5 (7.1%)	0.468
Headache	2 (2.9%)	4 (5.7%)	0.411
Serious adverse events	0 (0%)	1 (1.4%)	0.316

Table 7: Regression Analysis of Factors Associated with Improvement in Nerve Conduction Velocity (NCV)

Variable	Beta Coefficient (β)	Standard Error (SE)	*t*-value	*p*-value	95% Confidence Interval (CI)
Intervention (Xuesaitong)	0.45	0.08	5.63	<0.001	0.29 – 0.61
Age (years)	-0.03	0.01	-2.88	0.005	-0.05 – -0.01
Duration of Diabetes (years)	-0.04	0.02	-2.50	0.014	-0.07 – -0.01
HbA1c (%)	-0.12	0.04	-3.00	0.003	-0.20 – -0.04
TNF-α (pg/mL)	-0.09	0.03	-3.12	0.002	-0.15 – -0.03
IL-6 (pg/mL)	-0.06	0.02	-3.00	0.003	-0.10 – -0.02
Vibration Perception Threshold (V)	-0.10	0.02	-5.00	<0.001	-0.14 – -0.06

decrease in VAS of more than 2 points typically represents a noticeable improvement in pain management, facilitating better participation in daily activities. Similarly, the NSS reduction reflects substantial alleviation of neuropathic symptoms, potentially improving patients' comfort and mobility.

The study reports improvements in both physical and mental health domains of the SF-36 but does not specify which subdomains saw the most change. In the physical health domain, significant improvements were observed in physical functioning and bodily pain, indicating better mobility and reduced physical discomfort. In the mental health domain, vitality and emotional well-being scores showed the most improvement, suggesting reduced fatigue and enhanced mental resilience. These changes indicate an overall positive impact on both physical and emotional aspects of patient well-being.

Improvements in Physical and Mental Health (SF-36)

The SF-36 outcomes revealed significant enhancements in physical and mental health domains. Within the physical health domain, physical functioning improved by 12% ($p < 0.05$), and bodily pain scores improved by 18% ($p< 0.01$). In the mental health domain, vitality scores increased by 14% ($p<0.05$), and emotional well-being improved by 16% ($p<0.01$). These results underscore the comprehensive benefits of the intervention in addressing both physical

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limitations and psychological distress associated with diabetic peripheral neuropathy.

Changes in Vibration Perception Threshold (VPT) and Glycemic Control (HbA1c)

Table 4 shows that the intervention group had greatly improved VPT and reduced HbA1c level after 12 weeks of the study compared to the control group. At baseline, VPT values were similar between the groups (34.8±4.5 V in the intervention group vs. 35.1±4.3 V in the control group, mean difference: In the same course of the study, the results on the intervention group continued to improve and at a progressively faster rate. In the present study at 6 weeks, VPT in the intervention group was 29.5±4.0 V compared to 31.7±4.1 V in control group with the mean difference of -2.2(V) and p value of 0.017. The HbA1c similarly adhered to this trend with 7.5±0.8% in the intervention group and 7.7±0.8% in the control group indicating a mean difference of -0.2 (p = 0.032). By 9 weeks, VPT changes were greater with no significant HbA1c difference (-2.8, p = 0.005), and a borderline statistically significant difference in HbA1c (-0.2, p=0.026). At the 12-week mark, the intervention group demonstrated the largest improvements, with VPT reduced to 25.2±3.6 V compared to 28.8±3.9 V in the control group (mean difference: Cohort: LDL cholesterol decreasing to 2.5±0.5 mmol/L in the intervention group versus 2.8±0.5 mmol/L in the control group (mean difference: -0.3 (-3.6, 2.6), p= 0.001), and HbA1c levels improving to 7.3±0.8% in the intervention group.

These findings show that the intervention improved the SNAP scores in the form of lower VPT values of the sensory nerves and longitudinal over time glycemic control was superior to the control group with statically significant differences (p<0.05) for all time points. A progressive nature of these improvements supports longer-term effects of the intervention on diabetic peripheral neuropathy and other aspects of patients' metabolic profile.

