

Clinical Efficacy of Ultrasonic Medicinal Penetration in the Removal of Blood Stasis and Alleviation of Zhuyu Juanbi Formula in the Treatment of Peripheral Neuropathy Induced by Paclitaxel

Ying Zhang^{1,2}, Huixin Chen^{1,2,3}, Qirong Zhang^{1,2,3}, Yingjie Jia^{1,2*}, Dan Yi^{1,2}

¹The First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300381, China

²National Clinical Research Center of Acupuncture and Moxibustion, Tianjin 300381, China

³Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China

*Corresponding author: Yingjie Jia, jiayingjie1616@sina.com

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Abstract: *Objective:* To observe the clinical efficacy and differences of the Zhuyu Juanbi formula delivered through ultrasound at Zusanli on patients with chemotherapy-induced peripheral neuropathy (CIPN) due to paclitaxel injection. *Methods:* A total of 72 breast cancer patients with CIPN were randomly divided into two groups. The treatment group (36 cases) was treated with oral methylcobalamin plus ultrasonic medicine permeating Zhuyu Juanbi formulae, while the control group (36 cases) was treated with oral methylcobalamin alone. Following two 2 cycles of continuous treatment, the efficacy of peripheral neurotoxicity, TCM syndrome score, FACT/GOG-Ntx score, total neuropathy score, and safety indicators of gynecological cancer patients were observed in the two groups. *Result:* In the treatment of CIPN, the addition of ultrasonic medicine permeating Zhuyu Juanbi formulae was more effective than oral methylcobalamin alone in reducing peripheral neurotoxicity and improving the quality of life of patients. The difference between the two groups was statistically significant ($P < 0.05$), and ultrasound drug penetration Zhuyu Juanbi formulae significantly reduced the FACT/GOG-Ntx score and TNS score in the treatment group. In terms of drug safety, it rarely caused adverse reactions such as grade 3 and 4 leukopenia, and the safety profile was therefore good. *Conclusion:* The combination of ultrasonic medicine permeating Zhuyu Juanbi formulae and methylcobalamin has been demonstrated to be an effective treatment for peripheral neurotoxicity in patients with PIPN. It has been shown to significantly improve the clinical symptoms of PIPN patients, improve the quality of life of patients, and have a good safety profile.

Keywords: Chemotherapy-induced peripheral neuropathy (CIPN); Paclitaxel-induced peripheral neuropathy; Zhuyu Juanbi formulae; Ultrasonic drug delivery

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1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent neurological adverse effect associated with platinum, paclitaxel, fluorouracil, and other chemotherapeutic agents, with an incidence rate exceeding 60%^[1]. CIPN is commonly observed during the initial phases of chemotherapy and is characterized by symmetrical symptoms of burning, tingling, numbness, and sensory loss in the distal extremities. In addition, the presence of motor neuropathy is primarily indicated by diminished deep reflexes and ankle reflexes^[2,3]. Pharmacological interventions for CIPN in Western medicine only provide symptomatic relief. According to current guidelines, duloxetine is recommended as the first-line treatment option for alleviating CIPN^[4].

The understanding of CIPN in traditional Chinese medicine (TCM) can be classified as “paralysis” and “blood paralysis.” Paralysis is primarily caused by the blockage of meridians and collaterals by wind, cold, and dampness, whereas blood paralysis is mainly attributed to deficiencies in qi and blood and the obstruction of collaterals by blood stasis. Numerous studies have documented the use of traditional prescriptions like Huangqi Guizhi Wuwu Tang and Tonic Yanghuiwu Tang for internal treatment of this condition. However, the effectiveness of oral medications in treating CIPN is limited. Consequently, the external treatment of TCM has garnered increasing attention. This type of treatment offers advantages such as simplicity, convenience, cost-effectiveness, and efficacy. Lingtai Xu once remarked, “If the disease is localized between the skin, sinews, and bones, external treatment can be employed to facilitate the penetration of the medicine through the pores and into the meridians and channels, resulting in more pronounced effects than those achieved through oral administration.” Due to the common manifestation of numbness and tingling in the hands and feet, the application of TCM for external treatment of CIPN enables direct drug administration to the affected area. By utilizing ultrasonic drug delivery, the medication can permeate the skin, reach the targeted diseased tissues and organs as directed, and establish a drug concentration within a specific range. This approach achieves non-invasive targeted drug delivery, thereby facilitating the desired therapeutic outcome^[5].

