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Original article

A Case Series of Snake Venom Pharmacopuncture for Chemotherapy-Induced Peripheral Neuropathy: A Retrospective Observational Study

Si Yeon Song[1*], Kyeore Bae[1*], Kwhang Ho Shin[2], Hwa-Seung Yoo[1**]

[1] East-West Cancer Center, Dunsan Korean Medicine Hospital of Daejeon University, Daejeon, The Republic of Korea
[2] Dalraechon Korean Medicine Clinic, Yangyang-gun, Gangwon-do, The Republic of Korea

Key Words

Sadverse effects, peripheral nervous system diseases, pharmacoacupuncture treatment, snake venoms

Abstract

Objective: This case series aims to report the efficacy and the safety of using snake venom pharmacopuncture (SVP) for chemotherapy-induced peripheral neuropathy (CIPN).

Methods: Three heterogeneous cancer (1 endometrium, 1 cervix, and 1 prostate cancer) patients were referred to the East-West Cancer Center (EWCC), Dunsan Korean Medicine Hospital of Daejeon University, from August 02, 2017, to September 15, 2017, for treatment with SVP, and they were treated with SVP 4 times, 6 times, and 8 times, respectively. During the treatment period, the efficacy of SVP therapy was assessed by using the Numerical Rating Scale (NRS) and the Common Terminology Criteria for Adverse Events (CTCAE), and the stability was evaluated by using blood tests. Following each session, all patients were examined closely for any allergenic responses or adverse effects.

Results: All patients showed noticeable improvements of their NRS and CTCAE scores. Except for bleeding and bruising at the SVP injection site, no major side effects were noted. One of the patients reported mild chilling and a sore throat after receiving the second treatment; those symptoms went away after a few hours. No hematologic toxicity, hepatotoxicity, or nephrotoxicity was found on the blood test.

Conclusion: The results of this research suggest positive potential benefits of using SVP for treating patients with CIPN. Also, the excellent safety results of SVP seen in this research should lead to larger clinical trials aimed at developing SVP into a potential intervention for managing patients with the symptoms of CIPN.

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1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) involving sensory and motor nerve damage or malfunction is a common significant side effect that affects many patients receiving cancer treatment [1]. In most cases, symptoms start from the distal extremities involving the fingers and toes and spread to proximal parts [2]. When patients receive some chemotherapeutic agents such as taxanes and proteasome inhibitors, CIPN peripheral nerves can repair themselves reversibly, and symptoms may resolve over time. On the other hand, the use of agents such as platinum compounds results in irreversible CIPN that tends to be prolonged without improvement [3]. This severe CIPN

*Corresponding Author
Hwa-Seung Yoo. East-West Cancer Center, Dunsan Korean Medicine Hospital of Daejeon University, 75, Daedeok-daero, 176 beon-gil, Seo-gu, Daejeon, the Republic of Korea, 302-869. Tel: +82-42-470-9132 Fax: +82-42-470-9006 E-mail: altyhs@dju.kr

can lead to permanent symptoms and disability in up to 40% of cancer patients [4]. Although moderate-to-severe CIPN significantly reduces the physical abilities and the qualities of life of cancer survivors, currently, no standard treatment protocol for the prevention or management of CIPN is available, and current pharmacotherapy for CIPN has had limited efficacy.

Snake venom has the most attractive toxic potential for the development of anticancer agents. It is a complex mixture of peptides, enzymes, carbohydrates, minerals, and proteins with specific chemical and biological activities [5]. Snake venom components can be used for the treatment of cancer, arthritis, thrombosis, multiple sclerosis, pain, neuromuscular disorders, blood and cardiovascular disorders, infections, and inflammatory diseases [5]. Previous clinical and laboratory studies have reported that snake venom components have anticancer and analgesic effects [6-9]. Among the snake venom component, disintegrins such as cobrotoxin have been reported to have a substantial analgesic effect [6]. Cobra venom factor is crucial for the synthesis of immunoconjugates to carcinoma cells, and very minute doses of cobra venom have more enhanced analgesic activity than morphine and reduce intractable cancer [9]. Several therapeutic actions make snake venom an attractive option in the management of patients with cancer.

