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Therapeutic Efficacy of Traditional Chinese Medicine Syndrome-Based Formulae to Neuropathic Pain Caused by Chemotherapy

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Abstract

Objective: Chemotherapy-induced neuropathic pain (CINP) is a troublesome complication of anti-cancer treatment. The aim of this retrospective study was to investigate the effectiveness of classic Chinese herbal formulae (CHF) Huang Qi Gui Zhi Wu Wu Tang (HQGZWWT) and Dang Gui Si Ni Tang (DGSNT) in the treatment of CINP. **Materials and Methods:** Douleur Neuropathique 4 (DN4) and Functional Assessment of Cancer Therapy-General (FACT-G) questionnaires were rated at baseline and after 3-monthly CHF treatment. **Results:** By searching through our medical records of all the CIPN patients from 2018 to 2019, we identified and enrolled 37 patients with Deficiency-Cold syndrome in the study, for whom the treatment of neuropathic pain by regular pharmacotherapies had failed or intolerable. At the third month evaluation with the DN4 questionnaire, 13 patients had symptomatic remission, 15 patients remained stable, and 9 patients had no response to CHF. The 3-month mean DN4 score was significantly higher than that at the baseline ($P < .001$). After CHF treatment, significant differences in quality of life were noted in the physical, social, emotional, and functional well-being subscales, and in the total score, of the FACT-G ($P < .001$). No adverse events or instances of disease progression were observed. **Conclusions:** The results of our small study are the first in the literature to show the clinical effectiveness of CHF for CINP. Combination of HQGZWWT and DGSNT is well tolerated and may offer the possibility to ameliorate CINP more than conventional care can. It merits further investigation.

Keywords
neuropathic pain, side effect, chemotherapy, Chinese herbal formulae, cancer

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Introduction

Chemotherapy-induced neuropathic pain (CINP) is a long-lasting condition that is often progressive and irreversible. It is characterized by pain, numbness, tingling, edema, or paresis, and 30% to 40% of patients receiving chemotherapy may be thus afflicted.[1,2] Symptoms depend on the type of drugs used, the cumulative dose, the frequency, the duration, and patients' coexisting diseases. Sensory nerve fibers are more commonly affected, but motor and autonomic nerve fibers can also be involved.[3] Therefore, CINP can impact a patient's quality of life (QOL), sleep, and emotions, and it may be a major cause of debilitation that lasts several months beyond the cessation of treatment. Common chemotherapeutic agents (vinca alkaloids, platinum derivatives, taxanes, bortezomib, and thalidomide) are well-established causes of CINP. Taxanes, which are tubulin inhibitors, destroy neuronal axons, and platinum analogues can collect in the sensory nerve cell bodies of the dorsal root ganglia and cause DNA damage.[4] Although their mechanisms of action differ, such anticancer drugs have adverse—and often disabling—effects on patients.[5]

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Generally, CINP is observed in 60% and 30% of patients at 3 and 6 months, respectively, after cessation of chemotherapy.[6] In some cases, the pain persists for life, significantly increasing annual healthcare costs.[7] These primary chemotherapy drugs cannot be avoided because they are the first-line treatments for numerous types of cancer, such as breast, lung, gastric, and colorectal cancer, as well as multiple myeloma. Although pharmacological interventions such as anticonvulsants, antidepressants, and opioids have recently been apply to patients at risk, no definite treatments to prevent or cure CINP are currently available.[8,9] The only thing clinicians can do is adjust the dose or discontinue the chemotherapy if patients present worsening symptoms of neuropathy, based on the severity of this common adverse effect of cancer therapy.[9] Hence, alternative methods of treating CINP are worthy of exploration.

