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RESEARCH ARTICLE

Sweet Bee Venom Pharmacopuncture for Chemotherapy-Induced Peripheral Neuropathy

Jeungwon Yoon [1], Ju-Hyun Jeon [1], Yeon-Weol Lee [1], Chong-Kwan Cho [1], Ki-Rok Kwon [2], Ji-Eun Shin [3], Stephen Sagar [4], Raimond Wong [4], Hwa-Seung Yoo [1,*]

[1] *East-West Cancer Center, Dunsan Oriental Hospital of Daejeon University, Daejeon, Korea*
[2] *Korean Pharmacopuncture Institute, Seoul, Korea*
[3] *Department of Statistics, Chungnam National University, Daejeon, Korea*
[4] *Juravinski Cancer Center, McMaster University, Hamilton, Ontario, Canada*

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Abstract
Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is sensory and motor nerve damage to the peripheral nervous system caused by chemotherapeutic agents. It often causes pain and other varying degrees of neuropathic symptoms accompanied by functional limitations and reduced quality of life. Currently, there is no standard treatment protocol for the treatment of CIPN.
Objective: In need of more research to develop new therapeutic options focusing on their safety, efficacy, and long-term sustained clinical effects, a pilot study of sweet bee venom pharmacopuncture (SBVP) for CIPN was conducted to build up preliminary efficacy data in the process of preparing for a future larger scale randomized controlled SBVP trial for CIPN.
Methods: We conducted a prospective case series by analyzing the clinical observations made of CIPN patients treated with SBVP. A total of 11 eligible consecutive CIPN patients who visited East-West Cancer Center from June 1, 2010, to February 28, 2011, were treated with total of six SBVP treatments given within the 3-week period. The outcomes were measured using World Health Organization Common Toxicity Criteria for Peripheral neuropathy (WHO grading system), Patient Neurotoxicity Questionnaire (PNQ), Visual Analogue System (VAS), and Health-Related Quality of Life (HRQOL) collected at the baseline, post-second, fourth, and the final treatment. Patients were followed 3 weeks into no intervention to determine the sustained effects of pharmacopuncture.

* Corresponding author. East-West Cancer Center, Dunsan Oriental Hospital of Daejeon University, 1136 Dunsan-dong, Seo-Gu, Daejeon, Republic of Korea.
E-mail: altyhs@dju.kr

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Results: Both of the WHO CIPN grade and PNQ scores have shown a decrease in the level of neuropathy. VAS pain level has also shown a great decrease and improvement in patients' quality of life have also been detected though modest. Changes in WHO grade, VAS and Total HRQOL scores between the baseline and after the last treatment session were significant. Changes in WHO grade, Total PNQ, PNQ-sensory, VAS, Total HRQOL, and HRQOL-functional scores between the baseline and the 3-week follow-up were significant.
Conclusion: The positive result of the study supports the potential value of conducting a fully powered trial to explore further efficacy of SBVP for CIPN. However a single positive result within this pilot study must be interpreted with caution.

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a sensory and motor nerve damage to the peripheral nervous system caused by some chemotherapeutic agents. It often causes pain and other varying degrees of neuropathic symptoms accompanied by functional limitations and reduced quality of life. CIPN is one of the most common reasons that cancer patients stop their treatment early [1]. An estimated 30%—40% of cancer patients treated with chemotherapy experience CIPN and the severity of symptoms is known to be related to the cumulative dose of the drug received [1]. Peripheral nerves are able to repair themselves and symptoms may resolve over time, but if the damage is too severe, symptoms persist for months, years or indefinitely. CIPN usually starts in the tips of the fingers and toes gradually progressing up to the arms and legs. Sensory nerves are more at increased risk compared to motor nerves because most of the chemo drugs associated with CIPN are not able to enter the well-protected central nervous system, where the cell bodies of motor nerves are located [2]. Sensory symptoms include numbness, tingling, and burning/stabbing pain. Motor symptoms such as diminished or absent tendon reflexes, foot drop, and weakness of muscles are shown with high cumulative doses of selective chemo drugs. Commonly used chemotherapy agents associated with peripheral neuropathy are Taxanes, Vinca Alkaloids, and Platinum compounds. The onset and resolution of symptoms is variable. The platinum compounds have been reported to have a delayed onset of symptoms, up to several weeks after the last dose [2].