Accumulated studies have reported the effects of acupuncture and sweet bee venom pharmacopuncture for the treatment of patients with CIPN [10, 11]. However, to our knowledges, the efficacy of snake venom for the treatment of such patients has not been studied much. Snake venom pharmacopuncture (SVP) can be applied to patients whose CIPN symptoms have not been relieved with existing treatments such as antidepressants and anticonvulsants as an alternative clinical therapy. Accordingly, we report the results of our preliminary study, which was based on data collected as part of a routine clinical study, on the efficacy and the safety of SVP for the treatment of patients with CIPN.

2. Materials and Methods

2.1. Subjects' rights and welfare

This report presents the results of a retrospective analysis of clinical observations of a case series of patients with CIPN who had been treated with SVP. All data were collected as part of a routine clinical practice. Patients who visited the East-West Cancer Center (EWCC), Dunsan Korean Medicine Hospital, Daejeon University, the Republic of Korea, from 2 August to 15 September 2017, complaining of the symptoms of CIPN were treated with SVP. All treatments were performed with the consent of the patient. In accordance with the policy of our institution, a description of the treatment procedure, the potential side effects of the treatment, and the uncertain effectiveness of the treatment were given to the patients. This observational study gained ethical approval from Institutional Review Board (IRB), Dunsan Korean Medicine Hospital, Daejeon University, on October 27, 2017 (IRB number: DJDSKH-17-E-10-11).

2.2. Safety precautions and assessments

Cancer patients with at least 5 on a Numerical Rating Scale (NRS) for CIPN whose symptoms had not been managed with conventional medications or other therapies such as massage and other herbal extract pharmacopuncture, including sweet bee venom, were the subjects of SVP treatment. The patients with diabetic neuropathy, hepatotoxicity, or nephrotoxicity were excluded. Also, patients with other systemic disease accompanied by symptoms requiring different forms of intervention were excluded. In an attempt to reduce any severe allergic reactions to the SVP, we conducted snake venom tests on those who satisfied the inclusion criteria. Doctors were instructed to pay particular attention to safety issues, and after each treatment session, all patients were carefully examined for and questioned about any possible allergic responses.

2.3. Patients' characteristics

Three cancer patients (1 endometrium, 1 cervix, 1 prostate) with CIPN visited EWCC from 2 August to 15 September 2017 to be treated with SVP. Their symptoms included pain, numbness, cold sensitivity, and tingling in their hands, feet or lower limbs after having undergone chemotherapy for at least 28 days. Patient 1 was receiving chemotherapy with cisplatin + bevacizumab regimen. Patients 2 and 3 had received intravenous chemotherapy, but the data on the therapeutic agents were not collected. The NRS pain levels of the 3 patients ranged from 6 to 9, with 0 being painless and 10 the worst pain imaginable. The severity of CIPN was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.3 [12]. As a concurrent conventional medication, 300 mg/day of pregabalin was being administered to patient 1, but her CIPN was not being improved by pregabalin. Patient 2 had already ceased conventional medication due to its having had no effect. The data on the medications used for patient 3 were not collected. The patients' characteristics and the details of the CIPN symptoms are shown in Tables 1 and 2.

2.4. Treatment method

We followed the Standards for Repor ting Inter ventions in Clinical Trials of Acupuncture (STRICTA) 2010 recommended guidelines to report the treatment performed (Table 3) [13]. In the study, a technique called pharmacopuncture, which is a combination of acupuncture and injection with herbal medicine, was used. Pharmacopuncture is associated with the injection of medication (often originating from natural products) into acupuncture points that are connected to the symptom locations, as defined by Korean medicine. Acupoints were individually tailored according to symptoms.

The acupuncture points LI4 (Hapgok), TE3 (Jungjeo), LR3 (Taechung), GB41 (Jokimeup) were chosen based on the general principles of acupuncture and traditional Korean medicine theories of meridians and on the results of

a previous acupuncture study on CIPN that used these same points to relieve pain and numbness in patients with CIPN [14]. LR3 and GB41 were used in patients with CIPN symptoms in their lower extremities. Patients with CIPN symptoms in the upper extremities were treated at LI4 and TE3. Patients with CIPN symptoms in the upper and the lower extremities were treated with a combination of acupuncture points.