Chinese herbal formulae (CHF) have a history of thousands of years in most Asian countries. CHF not only improves recovery of nerve function[10,11] but also alleviates neuropathic pain by efficiently inhibiting inflammatory cytokines and reactive oxygen species (ROS) production.[12] In addition, CINP belongs to the category of Xue Bi in Traditional Chinese medicine (TCM). Xue Bi is defined as meridian retardation due to traumatic injuries, infections, metabolic problems, inherited causes, and drug toxins causing a lack of nourishment to the extremities, leading to numbness and pain. Therefore, CHF that actively promote the flow of Yang-*Qi* or disperse meridian stasis are usually applied to treat CINP; some herbs have demonstrated efficacy for improving microcirculation in patients with neuropathy.[13] For hundreds of years, Huang Qi Gui Zhi Wu Wu Tang (HQGZWWT) has been used to manage apathetic and painful symptoms by improving Yang-*Qi* deficiency. HQGZWWT was originally described in the classic TCM book, Jin Gui Yao Lue (Essential Prescriptions from the Golden Chamber), first published in 205 CE during the Han Dynasty. HQGZWWT is composed of 5 different herbs (*Rx. Astragali, Ram. Cinnamomi, Rx. Paeoniae Alba, Fr. Jujube*, and *Rz. Zingiberis Recens*), of which modified Gui Zhi Tang and Huang Qi are the backbone components. In Taiwan, HQGZWWT-based prescription was always considered for many patients turning to TCM clinics with the complaint of CINP after cancer treatment. Our previous report indicated that a combination of HQGZWWT and Dang Gui Si Ni Tang (DGSNT) could ameliorate oxaliplatin-induced neuropathy through strengthening neural perception in a case with the syndrome of *Qi*-Blood deficiency and Cold excess.[14]

Human studies of CHF for CINP are rare, and its clinical effectiveness has yet to be proven in real-world applications. Herein, we present a retrospective analysis of the outcomes of 37 consecutive CINP patients treated with combination of HQGZWWT and DGSNT to examine the therapeutic efficacy of this regimen.

Methods

All medical records at our TCM clinic from December 2018 to December 2019 were reviewed, particularly those of cancer patients in whom treatment of neuropathic pain with medications such as anticonvulsants, antidepressants, or topical local anesthetics had been intolerable or had failed. Diagnosis of CINP was made by the referring oncologist according to the International Classification of Diseases (ICD) version 10, code G62.0. Patients were included if their records indicated that they had presented with neuropathic symptoms of ≥grade 2 of the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 at least 3 months after completing a chemotherapy course with agents considered neurotoxic. Additionally, those CINP patients belonging to the "Deficiency-Cold syndrome" in the TCM rationale were enrolled. Patients who had intracranial or spinal cord tumors, stroke, prior neuropathy caused by diabetes mellitus, autoimmune disease, or infection, non-Deficiency-Cold syndrome, and who had received ≤3 courses of CHF treatment, were excluded. This study was approved by the institutional review board of Chang Gung Memorial Hospital (No. 202000107B0).

These patients received treatments in accordance with the Chinese Medicine Treatment for Peripheral Neuropathy (CMT-PN) protocol previously developed at our Integrative Cancer Center (Table 1).[15] The treatment consensus was based on expert judgments, clinical experience, and literature review of TCM syndrome differentiation, and it was supported by the Department of Chinese Medicine and Pharmacy, Taiwan Ministry of Health and Welfare (MOHW106-CMAP-M-114-112107). The syndrome types (Zheng) of CINP are divided into 5 syndromes on the basis of Yang-*Qi* deficiency: Wind syndrome, Cold syndrome, Dampness syndrome, Phlegm and Stasis syndrome, and *Qi* and Blood deficiency syndrome. For example, if CIPN patients have any of the symptoms associated with Deficiency-Cold, which presented with stabbing and cold sensation and aggravated by cold, the core CHF of HQGZWWT and DGSNT is used. HQGZWWT was developed to enhance the *Qi* and warm the channels and collaterals, which may promote nerve recovery. DGSNT, consisting of *Rx. Angelica Sinensis, Rx. Paeoniae Alba, Ram. Cinnamomi, Hb. cum Rx. Asari, Rx. Glycyrrhizae Preparata, Fr. Jujube*, and *Caul. Akebiae*, assists to nourish the blood, dispel cold, and stasis, so strengthening the ability of HQGZWWT to relieve pain. Both prescriptions of CHF were administered in the proportion of 1.5:1 at a total dose of 5 g 3 times per day, after each meal. The therapy was administered by qualified TCM physicians and both were provided by Sun Ten GMP Pharmaceutical Co., LTD in Taiwan.