Paclitaxel is a frequently utilized chemotherapeutic agent in clinical practice, and its administration can lead to the development of paclitaxel-induced peripheral neuropathy. It is noteworthy that this condition may persist and worsen even after discontinuation of the said chemotherapeutic agent^[6]. Research findings have indicated that the incidence of neuropathy is higher with injectable paclitaxel (albumin-bound) than with other adverse reactions, such as rashes. Specifically, the incidence of neuropathy is significantly elevated in comparison to other side effects^[7]. This study investigates the effects of ultrasonic Zhuyu Juanbi formula delivery on CPN treatment. The results provide valuable insights for the clinical management of this disease.

2. Materials and methods

2.1. Clinical data

A total of 72 breast cancer patients with peripheral neuropathy caused by treatment with injectable paclitaxel (albumin-bound) were recruited for this study. These patients were admitted to the oncology ward of the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine from February 2022 to January 2023.

2.2. Diagnostic criteria for diseases

2.2.1. Western medical diagnostic standards for breast cancer

- (1) The breast cancer diagnostic standards can be found in the “Breast Cancer Diagnostic and Treatment Guidelines (2018 Edition).” For histological typing, refer to the WHO Breast Tumor Classification (2012 Edition).
- (2) The staging standards for breast cancer can be found in the “AJCC Cancer Staging Manual (Eighth

Edition).”

- (3) The immunohistochemistry standards for breast cancer can be found in the “Breast Cancer Diagnostic and Treatment Guidelines (2018 Edition),” ER and PR positivity is defined as $\geq 1\%$ of positively stained tumor cells. HER-2 negativity is defined as HER-2 0 or 1+, and HER-2 gene amplification is confirmed through FISH for HER-2 2+ status. HER-2 gene amplification is defined as HER-2 3+ and/or *in situ* hybridization detecting HER-2 gene amplification (single-copy HER-2 gene > 6 or HER2/CEP17 ratio > 2.0).
- (4) The grading criteria for neurotoxicity can be found in the NCL-CTCAE5.0 neurotoxicity grading criteria, developed by the National Cancer Institute of the United States of America, for the diagnosis and grading of neurotoxicity in patients.

2.2.2. Diagnostic criteria for CIPN resulting from treatment with injectable paclitaxel (albumin-conjugated)

The diagnostic criteria, which have been formulated based on the guidelines provided by Neurology – Neurological Intoxications and Metabolic Diseases, are as follows: the presence of peripheral neuropathy that occurs either during or after chemotherapeutic treatment with injectable paclitaxel (albumin-conjugated), with the exclusion of any other diseases or treatments that could have caused the neuropathy. The clinical presentation includes symmetrical sensory abnormalities, such as burning, tingling, and numbness, primarily affecting the extremities in a glove-and-sock distribution pattern. Additionally, there may be a reduction in sensitivity to fine sensations, decreased or absent tendon reflexes, and diminished muscle strength. These symptoms may resolve spontaneously after discontinuation of the medication or persist for an extended period of time.

2.2.3. Diagnostic criteria for CIPN with qi deficiency and blood stasis in TCM

Based on the diagnostic criteria for qi deficiency and blood stasis outlined in the 10th edition of the national planning textbook for colleges and universities of traditional Chinese medicine, specifically “Diagnostics of Traditional Chinese Medicine” and “Internal Medicine of Traditional Chinese Medicine,” as well as the 2002 edition of “Guiding Principles for Clinical Research of New Traditional Chinese Medicines (Trial),” a set of relevant symptoms for peripheral neuropathy induced by chemotherapy with qi deficiency and blood stasis has been formulated. The primary symptoms include limb numbness, tingling in the hands and feet, fatigue, shortness of breath, and lethargy. The secondary symptoms include nail faults, pale skin, and subcutaneous petechiae. The tongue and pulse should be examined for pale or dark color, the presence of petechiae, white coating, and a fine or astringent pulse. The diagnosis of qi deficiency and blood stasis can be established only if one of the aforementioned primary symptoms is present, in addition to one or more secondary symptoms.