The current consensus is that management of CIPN should go by the same principles as any other types of neuropathic pain as there are lack of reliable and standardized means to diagnose, prevent and manage CIPN [3]. The diagnosis is made based on patient's history, clinical examination and supporting laboratory investigations including electromyography with nerve conduction studies, skin biopsies to evaluate cutaneous nerve innervation, and nerve and muscle biopsies for histopathologic evaluation. Making differential diagnosis is important to distinguish other causes of peripheral neuropathy, such as diabetes mellitus, alcohol abuse, renal failure and hereditary neuropathies. In general, when a patient treated with neurotoxic chemotherapy develops a peripheral neuropathy no further diagnostic investigations are warranted [4]. The goal of treatment focuses on easing the CIPN associated symptoms and relieving pain. For treatment of CIPN, tricyclic antidepressants nortriptyline, amitriptyline are commonly used medications. However, studies showed no success in demonstrating any statistically significant improvements in CIPN compared to placebo groups [5]. Anticonvulsants such as gabapentin and lamotrigine reported to be effective for treating number of other neuropathic syndromes showed no better efficacy over placebo in CIPN trials [6,7]. A combination of topical muscle-relaxant baclofen, antidepressant amitriptyline, and the analgesic ketamine, targeting CIPN through three separate pain control mechanisms are also being studied as a promising agent. A recent study concluded it to be somewhat effective in improving symptoms of CIPN [8]. Acetyl-L-carnitine (ALC), a substance previously tested positive in animal models and in patients with diabetic neuropathy, is now supported by present studies to use in cancer patients with paclitaxel or cisplatin induced neurotoxicity [9]. Duloxetine and venlafaxine, which are both serotonin- norepinephrine-reuptake inhibitors (SNRIs), have been shown to relieve diabetes induced neuropathy pain and are now being tested for CIPN [1]. A powerful antioxidant alpha-lipoic acid is being clinically applied for CIPN patients based on its evidence of benefits in diabetic neuropathy. No studies have been done using alpha-lipoic acid in the oncology population [10]. However, with no established treatment protocol for CIPN at this time, further research is encouraged incorporating various modalities to address all dimensions of CIPN and to develop new therapeutic options focusing on their safety, efficacy, and long-term sustained clinical effects.

Previous studies report efficacy of acupuncture for peripheral neuropathy [11,12]. Neurotrophins and cytokines are thought to be involved in the mechanisms of acupuncture for neuropathy [13]. Animal studies have shown that acupuncture treatments can accelerate nerve regeneration by stimulating nerve growth factors [14,15]. Improvement in nerve conduction with acupuncture treatment has been shown in peripheral neuropathic patients [16]. An induced increase in endorphin production may result in pain reduction [17—19]. Mediation of adenosine A1 receptors related to local anti-nociceptive effects of acupuncture has been demonstrated [20]. A randomized controlled trial on acupuncture treatment of peripheral neuropathy induced by paclitaxel or oxaliplatin was conducted comparing the acupuncture treatment group to the cobinamide injection group. Total effective rate for acupuncture group was 66.7% superior to that of 40.0% in medication group ($p < 0.05$) [21]. A case series of acupuncture for CIPN patients who have undergone carboplatin or paclitaxel treatment also provided consistent

evidence supporting its efficacy for CIPN [22]. Our previous case series for CIPN treated with pharmacopuncture demonstrated its superior efficacy with shorter treatment duration compared to the acupuncture treatment alone [23]. The animal toxicity studies support the safety of sweet bee venom pharmacopuncture (SBVP) [24]. Anti-inflammatory and analgesic effects of bee venom have been demonstrated in both animal and human model studies [25–28]. Despite these findings on neuropathy and its related symptoms using acupuncture, pharmacopuncture and bee venom treatment, Bee venom pharmacopuncture for direct CIPN treatment has not been much studied. Clinical guidelines subsequently suggest that CAM treatment including acupuncture needs to build more evidence to allow firm recommendation for the treatment of CIPN [29].

With this context, we have designed a pilot case series to build up preliminary efficacy data in the process of preparing for a future larger scale randomized controlled SBVP trial for CIPN.

2. Methods

2.1. Design

We conducted a prospective case series by analyzing the clinical observations made of CIPN patients treated with SBVP. This study design was based on the guidelines of the Medical Research Council, developing and evaluating complex interventions: new guidance [30]. The experimental design builds on accumulated clinical evidence and hypothesis that SBVP is effective for CIPN. The SBVP treatment is widely being applied for various pain and neurological symptoms as a part of norm oriental medical practice in Korea. In general, this pragmatic trial is best designed to provide clinical results that are directly applicable to patient and providers in clinical settings.