The researchers completed anonymous case-report forms to collect the patients' demographic information (age, sex), clinical information (type or stage of tumor, chemotherapeutic agents, and CINP history) and treatment record

Table 1. Treatment Protocol and Prescriptions of Chinese Herbal Formulae for Patients With CINP.

Main Chinese herbal formulae (CHF) (composition)	Accompanied TCM syndrome	Neuropathic symptoms and signs	Treatment principle	Combined CHF (composition)
Huang Qi Gui Zhi Wu Wu Tang *(Rx. Astragali, Ram. Cinnamomi, Rx. Paeoniae Alba, Fr. Jujube, Rz. Zingiberis Recens*)	Wind	Tingling, numbness, itching, scurrying pain, and sometimes radiation toward proximal limb	Dispels wind, warms the channels, and relaxes spasms	Xiao Xu Ming Tang *(Hb. Ephedrae, Rz. Chuanxiong, Rx. Aristolochiae Fangji, Sm. Armeniacae, Rx. Saposhnikoviae, Rz. Zingiberis Recens, Rx. Ginseng, Rx. Aconiti Lateralis Preparata, Cx. Cinnamomi, Rx. Paeoniae Alba, Rx. Scutellariae, Rx. Glycyrrhizae)*
	Cold	Cramping, spasm, cold and stiff feeling, relieved by warmness, and aggravated by coldness	Disperses cold, warms the channels, and nourishes the blood	Dang Gui Si Ni Tang *(Rx. Angelica Sinensis, Rx. Paeoniae Alba, Ram. Cinnamomi, Hb. cum Rx. Asari, Rx. Glycyrrhizae Preparata, Fr. Jujube, Caul. Akebiae)*
	Dampness	Soreness, heaviness, and aggravated by raining or humid	Dispels dampness, benefits Qi, invigorates blood circulation, and reduces swelling	Yi Yi Ren Tang *(Hb. Ephedrae, Ram. Cinnamomi, Rx. Angelicae Sinensis, Wine-Washed Rx. Paeoniae Alba, Rz. Atractylodis blended with Sm. Sesame Nigrum, Ginger-Fried Sm. Coicis, Rx. Glycyrrhizae Preparata, Rz. Zingiberis Recens)*
	Phlegm and Stasis	Tingling, swelling, fixed pain, and sometimes accompany with dark and mottled skin or nail	Dries phlegm and stasis, dredges the channels, and relieves pain	Erh Chu Tang *(Rz. Atractylodis, Rz. Atractylodis Macrocephalae, Rz. Arisaematis Preparatum, Per. Citri Reticulatae, Poria, Rz. Cyperi, Wine-fried Rx. Scutellariae, Rx. Clematidis, Rz. et Rx. Notopterygii, Rx. Glycyrrhizae, Rz. Pinelliae Preparatum)*
	Qi and Blood deficiency	Joint deformation, weakness, dizziness, trembling, and hard to grasp or stand	Replenishes Yang, warms, and tonifies *Qi* and blood	Shi Quan Da Bu Tang *(Rx. Astragali, Cx. Cinnamomi, Rx. Ginseng, Rx. Rehmanniae Preparata, Rz. Atractylodes Macrocephalae, Rx. Angelicae Sinensis, Rx. Paeoniae Alba, Rx. Chuanxiong, Poria, Rx. Glycyrrhizae)*