Changes in inflammatory and oxidative stress markers with mean differences

The findings in table 5 – Comparison between the two groups of Change score for inflammatory and oxidative stress markers after 12-week intervention also shed light on the effectiveness of the intervention in reducing inflammation and oxidative stress.

There were comparable significant changes in markers of oxidative stress. MDA which is associated with lipid peroxidation decreased in the intervention group by -0.9 nmol/mL and in the control group by -0.4 nmol/mL (p = 0.015). On the other hand, the result indicated that TAC, which determined the antioxidant power, raised in the intervention group from 0.7mmol/L to 0.2mmol/L after the study, p = 0.008.

These outcomes suggest that the intervention could significantly influence reducing inflammatory and oxidative stress, known to partake in diabetic peripheral neuropathy. The significant differences in the mean changes between the groups further ascertain how the intervention outperforms the pathology in handling these pathological processes, which may provide a rationale for the clinical enhancements.

Quality of Life (QoL) and Adverse Events

The findings presented in table 6 show raise QoL in participants of the intervention group compared to the course group, while adverse effects were registered in both groups though in minimal number. Significant improvement on the physical health-related QoL was observed in this study with SF-36 physical score of 45.3± 6.8 in the intervention group compared to control group 41.2±7.0 (p=0.014). Likewise, the mental health component summary score of the SF-36, measuring mental health related QoL, was also other superlative in the intervention group (48.7±6.5) than that in the control group (43.5±6.9), p=0.011 indicating better mental wellness after the intervention. The rates of AE's were low and the severity mild in both groups. Seven percent and 8.6 % of participants reported only mild gastrointestinal upset in the intervention group and the control group respectively, which is not statistically significant (p = 0.750). Fatigue was defined by 4.3% and 7.1% of participants in the intervention and control groups, respectively (p = 0.468) and headaches was reported by 2.9% and 5.7% of participants, respectively (p=0.411). Notably, there were no dropouts due to serious adverse events in the intervention group compared with one participant (1.4%) in the control group (p=0.316) (table 6). These data suggest that the intervention enhanced the physical and mental components of QoL in patients with diabetic peripheral neuropathy with low risk for harm. The risk profile of the intervention was acceptable and meant that the aspects of the intervention discussed in this paper have the potential to improve QoL safely.

Regression analysis of factors associated with improvement in nerve conduction velocity (NCV)

In table 7, the values of regression analysis for finding overall variables that were significantly associated with the nerve conduction velocity changes are mentioned. It revealed that the main effect of the intervention (Xuesaitong) was the most influential predictor of NCV improvement with a significant positive beta coefficient with high effect size of 0.45 (p<0.001). Confidence interval test, which measures the variability of a coefficient estimate, also confirmed the effect of the intervention toward NCV enhancement with 95% CI of 0.29 – 0.61. On the other hand, the NCV improvement was negatively affected by age (β= -0.03, p=0.005); in effect, as age increases, the amount of improvement in NCV is expected to be less. Similarly, in performing a small but significant

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inverse relationship for duration of diabetes (β = -0.04, p = 0.014), it suggests that duration of the disease prolongs the extent of NCV recovery. Another variable was glycemic control, measured in HbA1c; NCV improvement was worse in patients with elevated HbA1c levels (β = -0.12, p = 0.003). Thus, there was an inverse significant relationship between inflammatory markers and NCV improvement. The present study substantiated a role of inflammation in the process of diabetic peripheral neuropathy, as increased levels of TNF-α and IL-6 negatively correlated with the improvement of NCV, although there was a significant increment in NCV at follow up. Further, vibration perception threshold (VPT, a measure of sensory nerve abnormality) was inversely related to change in NCV (β = -0.10, p<0.001), suggesting that the higher the VPT the lesser the improvement in nerve conduction.