2.2. Patient characteristics

Samples were 11 eligible consecutive CIPN patients who visited East-West Cancer Center from June 1, 2010, to February 28, 2011. Patients were diagnosed based on their history and clinical evaluation including tendon reflex testing, muscle strength and tone, vibrational testing, and two-point discrimination. Their symptoms included pain, numbness, and burning/tingling sensations in the hands and feet after having gone through chemotherapy lasting for at least 28 days after treatment without previous history of neuropathy including diabetes neuropathy. Patients must have minimum Eastern Cooperative Oncology Group (ECOG) [31] performance status of 2 (ambulatory and capable of all self care but unable to carry out any work activities, up and about more than 50% of waking hours or greater) with no other coexisting infectious diseases and/or major systemic diseases except for cancer. Patients with history of sensitivity or allergic reactions to insect bites and stings were also excluded. The baseline characteristics of patients are shown in Table 1.

Patients were given verbal and written explanations on the treatment procedure, its unequally distributed efficacy, warning of potential allergic adverse reactions, and pain at the site of injection as part of our institutional policy. All treatments were conducted with patient consent. The study gained ethical approval from Institutional Review Board (IRB) of Dunsan Oriental Hospital of Daejeon University on May 24, 2010 (IRB number: DJDSOH-10-02).

Table 1 Baseline characteristics of patients.

Mean Age	49
Sex	8 female
	3 male
Cancer types	3 colon
	3 breast
	2 ovarian
	1 cervical
	1 lung
	1 gastric
Chemotherapy agents (PNQ differentiation)	8 taxanes, cisplatin or carboplatin 3 oxaliplatin
Affected area	4 lower extremities
	7 upper and lower extremities
WHO Grade System mean (SD): 0–4	2.22 (0.44)
PNQ mean (SD)	
PNQ Total: 0–8	2.67 (1.50)
Sensory: 0–4	2.11 (0.60)
Motor: 0–4	0.56 (1.13)
VAS mean (SD): 0–10	6 (1.94)
HRQOL mean (SD)	
HRQOL Total: 0-108	66.33 (12.42)
Physical: 0–28	17.11 (4.94)
Social: 0–28	17 (6.48))
Emotional: 0–24	15.22 (4.76)
Functional: 0–28	17 (4.18)
n	11

HRQOL = health-related quality of life; PNQ = Patient Neurotoxicity Questionnaire; SD = standard deviation; VAS = Visual Analogue System; WHO: World Health Organization.

2.3. Outcome measures

The clinical outcome measures included World Health Organization Common Toxicity Criteria for Peripheral neuropathy (WHO grading system), Patient Neurotoxicity Questionnaire (PNQ), Visual Analogue System (VAS), and Health-Related Quality of Life (HRQOL).

The WHO grading system was a primary outcome to evaluate the severity of neuropathy symptoms [32]. (Grade 0: no symptoms; Grade I: paraesthesia and/or decreased tendon reflexes; Grade II; severe paraesthesia and/or mild weakness; Grade III: intolerable paraesthesia and/or marked motor loss; Grade IV: paralysis). Postma and colleagues [33] evaluated the agreement among observers in the interpretation of the CIPN scales WHO, ECOG, Ajani and NCI-CTC 2.0 scales in 37 patients. Inter-observer agreement across all grades of severity were WHO

(83.8%), NCI-CTC 2.0 (45.9%), Ajani (56.7%), and ECOG (75.6%). The WHO grading system has its weakness in its relative paucity of sensory parameters [34]; therefore, we have also used PNQ as a complementary secondary measure as it assesses both motor and sensory symptoms distinctively. The PNQ is a patient-based neuropathy measurement tool that is used to measure neuropathy [35]. The PNQ comprises two items to identify the incidence and severity of sensory and motor disturbances depending on the types of chemotherapy drug received. The subjective responses to each item are graded from A (no neuropathy) to E (severe neuropathy). Compared to the widely used National Cancer Institute Common Toxicity Criteria (NCI-CTC), a physician-based neuropathy measurement tool, the PNQ was reported to be a more reliable and valid instrument to assess CIPN [36]. Studies have confirmed physician-based neuropathy measurement tool are associated with several important limitations such as under-reporting the incidence and severity of subjective symptoms leading to unreliable or inaccurate assessment of CIPN [37]. The NCI-CTC showed a consistent trend with that of the PNQ in terms of comparing the overall severe neuropathy [38]. The VAS is used to measure pain levels ranging from 0 to 10, with 0 being no pain and 10 the most excruciating pain [39]. The HRQOL evaluation is a valuable measure in cancer patients using the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire. The FACT-G version four-question questionnaire includes the four subscales: physical well-being (seven items), social well-being (eight items), emotional well-being (six items), and functional well-being (seven items) [40]. These subscales can be analyzed separately or summed up to produce a total HRQOL score [41]. The FACT-G has demonstrated reliability, validity, and responsiveness to change over time [42]. All data were collected at the baseline, postsecond, fourth, and the final sixth treatment. Patients were followed 3 weeks into no intervention to determine the sustained effects of pharmacopuncture.