(CINP symptom severity, QOL). The severity of the CINP symptoms and their effects on QOL were assessed at baseline and at 3-month follow-up visits after the CHF treatment. Symptom severity was measured with the Douleur Neuropathique-4 (DN4) questionnaire.[16] The DN4 comprises 10 items. Of these, 7 assess the quality of pain and the other 3 require a physical examination to detect sensory allodynia and touch-needle hypoesthesia. The items are scored dichotomously as "Yes" (1 point) or "No" (0 points), and the total score range is 0 to 10. Scores $\geq$4/10 are considered to indicate moderate to severe symptoms.[17] A study by Pérez et al[18] indicated that the DN4 has higher sensitivity (85%) than other measures of neuropathic pain. The DN4 was used as a quantitative tool to evaluate the efficacy of tapentadol in patients with CINP in a previous study.[19]

The Functional Assessment of Cancer Therapy-General (FACT-G) is a widely used scale for measuring health-related QOL in cancer patients.[20] The fourth version of the scale contains 27 Likert-type items assessing 4 subscales of well-being: 7 for the physical subscale, 6 for the emotional subscale, 7 for the social/family subscale, and 7 for the functional subscale. Respondents score each item on a scale of 0 to 4 (0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much). The total FACT-G score (range: 0-108) is calculated by summing the 4 subscale scores. Higher scores indicate better QOL.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the patients enrolled in the study and the disease activity level after CHF treatment. Categorical data were presented by number and percentage. Continuous data were calculated as median, mean, and range. Comparison of before and after treatment symptom severity score was analyzed using the paired sample *t*-test. The level of statistical significance was set at $P < .05$.

Results

After criteria assessment, a total of 37 cases were included. The demographic data of the sample are shown in Table 2. There were 15 female and 22 male patients, with an average age of 59.2 ± 10.3 years. The majority of the cancer types were colorectal, breast, and gastric cancer. About 12 patients (32.4%) had stages I and II, and 25 (67.6%) had stages III and IV. Of the drugs inducing peripheral neurotoxicity included in the study, oxaliplatin was the most common (43.2%), followed by cisplatin (27%) and paclitaxel (18.9%). The average duration of CINP was 17.9 ($\pm$22.3) months, and in 35.1% of the patients, symptoms had persisted for $>$1 year after chemotherapy. All patients (100%) had sensory neuropathy, 18 (48.6%) had motor neuropathy, and 6 (16.2%) had autonomic dysfunction at initial presentation.

Table 2. Characteristics of 37 patients enrolled in the study.

Variables	N (%)
Age (y)†	59.2 (10.3)
Sex	
Male	15 (40.5)
Female	22 (59.5)
Tumor	
Colorectal	11 (29.7)
Breast	6 (16.2)
Stomach	5 (13.5)
Lymphoma	3 (8.1)
Other (bladder, esophageal, NPC, ovarian, etc.)	12 (32.4)
TNM stage	
I	1 (2.7)
II	11 (29.7)
III	18 (48.6)
IV	7 (18.9)
Previous chemotherapy regimen	
Cisplatin	10 (27.0)
Carboplatin	4 (10.8)
Oxaliplatin	16 (43.2)
Paclitaxel	7 (18.9)
Docetaxel	4 (10.8)
Vincristine	2 (5.4)
Other (thalidomide)	1 (2.7)
Duration of NP	
3 mo-1 y	24 (64.9)
>1 y	13 (35.1)
Mean duration of NP (mo)†	17.9 (22.3)
Onset of NP after chemotherapy exposure (mo)†	3.8 (2.3)
Neuropathy	
Sensory	37 (100)
Motor	18 (48.6)
Autonomic	6 (16.2)

Abbreviation: NP, neuropathic pain.
†*M* (SD).