2.3. Inclusion and exclusion criteria

2.3.1. Inclusion criteria

- (1) Female patients diagnosed with breast cancer based on pathology or cytology.
- (2) Patients experiencing symptoms of peripheral neuropathy during or after treatment with paclitaxel (albumin-bound).
- (3) Patients aged between 18 and 80.
- (4) Patients currently undergoing chemotherapy or within 3 months from their last chemotherapy treatment.
- (5) Patients with peripheral neurotoxicity grade I–III.
- (6) Patients with an expected survival rate of at least 3 months, with a Kahn’s score ≥ 50 .

- (7) Patients who can comprehend the content of this study, cooperate with the CIPN grading evaluation, have no mental illness, are conscious and alert, have signed informed consent, and have demonstrated good compliance with regular follow-up. Additionally, patients should have a good understanding of CIPN grading and regular follow-up.

2.3.2. Exclusion criteria

- (1) The use of chemotherapeutic drugs other than injectable paclitaxel that can cause CIPN.
- (2) Hand and foot lesions caused by any other drugs or diseases.
- (3) Skin breakage at the treatment site, specifically the Zusanli, in individuals who cannot tolerate traditional Chinese medicines.
- (4) Concurrent localized diseases, such as venous thrombosis of the lower limbs.
- (5) A history of psychiatric diseases and severe cardio-cerebral and cerebral vascular diseases.
- (6) Patients with other neurological diseases.
- (7) Patients with severe abnormalities in liver and kidney function, as well as those suffering from organic diseases.
- (8) Poor compliance or simultaneous enrollment in other clinical studies.

2.3.3. Criteria for exclusion and dislodgement

- (1) Those individuals who did not receive standardized treatment after enrollment and had incomplete clinical data.
- (2) Individuals who took other medications that could impact the results of this study during the observation period.
- (3) Individuals who were unable to cooperate with the treatment due to allergies or other adverse reactions during the observation period.
- (4) Individuals who experienced rapid deterioration of their condition or were unable to receive treatment due to serious complications.
- (5) Individuals who voluntarily withdrew from the treatment due to personal reasons.

2.4. Grouping

Patients who fulfilled the criteria for natriuresis were allocated to two groups, namely the control group (administered methylcobalamin orally) and the treatment group (administered methylcobalamin orally + ultrasonic drug delivery of a self-formulated remediation formula for eliminating blood stasis, hereafter known as Zhuyu Juanbi formula). The allocation was done in a 1:1 ratio using the randomized numerical table method. Each group consisted of 36 cases. Baseline data of the patients in the two groups, including age, number of chemotherapy cycles, and pre-treatment pathology type, showed no statistically significant difference ($P > 0.05$).

2.5. Research Methods

- (1) Control group: Oral methylcobalamin tablets (0.5 mg, manufactured at Eisai (China) Pharmaceutical Co., State Pharmacopoeia: H20143107] given 1.5 mg/d, three times a day, orally, for 2 weeks.
- (2) Treatment group: In addition to the treatment received by the control group, the treatment group was subjected to ultrasonic drug delivery to eliminate blood stasis and alleviate paralysis. The procedure for conducting ultrasonic drug delivery involved the preparation and concentration of a TCM decoction (Zhuyu Juanbi formula) in the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine's herbal medicine decoction pharmacy. Subsequently, a 10 mL dosage of the drug solution

was injected into the specialized coupling piece and attached to the therapeutic head. The therapeutic head was then positioned on the bilateral Zusanli points, and ultrasonic delivery of the Zhuyu Juanbi formula was performed using the NAYA-01TD ultrasonic conductivity instrument (Beijing Noah Tongzhou Medical Technology Co., Ltd.). This treatment was administered once daily for 30 minutes, spanning two consecutive weeks. The self-formulated Zhuyu Juanbi formula consisted of the following ingredients: 10 g of astragalus, 5 g of *Pseudostellaria heterophylla* roots and rhizome, 5 g of safflower, 4 g of *Spatholobus suberectus* Dunn, 4 g of *Angelicae sinensis* roots, 3 g of *Ligusticum chuanxiong* rhizome, 3 g of *Salviae miltiorrhizae* Bunge, 4 g of *Clematis chinensis* Osbeck roots and rhizome, 3 g of *Cynanchum paniculatum* roots and rhizome, and 3 g of licorice.