2.4. Intervention

All treatments were given by one oriental medicine doctor with a minimum of 5 years of experience and post-board certification. All patients were given bee venom skin tests prior to the initial treatment to reduce any potential risk of adverse effects. Adverse events reported by patients to practitioner were recorded after each treatment session.

A total of six SBVP treatments were given within the 3-week period. Pharmacopuncture is a treatment modality yielding dual effect of pharmaceuticals and acupuncture by injecting pharmaceutical derivatives (often from natural products) into acupuncture points that are chosen in relation to the patient's diagnosis and symptoms based on Traditional Oriental Medicine theories. In this study, SBVP used incorporates melittin, an extracted active ingredient from bee venom with removed allergens such as phospholipase A_2 (PLA_2), hyaluronidase, and histamine. Melittin is a low molecular weight peptide composed of 26 amino acids, with a molecular weight of 2840. It is reported to have analgesic, anti-inflammatory and anti-cancer effects [43–46]. It is also reported to be effective for neurodegenerative diseases associated with microglial activation and other inflammatory symptoms [47]. Through SBVP treatment, synergistic effectiveness has been anticipated. The 0.1 mg/ml concentration of melittin was refined and prepared in the aseptic room of the Korean Pharmacopuncture Institute (KPI). Data supports its consistency, quality, and stability [48].

The acupuncture points of GB39, LV3 (four points bilateral) were used for lower extremities neuropathy and the acupuncture points of LI4, SJ5, GB39, and LV3 (eight points bilateral) were used for patients with both upper and lower extremities neuropathy. The LI4 and LV3 were chosen as they are the strong Qi and blood moving points of the body [49]. In Oriental Medicine, Qi and Blood stagnation is one of the main etiologies for Neuropathy [50]. The GB39 and SJ5 were chosen for their actions to relieve pain and treat weakness in the extremities [49]. A total of 26 1/2 (0.45 mm $\times$ 13 mm) sterilized disposable syringe needles were used as the delivery agent. The Depth of injection was 0.1 cun (epidermal injection) and the volume of SBVP injected for each acupuncture point was 0.1 ml based on the SBVP clinical guidelines [24].

2.5. Statistical analysis

Statistical analysis was performed using SPSS 18.0 (IBM SPSS Inc. statistics version 18.0). The paired *t*-test and Wilcoxon's signed rank test were used to compare the PNQ, VAS, WHO CIPN grade, and HRQOL between before and after two, four, and six treatments and 3 weeks after the final treatment. The analysis was done with the level of significance set at 0.05.

3. Results

3.1. Attendance levels, baseline characteristics, and interventional data

Of the 11 patients who visited the clinic for CIPN, eight patients attended all six treatment sessions. One patient discontinued treatment after the four treatment session as she had experienced swelling and itchiness at the injection sites. The second patient wished to discontinue the treatment due to mild fever of 38.2°C after the initial treatment. Another patient did not comeback after the first treatment session for personal reasons unrelated to the symptoms or the treatments given. The baseline data collected from participated patients prior to treatment are presented in Table 1.

Patients were advised to continue any supplements or medications while receiving treatment. None of the patients were on set medication schedule except for some over the counter analgesics Pro Re Nata. The nutritional supplements and other therapies used by patients included red ginseng, herbal tonics, massage, foot/hand soak, and pressure bands. Life style advice was offered to all patients most commonly in relation to avoiding aggravating activities and settings.

3.2. Outcomes measured at baseline, post-two, four, and six treatments and the 3-week follow-up

The outcomes for the WHO grading system, PNQ, VAS, and HRQOL at baseline and after 2, 4, 6 treatments and 3 weeks after the final treatment are shown in Table 2. The mean WHO grading system score has decreased from 2.22 baseline to 2.11, 1.78, 1.25, and 0.88 after the 3-week follow-up. The mean total PNQ has decreased from 2.67 baseline to 2.78, 2.22, 1.75, and 1.25 respectively. In a closer look, the mean PNQ sensory score was decreased from 2.11 to 2.22, 1.78, 1.38, and 0.75 respectively and the motor score has decreased from 0.56 to 0.78, 0.44, 0.38, and back up to 0.5 after 3 weeks. The mean VAS has decreased from a 6 baseline to 5, 3.78, 2.63, and 2.38 respectively. The mean HRQOL total score has shown an improvement of over 10 points from a 66.33 baseline to 72.44, 74.56, 72.75, and 77.25 respectively. The physical section has shown the most improvement from 17.11 to 19.67, 20.33, 20.5, and 20.75. The social section increased from 17 to 17, 17.89, 17.2, and 19.75, the emotional section from 15.22 to 17.56, 17.11, 16.13, and 17, and the functional section from 17 to 18.22, 19.22, 18.88, and 19.75, respectively. The graph results are displayed in Figs. 1—4 for the mean WHO grading system, PNQ, VAS, and HRQOL scores.