The changes in the symptomatic severity of the neuropathic pain were evaluated with the DN4 assessment. All enrolled CINP patients had positive DN4 results (scores ≥ 4) at baseline. A significant difference was observed in the mean degree of decrease in the severity of CINP at the 3-month evaluation, as shown in Table 3 ($P < .001$). Of the 37 patients, 28 had reductions in their DN4 scores. Among these 28, 7 had complete resolution, 6 had a partial response, and 15 were in a stable condition. In the remission group, 8 of the 28 patients (28.6%) had symptoms beyond 1 year after completing chemotherapy. At the 3-month evaluation, 9 of the 37 patients (24.3%) demonstrated no improvement. Additionally, no patients reported worsening of CINP symptoms after 3 months of therapy with the combined CHF.

Table 3. Response assessed by DN4 in patients with CINP (n = 37).

Disease activity level after CHF treatment[a]	N (%)
Full remission	7 (18.9)
Partial remission	6 (16.2)
Stable condition	15 (40.5)
Refractory response	9 (24.3)
Symptom severity score*	***M* (SD)**
Baseline	6.65 (1.34)
3 months after treatment	3.42 (2.65)

[a]Activity level after CHF treatment was classified according to the following criteria: Full remission: complete resolution of each item; Partial remission: reduction of more than 25%; Stable disease: change of less than 25%; Refractory response: no change.
*$P < .05$.

The improving degrees of the DN4 scores of the 10 items before and after 3 months of CHF treatment were as follows: brushing (65%), burning (62.5.8%), and electric shock (57.5%), and hypoesthesia to prick (57.5%; Figure 1).

As shown in Figure 2, after CHF treatment, the CINP patients showed significant improvements in global/QOL ($P < .001$), and in the physical ($P < .001$), functional ($P < .001$), emotional ($P < .001$), and social well-being ($P < .001$) subscales. Meanwhile, neither adverse events nor tumor progression during CHF treatment were reported at our chart review.

Discussion

To the best of the authors' knowledge, this study is the first to report the effects of CHF on the severity of CINP in cancer patients. Our results show that, of the 37 patients who presented with at least CTCAE grade 2 neuropathy, 28 patients (75.7%) experienced amelioration of symptoms at 3 months after the start of the CHF therapy, and 7 (18.9%) of them reported that their CINP symptoms were completely resolved. Given the low likelihood of the improvement being part of the natural course of CINP, it is highly probable that the improvement was related to the Zheng-based CHF intervention, for half of the patients had been symptomatic more than 1 year. In a study by Zanville et al,[21] the prevalence of remaining CINP at the first year post-treatment in breast cancer patients was about 50%. A similar result was reported in another study, in which 60% of patients treated with oxaliplatin exhibited symptoms of neuropathy 6 months after the cessation of treatment.[22] Some patients have reported that the symptoms can persist for 5 or 6 years after they finish chemotherapy.[23,24] Longer persistence of CINP is associated with a lower possibility of reversibility, and it may cause a symptom burden for