Snake venom pharmacopuncture in a concentration of 10 mg/mL was refined and prepared in an aseptic room at the Korean Pharmacopuncture Research Institute. Sterilized disposable syringe needles (26 Gauge × 1/2; 0.45 mm × 13 mm) were used. The depth of SVP injection was 0.5 cm. The volume of SVP for each acupuncture point was 0.25 mL. Patients 1, 2, and 3 were treated with SVP for 4 times, 6 times, and 8 times, respectively, with 3 to 4 days between treatment sessions. The actual treatment session was completed within 10 minutes because it was a series of quick epidermal injections. The SVP treatments were carried out by a certified Korean medicine doctor with more than three years of clinical experience. In every treatment session, after the SVP treatment, all patients received electroacupuncture for CIPN for 15 minutes.

2.5. Efficacy and safety assessments

Patient-reported outcomes, NRS scores and CTCAE symptoms, were reported before and after each treatment session. The NRS and the CTCAE are methods used as a measure of therapeutic efficacy. The NRS measures pain intensity on a scale from 0 to 10. A score of 0 shows absence of pain, and a score of 10 represents the worst pain imaginable. The CTCAE uses five grades: grade 1 is associated with mild symptoms, and grade 5 indicates death related to an adverse effect. In addition, for a toxicity assessment, blood tests were conducted during each treatment session.

3. Results

Patients 1, 2 and 3 with CIPN received 4, 6, and 8 SVP treatment sessions, respectively. The NRS score showed a significant decrease in all patients with progression of treatment (Figure 1). The CTCAE grade of CIPN on neuralgia and paresthesia also decreased from 2 to 1 in all patients. One patient felt mild chilling with a sore throat temporarily after the second SVP treatment session. However, it did not recur after any of the following four treatments. At times, patients showed faint bruises, bleeding, or pain at the injection sites shortly after treatment. However, no related severe adverse effects, such as allergic reactions, were observed (Table 2). Based on the results from the blood test performed between treatment sessions, no hematologic toxicity, hepatotoxicity, or nephrotoxicity was observed in any patient.

4. Discussion

CIPN is a common, but significant, clinical problem induced by the treatment of patients with many types of cancer. It may be caused by treatment with multiple chemotherapeutic agents, such as platinum compounds (cisplatin, carboplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinblastine), thalidomide, and bortezomib [15]. Symptoms of CIPN, such as sensory symptoms, ataxia, pain, and severe numbness, can be disabling and interfere with a patient's daily activities and quality of life. A number of experimental symptomatic treatments, including antioxidant, anticonvulsant, antidepressant, calcium, and magnesium infusions, neurostimulation techniques, topical analgesic creams, acupuncture, and dietary modification, are being studied in patients with CIPN [15]. While a number of potential approaches are being investigated in clinical trials, efforts to support the introduction of neuroprotective therapies in clinical trials for patients with CIPN have had limited success. According to a clinical practice guideline published by the American Society of Clinical Oncology in 2014, the only recommended medication for patients with CIPN is duloxetine. Also, antidepressants involving gabapentin and nortriptyline, and a compound topical gel containing baclofen, amitriptyline HCL, and ketamine can be administered based on data supporting their effects when used to treat patients with other types of neuropathic pain [16]. CIPN remains a clinically significant and potentially serious side effect of cancer treatment. However, currently, no therapies with a confirmed benefit are available for clinical use in patients with CIPN. Neuropathic symptoms may also interfere with treatment, leading to a dose reduction or the early cessation of chemotherapy, thereby potentially impacting patient survival [15]. Therefore, further clinical studies are required to find alternative treatments for addressing CIPN.

Snake venom is a complex mixture of biologically active proteins, peptides, enzymes, and organic and inorganic compounds [5]. Protein and peptides make up 90% to 95% of the dry weight of venom. Snake venom contains cytotoxins, hemotoxins, cardiotoxins, neurotoxins, nerve growth factor, inorganic cations, such as zinc, potassium, calcium, sodium, and magnesium, etc. Phospholipase A2, ancrod, cobra venom factor, peptides, crotoxin, cytotoxins CT1, CT2 and CT3, L- amino acid oxidases (LAAOs), lectins, metalloproteinases, serinoproteases, disintegrins, hyaluronidase, cholinesterases, salmosin, cathelicidin-BF, aggretin, obtustatin, rhodostomin, albolabrin, colombistatin, saxatilin, and lebecetin are some of the components separated from various types of snake venom and have shown promise in their applications for the management of patients with various human cancers [9]. Several studies have been conducted on the effect of snake venoms on tumor cell cultures, and some of those studies were phase I and phase II clinical trials [5]. Some snake venom toxins have found potential uses that include antitumor, anticoagulating, antimicrobial, and analgesic activities [5]. Phospholipase A2 (PLA2, lecithinase), snake venom serine protease (SVSP), snake venom metalloprotease (SVMP), L-aminoacid oxidase (LAO), phosphoesterases, distinegrin, and C-type lectin protein act on blood clotting factors, platelet receptors, the matrix of the sur-