A statistically significant improvement was shown in WHO grade, VAS, and Ttotal HRQOL scores in comparison between the baseline and after the last treatment session result outcomes (Table 3). In comparison between the baseline and the 3-week follow-up of the result outcomes, statistically significant differences were found in WHO grade, Total PNQ, PNQ-sensory, VAS, Total HRQOL, and HRQOL-functional scores (Table 4).

3.3. Adverse events

The adverse events were reported using National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) [51]. CTCAE is a widely accepted standard classification and severity grading scale for adverse events throughout the oncology community. One patient discontinued the treatment due to CTCAE grade 2 swelling and itchiness at the injection site. She had reported mild itchiness after receiving the third treatment, which went away after few hours. After the fourth treatment the itchiness came back with inflamed swelling lasting for couple of days this time. The patient was checked by a medical doctor on site for the allergic symptoms but did not pursue any medical treatment as it was seen unnecessary. Despite the adverse event, she wished to continue the SBVP treatment but to her best interest we advised she discontinue any further treatments. Second patient experienced CTCAE grade 1 mild fever of 38.2°C after the initial treatment session. Although the relationship between the fever and SBVP was not clear, the patient wished to discontinue the treatment. She was prescribed an antipyretic medication. The laboratory findings reported no signs of organ toxicity in all cases.

4. Discussion

4.1. Key findings

This pilot case series has met the objectives by helping us identify useful information to conduct future larger scale SBVP trial for CIPN. With regards to the capability of recruitment for future trial, number of patients collected for the study was less than we had expected. A total of 11 eligible patients had shown with only 8 patients completing all treatment sessions to obtain significant data.

The efficacy results were satisfactory and consistent with the previous study of positive outcome in treating CIPN with SBVP [23]. Decrease was seen in neuropathy measures of WHO grading system and PNQ, pain levels were also decreased according to the VAS pain scale. Quality of Life was increased following the HRQOL questionnaire. The result findings showed a statistically significant reduction in WHO grade, VAS and Total HRQOL scores in comparison

Table 2 Patient outcomes at baseline, post-two, four, and six treatments and 3-week follow-up.

	Baseline	After 2 tx	After 4 tx	After 6tx	3 wks p tx
WHO Grade System mean (SD)	2.22 (0.44)	2.11 (0.33)	1.78 (0.44)	1.25 (0.46)	0.88 (0.35)
PNQ mean (SD)					
PNQ total	2.67 (1.50)	2.78 (.1.39)	2.22 (0.83)	1.75 (0.71)	1.25 (0.71)
Sensory	2.11 (0.60)	2.22 (0.44)	1.78 (0.44)	1.38 (0.52)	0.75 (0.46)
Motor	0.56 (1.13)	0.78 (1.2)	0.44 (0.88)	0.38 (0.74)	0.5 (0.76)
VAS mean (SD)	6 (1.94)	5 (1.73)	3.78 (1.48)	2.63 (1.41)	2.38 (1.69)
HRQOL mean (SD)					
HRQOL total	66.33 (12.42)	72.44 (11.74)	74.56 (14.6)	72.75 (12.83)	77.25 (11.2)
Physical	17.11 (4.94)	19.67 (5.07)	20.33 (5.41)	20.5 (3.38)	20.75 (3.33)
Social	17 (6.48)	17 (5.66)	17.89 (5.56)	17.25 (4.77)	19.75 (3.41)
Emotional	15.22 (4.76)	17.56 (3.78)	17.11 (4.34)	16.13 (5.06)	17 (4.34)
Functional	17 (4.18)	18.22 (3.77)	19.22 (5.09)	18.88 (4.82)	19.75 (3.99)

HRQOL = health-related quality of life; PNQ = Patient Neurotoxicity Questionnaire; SD = standard deviation; VAS = Visual Analogue System; WHO = World Health Organization.