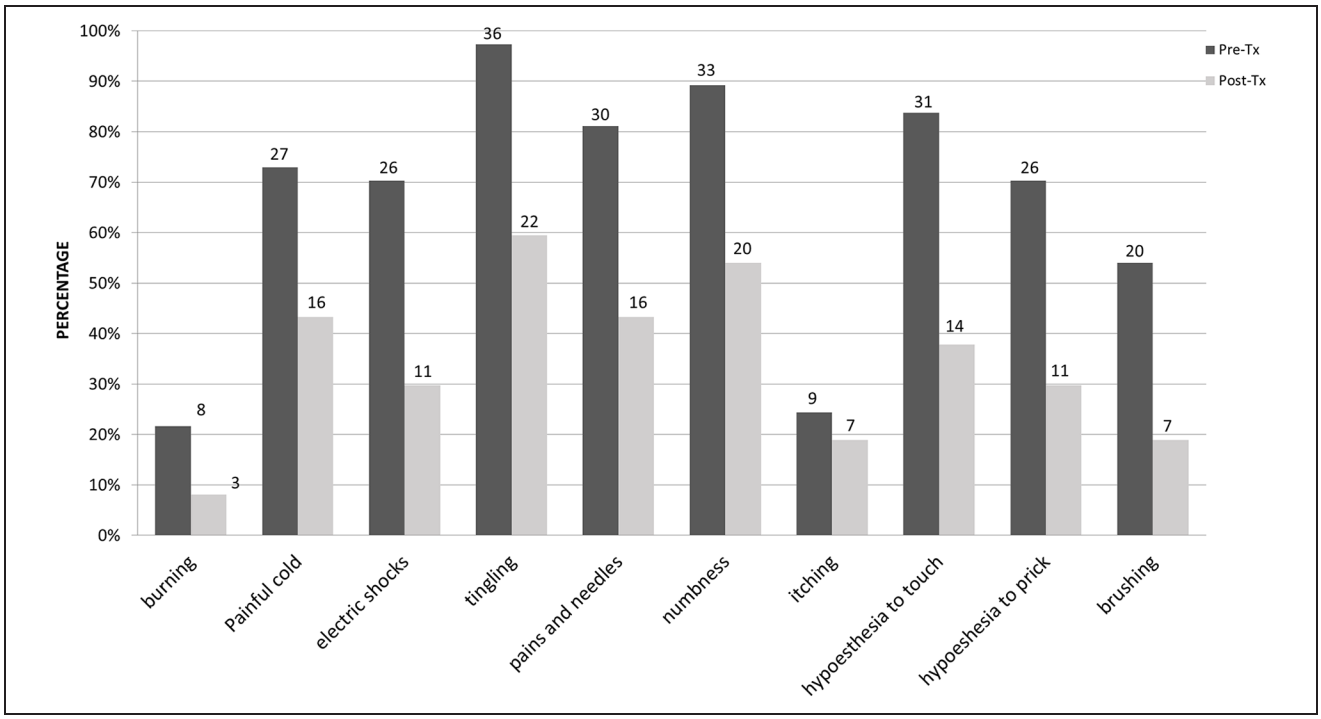

Figure 1. DN4 scores for the evaluation of the CINP symptoms at baseline and after Chinese herbal formulae treatment (black column: pre-Tx; gray column: post-Tx) Tx: treatment.

cancer survivors because they are more likely to seek analgesics.[24] Our results suggest the potential treatment effects of CINP due to CHF, not only to accelerate the recovery from symptoms but also to reduce the duration of persistence and late toxicity.

Duloxetine is the only pharmaceutical that has shown a positive effect on CINP, and it was the first to be recommended by the American Society of Clinical Oncology (ASCO) guidelines.[9] In a registration trial of duloxetine for CINP in patients with any cancer type after taxane or oxaliplatin therapy, over half (59%) of the patients who had received duloxetine reported decreased pain, as compared to 38% of the patients who received a placebo.[25] However, the fatigue and nausea associated with the use of duloxetine led to a dropout rate of 12%.[25] Some review articles have noted that glutamine, omega-3 fatty acids, gabapentin, and opioids provide benefits to patients at risk.[8,26] However, these drugs cannot improve the negative symptoms of neuropathy, such as weakness, tiredness, numbness, or imbalance of gait.[27] Currently, no pharmaceutical interventions have been established as sufficient and safe treatments for CINP.