rounding blood vessels, and the vascular endothelial cell layer, resulting in anticoagulant, anti-thrombotic effects. The effect of venom and its impact on humans depend on the type and the amount of the venom injected and the location where it is injected [17]. Other parameters, such as general health, gender, size, and age, also influence the results achieved using snake venom as a treatment [17].

The ability of snake venoms to work in tumor cells has long been known. Venom from snakes is an important agent for curing patients with many types of cancers. Numerous reports have shown that snake venom inhibits cell proliferation and promotes cell death by other means. The cytotoxic effects of snake venom have the potential to destroy tumor cells. Accumulated publications demonstrate the anti-cancer potential of disintegrins, which is among snake venom components [18]. Snake venom disintegrins usually contain integrin for developing therapeutics for cancer treatments. Integrins are vital in cell adhesion, cell migration, tissue organization, cell growth, hemostasis, and inflammatory responses, so they are the subjects of research designed to develop new drugs for treating patients with cancer [19].

Several studies on the analgesic effects of snake venoms have been reported. Analgesic responses can be induced by the central cholinergic neurons (cobratoxin), the central and the peripheral nervous systems (crotamine and mambalgin), and the opioid and the nitric-oxide systems (hannalgesin) in the antinociceptive pathway [8]. The results of a randomized, double- blind, cross-over study and an open-label study of a compound analgesic formulation combining cobrotoxin, tramadol hydrochloride, and ibuprofensuggested a significant improvement in cancer patients with chronic moderate-to-severe cancer pain. The frequency of adverse events was similar to that of tramadol hydrochloride [6]. In addition, the antinociceptive effect of the analgesic peptide crotalphine from the venom of the South American rattlesnake (Crotalus durissus terrificus) was evaluated in an experimental model of neuropathic pain induced in rats by chronic constriction of the sciatic nerve [20].

Previous studies have reported the pain-relief and anticancer effects of snake venom components. However, studies on cancer-related pain are scarce so for establishing a baseline, a need exists for a report on the stability and the clinical outcome of using snake venom components for treating cancer-related pain. This study has strengths. Although it is a small size observational study, it suggested the potential efficacy and safety of SVP for use as an alternative treatment method for treating the symptoms of CIPN in patients with cancer. SVP can be applied to patients for whom current conventional medications and existing Korean medicinal treatments, such as standard acupuncture, electroacupuncture, and other herbal extracts pharmacopuncture, have failed to relieve the symptoms of CIPN. However, this study does have limitations: The data on patients' clinical history, such as chemotherapeutic agents used, were incomplete due to the data having been collected from the medical chart at an optional Korean medicine clinic, not a mainstream Western medicine cancer center. Also, although researchers regard SVP as a major treatment for reducing pain, its association in this study with the effects of electroacupuncture conducted on three patients in every session must be interpreted carefully. The safety results of the SVP therapy merit further investigation in a larger size trial before it can be considered as a potential treatment for patients with CIPN. We also expect treatment with SVP to be an alternative treatment for improving the quality of life and relieving the symptoms of cancer patients suffering from CIPN.

5. Conclusion

The results of this study suggest that SVP has potentially positive benefits for cancer patients with CIPN. The adverse events observed in the three cases were well controlled, and no other severe adverse effects were reported. If the efficacy of SVP as an intervention for managing patients with CIPN is to be demonstrated and the safety of SVP is to be established, future rigorous research efforts with large numbers of participants are required.

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Table 1 Characteristics of patients treated with snake venom pharmacopuncture

Patient	Age (years)	Gender	Cancer type (stage)	Chemotherapeutic Agents/Route of Administration	Number of Chemotherapy Cycles	Number of SVP• Treatments
1	61	Female	Endometrial CA† (IIB)	Cisplatin + Bevacizumab/ IV‡ injection	7	4
2	54	Female	Cervical CA† (IV)	UK§/ IV‡ injection	6	6
3	64	Male	Prostate CA† (UK§)	UK§/ IV‡ injection	6	8

•SVP: snake venom pharmacopuncture; † CA: cancer; ‡ IV: intravenous; § UK: unknown.