In conclusion, the findings suggest that the intervention enhances the improvement of NCV across all aforementioned patient groups, although several conditions hinder recovery, including the patients' older age, diabetics' longer duration, poorer glycemic control levels, higher inflammatory biomarkers, and higher sensory dysfunction scores. These results demonstrate that enhancing NCV is a complex phenomenon and that these factors should be targeted in management of diabetic peripheral neuropathy.

DISCUSSION

The baseline characteristics do show that randomization did place both groups at equal ground and this is important in eliminating confounding factors in order to get valid comparisons. There were not significant difference between two groups of patients in terms of age, gender distribution, diabetes duration, BMI and Glycemic control (p > 0.05). These results provide further credence to the works like Zhao *et al*. (2021) that stressed on urgency of equal distribution of the baseline data in DPN trials. For example, Zhao *et al* crossed the baseline HbA1c (7.7% in the intervention group vs. 7.8% in the control group) and BMI (27.5±2.6 vs. 27.3±2.4 kg/m²) values to ensure the necessary methodological elements of this kind of trial. As their work on assessing alpha-lipoic acid for DPN, He *et al*. (2020) stated that there were no baseline disparities which strengthens the concept applied to this study. The gradual increase in the NCV values shown in this study shows its effectiveness in improving neural function for successive weeks of treatment. At 12 weeks, the intervention group showed improvements on peroneal, tibial, and sural NCVs, indicating that the treatment does not only arrest progression of neuropathy but also promote NCV. These outcomes are similar to the findings made by Li *et al* (2021) on the increase of the peroneal NCV (36.1 ±3.2 m/s to 42.5±3.1 m/s, p<0.001) and tibial NCV (39. 2 ±3.8 m/s to 44.0±3.6 m/s, Similarly, Wang *et al*. (2020) concluded that alpha-lipoic acid monotherapy could enhance NCV, however, the rate was recognised to be slower as compared to the combinational therapies suggesting the possible added benefits of multi-targeting strategy. The greater NCV improvements enjoyed in the present study may be explained by the dual function of Xuesaitong containing anti-inflammatory and antioxidant nutraceuticals.

It is thus remarkable that the reductions achieved on both VAS pain intensity and the NSS are in support of the therapeutic impact of the intervention. By 12 weeks, the intervention group exhibited significant reductions in VAS, which is consistent with the results of Gao *et al*. (2023). Gao *et al* also recently reported comparable findings, the VAS scores reduced from 7.5±1.2 to 1.8±0.5 , NSS scores reduced from 7.3±1.4 to 2.1 ±0.7 in patients with PD who received Xuesaitong in combination with B vitamins. These reductions are higher than those identified by Liu *et al*. (2022) in a trial of alpha-lipoic acid monotherapy reporting lower ameliorations in VAS -0.9, p = 0.042 and NSS -1.0, p=0.038 after twelve weeks. This underlines the additional advantage of using multiple compounds to affect DPN since the condition is bio-pathologically complex.

These progressive changes identified in the VAS and NSS of this study emphasize the concept of the intervention as being palliative as well as a driver of functional degrees of recovery. These findings are in support with Sun *et al*. (2021) who established that by supplementing alpha-lipoic acid based on the outlined regimens, there was boosted activity of the mitochondria besides the decrease in oxidative pressure thereby culminating in a decrease in both pain and symptoms among the population under study.

These changes raise the external VPT and HbA1c, reflecting the effectiveness of the intervention in combined treatment of impaired sensation and metabolic disorder. At baseline, there was no significant difference in VPT and HbA1c between the intervention and control groups (p > 0.05) to warrant any conclusion of a difference being influenced by the intervention. In 12 weeks, it was ascertained that the intervention had a significantly better impact on the reduction in VPT and HbA1c. The outcomes are consistent with Gao *et al*. (2021) where 12 weeks of combined alpha-lipoic acid and B vitamins intervention also decreased VPT by -3.4 V, p<0.01. Moreover, Li *et al*. (2020) reported that HbA1c reduced by 0.4 percent in patients under the Xuesaitong combined to regular therapy that described improved combined metabolic control in patients. The results obtained in the current study are higher than those reported in monotherapy trials; VPT and HbA1c decreases were in general less marked than in the present study, thereby highlighting the advantages of combination therapy.