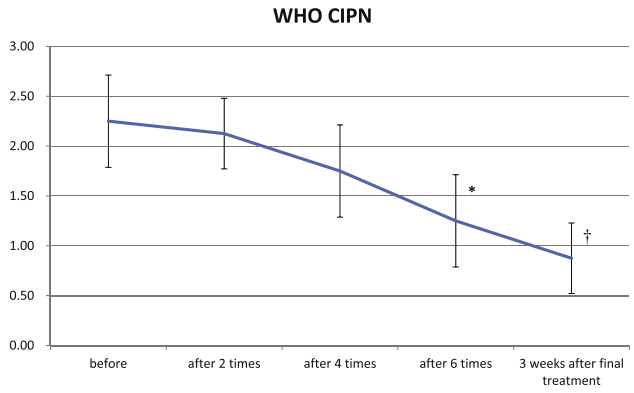

Figure 1 Graph displaying mean WHO grading system scores. The mean WHO grading system score (range 0—4) has decreased from 2.22 to 1.25 after the final treatment and 0.88 after the 3-week follow-up. *$p < 0.01$. †$p < 0.001$. WHO CIPN: World Health Organization Chemotherapy-Induced Peripheral Neuropathy.

between the baseline and after the last treatment session result outcomes. In comparison between the baseline and the 3-week follow-up of the result outcomes, statistically significant differences were found in WHO grade, Total PNQ, PNQ-sensory, VAS, total HRQOL, and HRQOL-functional scores.

The consistent positive results maintained between the last treatment and the 3-week follow-up suggest the sustained efficacy of SBVP for a certain period of time. The assessment tools used to measure patients neuropathic condition and quality of life has touched different aspects of patients' physical and emotional changes. Both of the WHO CIPN grade and PNQ have shown decrease in the level of neuropathy. More specifically, the PNQ has revealed that the CIPN patients assessed complained more of the sensory

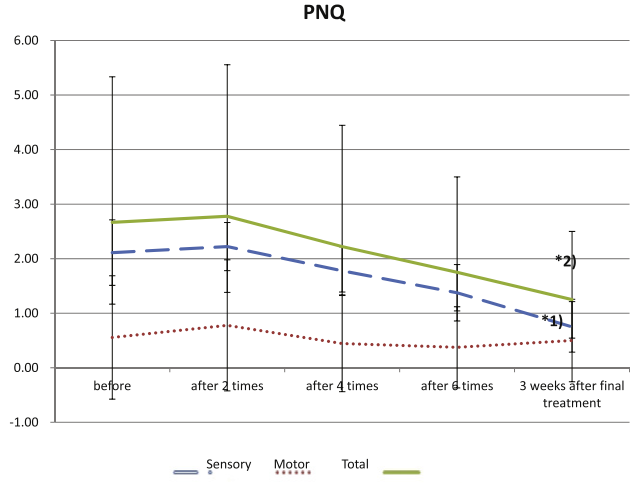

Figure 2 Graph displaying mean PNQ scores. The mean PNQ-total score (range 0—8) has decreased from 2.67 to 1.75 after the final treatment and 1.25 after the 3-week follow-up. The mean PNQ-sensory (range 0-4) has decreased from 2.11 to 1.38 and 0.75, respectively, and the mean PNQ-motor (range 0-4) has decreased from 0.56 to 0.38 and 0.5, respectively. *$p < 0.01$. 1 = sensory; 2 = total; PNQ = Patient Neurotoxicity Questionnaire.

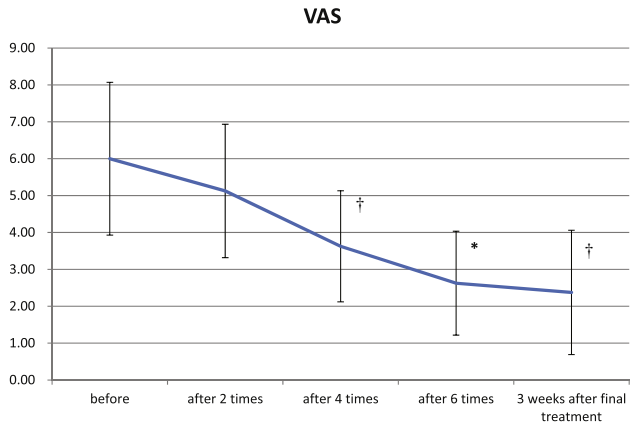

Figure 3 Graph displaying mean VAS scores. The mean VAS score (range 0—10) has decreased from 6 to 2.63 after the final treatment and 2.38 after the 3-week follow-up. *$p < 0.05$. †$p < 0.01$. VAS = Visual Analogue System.