With consideration of the pathogenesis of CINP, some compounds from medicinal plants have been developed to manage CINP. These compounds block ion channels, target inflammatory cytokines, and reduce oxidative stress.[14] For example, *Acorus calamus* can reduce vincristine-induced neuropathy in rats by lowering the levels of TNF-α, superoxide anions, myeloperoxidase activity, and total calcium.[28] In platinum-treated rats, *Curcuma longa* reversed the alteration of plasma neurotensin and prevented demyelization along the sciatic nerve.[29] These properties may be beneficial for the prevention of CINP; however, in our view, treatment of persistent CINP should focus on nerve regeneration, especially after various attempts. According to TCM theory, a highly important factor in the pathogenesis of CINP is Yang-*Qi* deficiency. Thus, the key treatment principle is to warm the Yang-*Qi*. Many single herbs have been shown to have anti-apoptosis effects, regulate the production of neurotrophic factors in Schwann cells in in vitro and in vivo trials. Some examples are *Rx. Ginseng*,[30] *Rx. Astragali*,[11,13] and *Ram. Cinnamomi*.[31] A meta-analysis showed that HQGZWWT can facilitate nerve regeneration, increase blood flow, and nourish peripheral nerves.[32] In addition, several CHF, such as Er Zhu Tang, Ji Sheng Shen Qi Wan, and DGSNT,[33] are known to regulate the immune system and to eradicate sequentially pathogens, including dampness, cold, or stasis. Therefore, these Yang-*Qi*-warming single herbs or CHF are important components of our CMT-PN for the treatment of CINP.

Unlike Western medicine, which employs conventional chemical agents to focus on specific individual targets, CHF can have affected multiple targets to produce therapeutic effects. Therefore, to some extent, an effective single herb or CHF may offer a micro-environment that is favorable for