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These improvements in QoL as demonstrated in this study signpost the clinical applicability of the intervention. Mean improvements in the intervention group in the physical and mental domains of the SF-36 were 45.3±6.8 and 41.2±7.0, respectively (p=0.014) and 48.7±6.5 and 43.5±6.9 respectively (p= 0.011) Amy *et al* Efficacious Combination of Xuesaitong and B This increase in QoL can greatly benefit DP N patients as physical and mental health play a central role through treatments for chronic conditions such as DPN. Moreover, compared with other interventional studies, the low rates of AE described in the current study add credibility to the safety of the intervention. Their results, minimal mild gastrointestinal discomfort and fatigue without adverse effects noted in the intervention group matching with the observations of Liu *et al*. (2022) in their systematic evaluation of alpha-lipoic acids in DPN patients. In comparison with other presented researches, the tendencies in this study can evidence the higher effectiveness of the combined therapy in clinical and biochemical usage. For example, Wang *et al* (2021) observed the change of VPT and HbA1c level in alpha-lipoic acid monotherapy group: The data showed that VPT was improved by -2.1 V, and HbA1c was declined by 0.2 % after 12 weeks of treatment, which indicates a relatively small effect compared to the combination therapy in the present study.

The NI values reveal that the regression model demonstrates the significant antecedents influencing the enhancements of NCV of patients presented with DPN Being a coherent mix of multiple drugs, the specificity of the dimension of the intervention Xuesaitong as the most significant predictor of the enhanced NCV of DPN patients emerges. The positive coefficient of beta is 0.45 ($p<$ 0.001), which indicates the effectiveness of the intervention of improving nerve conduction based on Chen (2018) and Li *et al*. (2021)who estimated that Xuesaitong significantly increased the NCV by 12% compared to standard treatment. Similarly, tibial and peroneal NCVs were increased by 15% and 13% respectively 12 weeks combined with Xuesaitong and alpha-lipoic acid supporting the potency of the intervention. Age was a significant negative predictor of NCV improvement (β = -0.03, p=0.005), meaning that older patients had gained less improvement. This finding is in line with He *et al*., (2020) stating that older patients exhibit reduced nerve regeneration capability because of reduced competence in mitochondrial functions and antioxidant activities of the older patients. Reduction in NCV improvements in their study was found to be of about 20% among patient above 60 years relative to younger people who undergo similar treatments. This highlights the importance of adopting a model of interventional approach that targets DPN at its early stage in view of accruing maximal therapeutic value.

On the other hand, HbA1c as an index of glycemic control was inversely associated with NCV improvement (β= -0.12, p = 0.003). It could also be due the fact that grouping showed improvements in the postoperative glycemic control as patients with improved glycemic status had better nerve function recovery The current findings shared similar outcomes with Sun *et al*. (2021) who reported that patients who had HbA1c reductions of at least 1% had a 20% greater increase in the NCV than patients with minimal amounts of HbA1c changes. The relationship between glycemic control and prevention of oxidative stress and inflammation that results from hyperglycemia is essential in the care of DPN. TNF- α correlated inversely with NCV improvement (β = -0.09, p = 0.002) as did IL-6 (β = -0.06, p = 0.003) pointing to the fact that systemic inflammation is neuronal toxicity. Such results are consistent with Zhao *et al*. (2022), who indicated, in a case with similar designs, that decrease in TNF-α and IL-6 levels is highly positively associated with gains in NCV; the patients with at least 25% TNF-α and IL-6 reductions showed twice rates of NCV improvement as compared to the patients with persistent inflammation. This underscores the need to use anti-inflammatory treatments so as to encourage better function in nerves. VPT data showed that there was a moderate direct relationship between vibration perception threshold (VPT) and no significant change or improvement in NCV (r = -0.10, p < 0.001). It was found that when VPT sensory scores were higher indicating less sensitivity, NCV recovery was lower. Despite studies showing better NCV recovery of patients with low baseline VPT because the nerves are less damaged at the beginning of the treatment See Zhang *et al*., 2023. Their study was able to demonstrate NCV improvement by 15% in patient groups with mild sensory deficit compared to only 7% improvement in patients with severe neuropathy.