symptoms than the motor symptoms. The SBVP treatment has also resulted in a greater decrease in the sensory symptoms. This observation can be justified by two explanations. One, SBVP's possible capability to target sensory

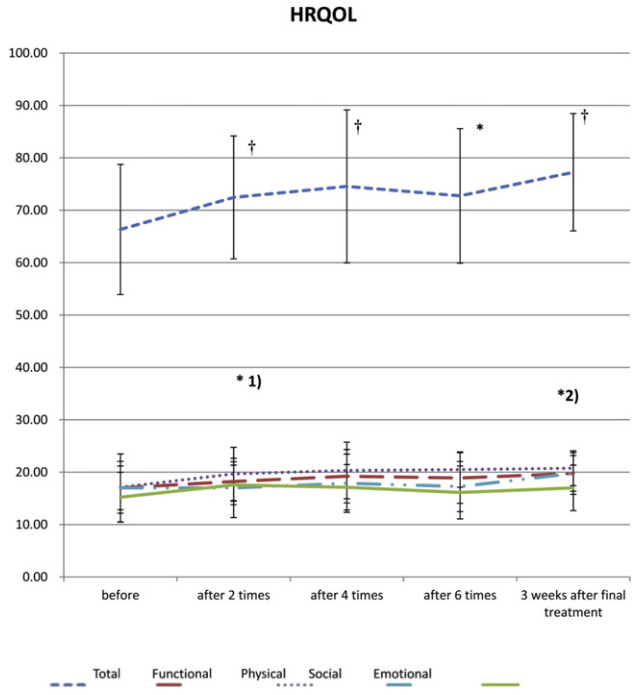

Figure 4 Graph displaying mean HRQOL Scores. The mean HRQOL-total score (range 0—108) has increased from 66.23 to 72.75 after the final treatment and 77.25 after the 3-week follow-up. The mean HRQOL-physical (range 0—28) has increased from 17.11 to 20.5 and 20.75, respectively and the mean HRQOL-social (range 0—28) has increased from 17 to 17.25 and 19.75, respectively. The mean HRQOL-emotional (range 0—24) has increased from 15.22 to 16.13 and 17, respectively, and the mean HRQOL-functional (range 0—28) has increased from 17 to 18.88 and 19.75, respectively. *$p < 0.05$. †$p < 0.01$. 1 = emotional; 2 = functional; HRQOL = health-related quality of life.

Table 3 Paired difference between bean variances of the baseline and after the last treatment session in outcome results.

	Paired difference test					*t* test	d.f.	*p* value
	Mean	SD	SEM	95% CI				
				Lower	Upper			
WHO grade	1.000	0.756	0.267	0.368	1.632	3.742	7	0.007*
PNQ total	1.00	1.51	0.53	−0.26	2.26	1.871	7	0.104
Sensory	0.75	1.04	0.37	−0.12	1.62	2.049	7	0.080
Motor	0.25	0.89	0.31	−0.49	0.99	0.798	7	0.451
VAS	3.375	2.722	0.962	1.099	5.651	3.507	7	0.010†
HRQOL	−5.500	4.928	1.742	−9.620	−1.380	−3.157	7	0.016†
Physical	−3.500	5.292	1.871	−7.924	0.924	−1.871	7	0.104
Social	1.125	2.696	0.953	−1.129	3.379	1.180	7	0.276
Emotional	−1.250	4.132	1.461	-4.704	2.204	−0.856	7	0.420
Functional	−1.875	2.532	0.895	−3.992	0.242	−2.095	7	0.074

*$p < 0.01$.
†$p < 0.05$.
CI = confidence interval; d.f. = degrees of freedom; HRQOL = health-related quality of life; PNQ = Patient Neurotoxicity Questionnaire; SD = standard deviation; SEM = standard error of mean; VAS = Visual Analogue System; WHO = World Health Organization.

function repair and two, early sensory nerve damage initiating faster natural recovery process of the sensory nerves. Typically chemo drugs have much easier access to the sensory nerves compared to the well-protected motor nerves [2]. Most patients who came for the treatment were exposed to long cycles of chemo. VAS level has also shown a great decrease in pain levels and improvement of quality of life has been detected though modest.