2.6. Observation indicators and efficacy evaluation criteria

2.6.1 Criteria for evaluating the effectiveness of peripheral neurotoxicity

This study utilizes the NCL-CTCAE Version 5.0 (2017 edition) grading standard developed by the National Cancer Institute of the United States to assess the grading of peripheral neurotoxicity both before and after treatment. Additionally, the standard for evaluating the effectiveness of peripheral neurotoxicity is based on the Guiding Principles for Clinical Research on New Chinese Medicines (for Trial Implementation) established by the State Drug Administration of the People's Republic of China in 2002.

The efficacy of the treatment is determined as follows: (1) Very effective: A reduction of two or more grades in peripheral neurotoxicity grading after treatment. (2) Effective: A reduction of one grade in peripheral neurotoxicity grading after treatment. (3) Ineffective: No reduction or worsening of peripheral neurotoxicity grading.

Effective rate = (number of very effective cases + number of effective cases) ÷ total number of cases in the group × 100%.

2.6.2. Evaluation of TCM evidence points.

Based on the TCM diagnostic criteria for CIPN with qi deficiency and blood stasis as described in the previous section, a TCM syndrome point scale was developed. Each main symptom entry was scored from 0 to 6 points based on the severity, ranging from none to severe. Similarly, each partial symptom entry was scored from 0 to 3 points based on the severity, ranging from none to severe. The scores were recorded before and after treatment. The clinical symptom score was calculated using the formula: (pre-treatment score - post-treatment score) ÷ pre-treatment score × 100%.

Referring to the "Evaluation Methods and Selection Criteria of Chinese Medicine Efficacy," the efficacy evaluation will be conducted according to the following criteria: (1) Cured: symptoms disappeared, and the number of evidence points reduced by 95% or more; (2) Very effective: the symptoms significantly improved, and the number of evidence points reduced by 70% or more; (3) Effective: the symptoms improved, and the number of evidence points reduced by 30% or more; (4) Ineffective: the symptoms have not improved or even aggravated, and the number of evidence points reduced by less than 30%.

2.6.3. FACT/GOG-Ntx Scores

The FACT/GOG-Ntx scale is a validated questionnaire utilized in the field of gynecologic oncology to evaluate the severity of neurotoxicity among patients and its impact on their quality of life. This instrument is comprised of a total of 13 questions, each of which is scored on a scale ranging from 0 to 4. A score of 0 signifies the absence of symptoms, while a score of 4 indicates a highly pronounced presence of symptoms. The questions pertain to the occurrence of neurological symptoms experienced by the patients within the past week, primarily

focusing on peripheral neurotoxicity symptoms. The questionnaire serves to demonstrate the effectiveness of the combination of traditional Chinese medicine and Western medicine in terms of mitigating peripheral neurotoxicity symptoms experienced by patients.

2.6.4. TNS scores

The Total Natural Score (TNS) is a composite score with a wider range (0–40 points) that assesses symptom scores alongside objective scores for sensory deficits and neurophysiological parameters. The scores of both groups were documented before and after treatment.

2.6.5. Evaluation of safety indicators

Observation records and determinations were conducted according to the guidelines established by the World Health Organization (WHO). These findings were documented in an observation table, and blood routine, liver, and kidney functions were reassessed weekly starting from the initiation of treatment. A comprehensive evaluation was performed after the completion of 2 cycles of treatment.

2.7. Statistical analysis

All data were processed statistically using the SPSS 26.0 statistical software. Measured data were expressed as mean \pm standard deviation (SD) when normally distributed. The analysis of data was performed using chi-square and t-tests. Non-normal distribution was described by median (p50) and interquartile spacing (p25 and p75), and the comparison of data was conducted using rank sum tests. Rank sum tests were also used for the analysis of rank data, while the chi-squared test was employed for the treatment of count data. Differences were considered statistically significant for P -values < 0.05 .