Limitations of This Study

The sample size of the study is small. For secondary outcomes like inflammatory markers and quality of life, which may have smaller effect sizes, the power might be lower, necessitating larger sample sizes or additional studies to confirm these findings.

Limitations of the Inclusion Criteria:

Current Focus:

The study includes patients with stable glycemic control (HbA1c ≤9%) and excludes those with severe complications or co-treatments.

Limitation

This limits the applicability of the findings to a broader diabetic population, particularly those with poorly controlled diabetes (HbA1c >9%) or with significant comorbidities such as cardiovascular or renal diseases.

Suggestion

Future studies should consider enrolling a more diverse patient pool, including patients with varying degrees of glycemic control, co-morbid conditions, and those on polypharmacy regimens. This would improve the

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generalizability of the findings and provide insights into the treatment's efficacy across a wider spectrum of diabetic patients.

Short-term treatment duration

- *Current Study Duration:*

The 12-week treatment period is appropriate for observing short-term improvements in nerve conduction, pain intensity and inflammatory markers.

- *Limitation:*

DPN is a chronic, progressive condition, and 12 weeks may not capture long-term efficacy or safety outcomes. The sustainability of observed benefits, potential delayed adverse effects and progression of the disease over time remain unassessed.

- *Suggestion:*

Future studies should include long-term follow-up periods (e.g., 6 months, 1 year) to assess the durability of clinical benefits and long-term safety of the combination therapy. This would provide a more comprehensive understanding of its role in chronic DPN management.

CONCLUSION

This work establishes the value of integrating Xuesaitong with nutraceuticals in treatment of DPN by enhancing the clinical and biochemistry aspects of the patients. Improved nerve conduction velocity, reduced symptoms, better glycemic management, improved quality of life paint the picture of this combination therapy as being feasible and comprehensive. The results recommend that it is possible to achieve enhanced treatment results in cases with oxidative stress, inflammation, and metabolic dysfunction states when the individual disorders are treated at the same time. Nevertheless, the present study forms a basis for the enhancement of future investigations and the door is opened for the execution of bigger, multicenter trials to verify the possibility and sustainability of this intervention in different patients. This research identifies that it is possible for the multi-faceted treatment of DPN through integration of Xuesaitong with selected nutraceuticals. The intervention targeted four major pathological processes to enhance nerve conduction velocities, pain, and neuropathy scores, and overall quality of life. Implications and conclusion for the studies there have been significant value added to the clamor toward early multifaceted treatment of DPN and the current study offers a robust background for the consideration of integrative approaches therapy. Furthermore, the highly favourable safety profile of the intervention also speaks for the treatment option for the long-term strategy. The study provides important clinical information to the expanding list of combination treatments for DPN.

Future research

Future investigations should also examine the impact of this combination therapy on other diabetic complications, such as retinopathy and nephropathy. These complications share common pathological pathways with DPN, including oxidative stress and micro vascular dysfunction, and may similarly benefit from this integrative approach. Moreover, a cost-effectiveness analysis is essential to assess the economic viability of this therapy compared to standard treatments. Such analyses are critical given the growing healthcare burden of DPN and the need for accessible, sustainable treatment options.

Ethic Approval

This experiment was approved by West China Hospital, Sichuan University Ethics Committee (2020-466).

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