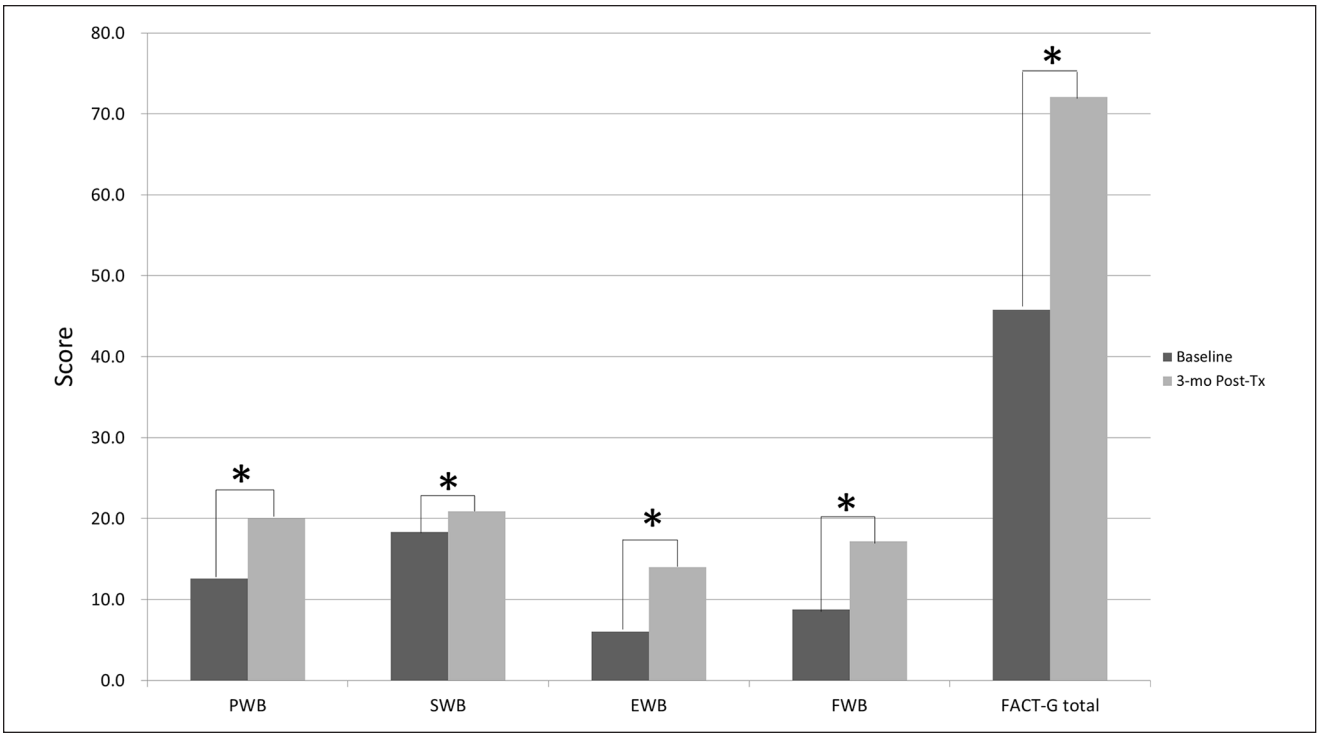

Figure 2. Quality of life before and after Chinese herbal formulae treatment (n = 37) (black column: pre-Tx; gray column: 3-months post-Tx).
*$P < .005$.

the repair and regeneration of nerve tissue. The combination of HQGZWWT and DGSNT was developed according to knowledge of CINP pathology, up-to-date ethnopharmacology in CHF, and precise judgments of TCM syndrome patterns. Although it is difficult to demonstrate the effects in randomized control trials, which are considered the gold standard for medical research, observational studies can establish evidence that can more easily be applied to patients in the real world and may correspond to the current characteristics of TCM.[34] Understanding the changes in biochemical characteristics associated with TCM syndrome identification will facilitate a new approach to disease diagnosis and stratification, which will potentially lead to personalized medicine strategies for a range of specific diseases that lack therapeutic solutions.[35] This formula is an innovative practice designed to provide a patient-centered service and to compensate for the insufficiency of conventional medicine in treating CINP. To be sure, many widely-used and experimentally-validated CHF in our CMT-PN protocol were intended to promote the healing potential of patients with persistent CINP. Those drugs work for specific groups, and determining the crucial components will require further extensive clinical testing.

During the 3 months of CHF treatment, individuals reported a mean decrease in the DN4 score (6.65 vs 3.42). The current study used the DN4 to measure pain relief, a common measure of neuropathic pain. However, the evaluation of CINP with scales and scores, though an important issue, goes beyond the National Cancer Institute toxicity scale (NCI-CTC). A research finding on the use of careful instruments has not been conclusive. Increasingly, measures of QoL such as the EORTC-QLQ-CIPN-20[36] or FACT-G are used.[37] Indeed, a mean difference was observed between the FACT-G scores at baseline and at 3-month follow-up. CHF-related clinically meaningful remission of CINP symptoms, such as paresthesia, tingling, hypoesthesia, or numbness, may be directly comparable via improvements in QOL.

There are limitations to this study. First, we were not able to assume that CINP is completely reversible after CHF treatment or to examine the long-term effects due to the lack of a definitive assessment. Electromyography and nerve conduction velocity are standard neurophysiological tests; however, changes in these tests are not correlated with clinical findings of CINP.[38] Second, some CHF prescriptions and the mechanisms of nerve repair remain unclear, warranting further study. This study was a retrospective single-center study with a small sample. It lacked a control group for comparison, such as non-TCM syndrome and/or non-CHF treatment, and the results might have been subject to selection bias. Statistical results must be interpreted with caution in this setting.

Conclusion

The high symptom resolution rate, improvement of health-related QOL, and safety attest to the possible role of our CHF therapy in the treatment of CINP. This study shows that the combination of HQGZWWT and DGSNT might provide an important opportunity to alleviate CINP in patients with Deficiency-Cold syndrome with a history of intolerance or failure with prior treatments. Further research will be needed to clarify the clinical value of CHF and the mechanisms that may induce recovery of nerve function in patients with CINP. Meanwhile, a larger, randomized controlled trial to validate our results and examine CHF therapy for use as an alternative therapy is needed.

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Author Contributions

M-Y Tsai designed the study. Y-W Liu acquired the data. Y-H Chen and M-Y Tsai analyzed the data and drafted the figures. Y-J Chen and Y-W Liu wrote the manuscript. M-Y Tsai revised the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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