3. Results of treatment

3.1. Efficacy of peripheral neurotoxicity

3.1.1. Comparison of peripheral neurotoxicity grading between the two groups before treatment

The pre-treatment grading of peripheral neurotoxicity in the two groups (Table 1) was as follows: in the treatment group, there were 9 cases (26%) classified as grade 1, 15 cases (43%) classified as grade 2, and 11 cases (31%) classified as grade 3. In the control group, there were 8 cases (24%) classified as grade 1, 13 cases (40%) classified as grade 2, and 12 cases (36%) classified as grade 3. The grading of peripheral neurotoxicity in the two groups before treatment was analyzed using the rank-sum test, yielding a Z -value of -0.628 and a P -value of 0.530 . The difference in grading before treatment was not found to be statistically significant.

Table 1. Comparison of peripheral neurotoxicity grading before treatment (cases, n)

Group	n	Grade 1	Grade 2	Grade 3	Grade 4	Z	P
Treatment group	35	9	15	11	0	-0.628	0.530
Control group	33	11	13	9	0		

3.1.2. Comparison of peripheral neurotoxicity grading between the two groups before and after treatment

The peripheral neurotoxicity grading of the patients before and after treatment in the treatment group showed $Z = -4.863$ and $P < 0.001$, while the control group showed $Z = -3.243$, $P = 0.001$, suggesting that the difference between the two groups before and after the treatment was statistically significant (Table 2).

Table 2. Comparison of peripheral neurotoxicity grading before and after treatment (cases, *n*)

Grade	Treatment group		Control group		Z	P
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment		
Grade 0	0	15	0	7		
Grade 1	9	13	7	12	-2.240	0.025
Grade 2	15	4	12	8		
Grade 3	11	3	14	6		
Z	-4.863		-3.243			
P	0.000		0.001			

3.1.3. Comparison of peripheral neurotoxicity efficacy between the two groups after treatment

Table 3 shows that both groups demonstrated an improvement in the grading of peripheral neurotoxicity following treatment. The treatment group exhibited an effective rate of 74.28%, while the control group achieved a rate of 57.57%. The rank sum test showed that $Z = -2.189$, $P = 0.029$, indicating a statistically significant difference in efficacy between the two groups.

Table 3. Comparison of graded efficacy of peripheral neurotoxicity after treatment (cases, *n*)

Group	<i>n</i>	Very effective	Effective	Ineffective
Treatment group	35	15	11	9
Control group	33	7	10	16
Z			-2.189	
P			0.029	

3.2. Comparison of TCM evidence points

The TCM evidence points suggest that the two groups had TCM symptom points that followed a normal distribution with chi-squared before treatment. By conducting a *t*-test on two independent samples, the results showed that $t = -0.707$, $P = 0.098$, indicating no statistically significant difference in TCM symptom points between the two groups before treatment, thereby making them comparable. After treatment, the TCM symptom points of both groups were tested for normal distribution and uniform variance. The paired-sample *t*-test revealed a significant difference between the two groups before and after treatment, with $P < 0.001$. The treatment led to an improvement in the main clinical symptoms of patients in both groups, resulting in a decrease in TCM symptom points. Moreover, the TCM symptom points of the treatment group were significantly lower than those of the control group ($P < 0.001$), as shown in **Table 4**.

Table 4. Comparison of TCM evidence points before and after treatment in the two groups (points, mean \pm SD)

Group	<i>n</i>	Pre-treatment	Post-treatment
Treatment group	35	14.7 \pm 1.8	6.2 \pm 1.9 [†]
Control group	33	15.1 \pm 2.5	9.4 \pm 1.7 [‡]
<i>t</i>		-0.707	-7.317
<i>P</i>		0.098	0.000

[†]Comparison of TCM evidence points before and after treatment in the treatment group $P < 0.001$; [‡]Comparison of TCM evidence points before and after treatment in the control group $P < 0.001$

3.3. Comparison of FACT/GOG-Ntx scores

The FACT/GOG-Ntx scores of the two groups before and after treatment showed a skewed distribution. The FACT/GOG-Ntx scores of the two groups before treatment were comparable by rank sum test ($Z = -1.637$, $P = 0.102$), with no statistical difference. The FACT/GOG-Ntx scores of both groups decreased after treatment, and the treatment group was better than the control group ($Z = -6.991$ by rank sum test, $P < 0.01$), indicating a statistically significant difference (Table 5).