4.2. Mechanisms of SBVP and future research

Different mechanisms of how SBVP works is still in question. According to a rat neuropathic pain model study [52] treated with diluted bee venom epipuncture, intrathecal pretreatment with naloxone (opioid receptor antagonist) did not reverse the antihyperalgesic effect of the diluted bee venom, whereas pretreatment with idazoxan (alpha2-adrenoceptor antagonist), completely blocked its effect. The BV reduces the hyperalgesia associated with inflammation and is dependent on the activation of alpha2-adrenoceptors, but not opioid receptors. This may explain BV's efficacy for patients with painful peripheral neuropathy, especially for those who are poorly responsive to opioid analgesics. In central and peripheral nervous systems, catecholamines such as norepinephrine (noradrenaline) and epinephrine (adrenaline) signal through the alpha2-adrenergic receptors. Thus our speculation is that SBVP treatment may work in the similar mechanisms as the norepinephrine reuptake inhibitors or adrenergic reuptake inhibitors.

Another speculation is that SBVP treatment involves resetting the glutamine transporter mechanism through

Table 4 Paired difference between mean variances of baseline and 3-week follow-up in outcome results.

	Paired Difference Test					*t* test	d.f.	*p* value
	Mean	SD	SEM	95% CI				
				Lower	upper			
WHO grade	1.375	0.518	0.183	.942	1.808	7.514	7	0.000*
PNQ total	1.50	1.07	0.38	0.61	2.39	3.969	7	0.005†
Sensory	1.38	0.74	0.26	0.75	2.00	5.227	7	0.001‡
Motor	0.13	0.64	0.23	−0.41	0.66	0.552	7	0.598
VAS	3.625	2.326	0.822	1.680	5.570	4.408	7	0.003†
HRQOL	−10.000	7.251	2.563	−16.062	−3.938	−3.901	7	0.006†
Physical	−3.750	5.175	1.830	−8.077	0.577	−2.049	7	0.080
Social	−1.375	3.662	1.295	−4.437	1.687	−1.062	7	0.323
Emotional	−2.125	3.980	1.407	−5.452	1.202	−1.510	7	0.175
Functional	−2.750	2.493	0.881	−4.834	−0.666	−3.120	7	0.017‡

*$p < 0.001$.
†$p < 0.01$.
‡$p < 0.05$.
CI = confidence interval; d.f. = degrees of freedom; HRQOL = health-related quality of life; PNQ = Patient Neurotoxicity Questionnaire; SD = standard deviation; SEM = standard error of mean; VAS = Visual Analogue System; WHO = World Health Organization.

an initial agonist activity followed by an irreversible antagonism of the glutamate transporter. Intradermal injection of melittin produces temporary pain and a short-lived neurogenic-inflammation-skin temperature increase [53]. Clinically, after 1 week, the pain appears to subside, suggesting that the glutamine-transporter mechanism is reset and hypersensitivity is reduced. The primary sensitization of bee venom contributes to the development of contralateral heat hyperalgesia involving both N-methyl-D-aspartate (NMDA) and non-NMDA receptor activation in the spinal cord during the process [54]. However, the animal study suggested the mechanisms between the bee venom-induced heat hyperalgesia identified in the injection site and the contralateral site in a rodent model was different, as the injection site hyperalgesia coexisted with the mechanical hyperalgesia while the other did not [55]. Studies were conducted to compare the pre-treatment with either NMDA or non-NMDA receptor antagonist and its relationship with bee venom injection induced central origin or contralateral/secondary heat hyperalgesia [55,56]. As a result, NMDA receptors were found to be involved in both development and maintenance (persistent firing of the dorsal horn wide-dynamic-range neurons) of the contralateral and secondary heat hyperalgesia. Non-NMDA receptors were only involved in induction, the processes of the primary heat and mechanical hyperalgesia [52,53]. Another study also reports the pivotal role of peripheral NMDA receptor in the bee venom-induced persistent nociception and hyperexcitability [57].

More research will be needed to evaluate the different mechanisms of SBVP in CIPN. A prospective trial comparing the effect of SBVP in different chemotherapy classification agent-induced neuropathy models would be helpful in attaining more information with relevance to its mechanisms.

4.3. Limitations

The limitation of the study includes the small sample size that lacks statistical representation to apply the efficacy results to the general public. This observational study may have biased outcome as the patients have voluntarily admitted themselves to the treatment. The placebo effect in correlation with the natural healing process of CIPN and other interventional variables were not taken into consideration. However for CIPN, the underlying etiologies can differ from patient to patient depending on the chemotherapeutic agent, their physical constitution, and other variable factors that may come into play. Therefore one must be aware of the realistic limitations of the natural healing time when conducting future trials. Selection bias may also be present, as the study was based in one oriental medicine hospital. With these limitations, the results should be interpreted with caution.

5. Conclusion

The positive result of the study supports the potential value of conducting a fully powered trial to explore further efficacy of SBVP for CIPN. However, a single positive result within this pilot study should be carefully interpreted.

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