Table 2 Details of CIPN•symptoms, CTCAE† grade change, and side effects after SVP‡ treatment

Patient	Areas affected	CIPN•symptoms	CTCAE† Grade change after SVP‡ treatment	Side effects
1	Both lower limbs, feet	Numbness, sensitivity to cold	Neuralgia 2→1 Paresthesia 2→1	Bruising, pain
2	Both lower limbs, feet	Numbness, tingling	Neuralgia 2→1 Paresthesia 2→1	Mild chilling, sore throat, bruising
3	Both hands, feet	Numbness, tingling	Neuralgia 2→1 Paresthesia 2→1	Bruising, bleeding

•CIPN: chemotherapy-induced peripheral neuropathy; † CTCAE: common terminology criteria for adverse events; ‡ SVP: snake venom pharmacopuncture.

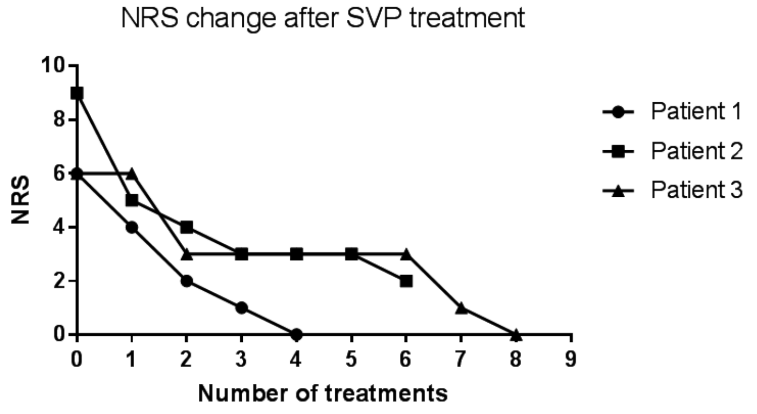

Figure 1 Change in the score on the Numerical Rating Scale (NRS) after snake venom pharmacopuncture (SVP) treatment.

Table 3 Methodological aspects of acupuncture treatment according to the items in STRICTA*, 2010

STRICTA* Items	Details	Study design
1. Acupuncture rationale	a. Style of acupuncture b. Reasoning for treatment provided c. Extent to which treatment was varied	a. Pharmacopuncture b. Pharmacopuncture is associated with injection of medication (often originating from natural products) into acupuncture points that are connected to the symptom locations, as defined by Korean medicine. c. Individually tailored treatment according to symptoms
2. Details of needling	a. Number of needle insertions per subject per session b. Names/locations of points used (uni/bilateral) c. Depth of insertion - specified unit or tissue level d. Response sought e. Needle stimulation (manual/electrical) f. Needle retention time g. Needle (type, diameter, length, manufacturer, or material)	a. 4 - 8 b. LI4 (Hapgok), TE3 (Jungjeo), LR3 (Taechung), GB41 (Jokimeup), bilateral c. 0.5 cm d. Volume of injection was 0.25 ml in each acupoints. e. Stimulation by injected medication f. Within 10 minutes g. Sterilized disposable syringe needles (26 Gauge × ½; 0.45 mm × 13 mm)
3. Treatment regimen	a. Number of treatment sessions b. Frequency and duration of treatment session	a. 4, 6, 8 times for patients 1, 2, 3, respectively b. 3- to 4-day intervals between treatments
4. Other components of treatment	a. Details of other interventions administered to the acupuncture group b. Setting/context of treatment, instructions to practitioners, and information and explanation to patients	a. Patients with other systemic disease accompanied by symptoms requiring different forms of intervention were excluded. b. Skin tests of snake venom were conducted on those who satisfied the inclusion criteria to reduce any severe allergic reactions. Medical doctors were instructed to pay particular attention to safety issues, and all patients were closely examined and questioned for any possible allergic responses after each treatment session.
5. Practitioner's background	Description of participating acupuncturists	Treatments were carried out by a certified Korean medicine doctor with more than 3 years of clinical experience.
6. Control of comparator interventions	a. Rationale for the control or comparator in the context of the research question b. Precise description of the control or comparator	Not applicable

* STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture.

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