Table 5. Comparison of FACT/GOG-Ntx scores before and after treatment [score, p50 (p25, p75)].

Group	<i>n</i>	Pre-treatment	Post-treatment
Treatment group	35	17.0 (15.0, 22.0)	8.0 (7.0, 10.0) [†]
Control group	33	18.0 (17.0, 23.0)	16.0 (14.0, 20.0) [‡]
<i>Z</i>		-1.637	-6.991
<i>P</i>		0.102	0.000

[†]Comparison of FACT/GOG-Ntx scores before and after treatment in the treatment group $P < 0.01$; [‡]Comparison of FACT/GOG-Ntx scores before and after treatment in the control group $P < 0.05$

3.4. Comparison of TNS scores

The TNS scores of the two groups before treatment were collected as measurement data, which were found to follow a normal distribution through the chi-squared normality test. A *t*-test was conducted on the two independent samples, resulting in $t = -1.119$ and $P = 0.263$. It was concluded that the difference was not statistically significant, indicating that the groups were comparable. Furthermore, the post-treatment TNS scores of both groups also exhibited a normal distribution when examined using the chi-squared test. Subsequently, a two independent samples *t*-test was performed, yielding $t = -2.508$ and $P = 0.015$. This indicated that the difference in TNS scores after treatment between the two groups was statistically significant, as shown in Table 6.

Table 6. Comparison of TNS scores before and after treatment in the two groups (points, mean \pm SD)

Group	<i>n</i>	Pre-treatment	Post-treatment
Treatment group	35	13.09 \pm 1.652	10.11 \pm 1.711 [†]
Control group	33	12.64 \pm 1.410	11.15 \pm 1.698 [‡]
<i>t</i>		-1.119	-2.508
<i>P</i>		0.263	0.015

[†]Comparison of TNS scores before and after treatment in the treatment group $P < 0.01$; [‡]Comparison of TNS scores before and after treatment in the control group $P < 0.01$

3.5. Safety observations

It was determined based on the criteria established by the WHO and classified into grades 0, I, II, III, and IV. This study revealed that the primary toxic reactions observed in all participants after treatment were reductions in hemoglobin (HGB), neutropenia (NEUT), and platelet (PLT) levels, among others. These reactions were not severe, and no patients exhibited any allergic reactions to the medication. Although the rank-sum test did not demonstrate statistical significance in comparing the safety of the two groups ($P > 0.05$), the incidence of adverse reactions in the treatment group was significantly lower. The majority of adverse reactions were categorized as grade 1 and 2, with only a few cases of grade 3 and 4 reactions. Specifically, there was only one case of grade 3 neutropenia and one case of grade 3 leukopenia, as shown in Table 7.

Table 7. Comparison of the safety of patients in the two groups (cases, *n*)

Index	Group	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Z	P
HGB	Treatment group	25	10	0	0	0	-1.186	0.236
	Control group	19	14	0	0	0		
NEUT	Treatment group	31	2	1	1	0	-1.441	0.149
	Control group	25	2	3	3	0		
WBC	Treatment group	31	0	3	1	0	-1.192	0.233
	Control group	25	5	2	1	0		
PLT	Treatment group	31	4	0	0	0	-0.449	0.653
	Control group	28	5	0	0	0		
AST	Treatment group	35	0	0	0	0	-1.467	0.142
	Control group	31	2	0	0	0		
ALT	Treatment group	35	0	0	0	0	-1.030	0.303
	Control group	32	1	0	0	0		

4. Discussion

Based on literature reviews and clinical experience, the treatment of this disease is suitable for benefiting qi and activating blood circulation. This approach is combined with the academic thought of “deposing turbidity and cultivating the root” by the nationally renowned TCM practitioner Prof. Yingjie Jia. A self-designed formula for removing blood stasis and alleviating paralysis, featuring *Angelica sinensis*, *Spatholobus suberectus* Dunn, and safflower, has the potential to activate blood circulation and remove blood stasis, while also tonifying blood without causing harm. This formula reflects Professor Jia’s academic idea of “activating blood circulation and removing blood stasis without moving the blood” [8]. *Salviae miltiorrhizae* Bunge (Dangshen) enhances blood circulation and stimulates menstruation, while *Clematis* root (Weilingxian) and *Cynanchum paniculatum* roots and rhizome (Xuchangqing) help eliminate wind and dampness, facilitating the activation of menstruation and channels and collaterals. These herbs serve as adjuvants. Additionally, licorice harmonizes the effects of the various medicines.

Ultrasonic drug delivery is an emerging treatment approach that utilizes the ultrasonic diffusion effect to alter cell membrane permeability, allowing the drug to penetrate the skin and enter the body. The drug then follows a predetermined route to reach the affected tissues and organs, resulting in localized drug concentration. This targeted drug delivery approach is non-invasive [9]. Compared to traditional methods, ultrasound-conductive drug delivery offers several advantages: direct administration to desired tissues and organs, bypassing the liver’s “first-pass effect” and gastrointestinal degradation, enhanced drug circulation, and it is non-invasive, painless, convenient, and easily acceptable. The Zusanli point belongs to the foot yangming stomach meridian. It is located three inches below the calf’s nose point, on the front edge of the tibia, outside the one cross finger. This point is often chosen to strengthen the body. In this study, ultrasonic drug delivery was used to penetrate the Zusanli point, enhancing the body’s positive qi to resist harmful elements.

After two treatment cycles, the neurotoxicity grading of both groups decreased. The peripheral neurotoxicity efficacy of the treatment group significantly improved compared to the control group, with a statistically significant difference. This indicates that the topical application of the formula for removing

blood stasis and remitting paralysis, combined with methylcobalamin, is more effective in treating CIPN than methylcobalamin alone. After oral absorption of methylcobalamin and the liver first-pass effect, the drug's efficacy is weakened. However, the formula for removing blood stasis and remitting paralysis acts directly on the lesion through superconducting drug penetration, resulting in a fast onset of action, repair of damaged peripheral nerves, timely restoration of sensory function, and improvement in immune function. Therefore, it is recommended that the formula be considered for clinical use. Both groups experienced a reduction in TCM points after treatment, with the treatment group showing more significant changes than the control group. Additionally, the mean FACT/GOG-Ntx score in the treatment group was lower than that of the control group after treatment, with a statistically significant difference. This indicates that the combination of Chinese and Western medicine is an effective treatment for PIPN, as it stimulates blood circulation and removes blood stasis. The TNS scores of both groups were reduced after treatment, with the treatment group showing a statistically significant lower mean value compared to the control group. Methylcobalamin, as a neuroprotective agent, only alleviates neurological symptoms. The prescription for removing blood stasis and alleviating paralysis not only relieves local symptoms such as tingling and numbness but also improves symptoms of mental fatigue by adding astragalus, ginseng roots and rhizome, and other TCM herbs to support and replenish deficiency. Each TCM decoction contains multiple ingredients. Astragalus polysaccharide, the primary drug in the prescription, has anti-tumor and immune-enhancing effects. Astragalus saponin acts as an antioxidant, and astragalus flavonoids have antiviral effects^[10]. The combined action of multiple traditional Chinese medicines can improve symptoms of CIPN in various ways.

After treatment, both groups exhibited abnormalities in blood routine as well as liver and kidney functions. However, none of the patients experienced drug allergies, and the incidence of adverse reactions was lower in the treatment group. Grade 1 and 2 adverse reactions were the most common, while grade 3 and 4 adverse reactions occurred infrequently. The findings of this study indicate that the combination of ultrasonic electroconductivity and methylcobalamin effectively mitigates peripheral neurotoxicity in patients with CIPN. Furthermore, this treatment significantly improves the clinical symptoms and quality of life of CIPN patients while ensuring their safety.

Disclosure statement

The authors declare no conflict of interest.

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