Pain Management Nursing 20 (2019) 623–632

Contents lists available at ScienceDirect

Pain Management Nursing

journal homepage: www.painmanagementnursing.org

Preliminary Effectiveness of Auricular Point Acupressure on Chemotherapy-Induced Neuropathy: Part 2 Laboratory-Assessed and Objective Outcomes

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ARTICLE INFO

Article history:
Received 2 June 2018
Received in revised form
18 March 2019
Accepted 24 April 2019

ABSTRACT

Purpose: To manage chemotherapy-induced neuropathy (CIN), this paper explores reliable and valid objectives measures to evaluate the treatment effects of auricular point acupressure (APA).
Design/Method: This study was a repeated-measures one-group design. Participants received four weeks of APA to manage their CIN. The laboratory-assessed and objective outcomes included quantitative sensory testing, grip and pinch strength, and inflammatory biomarkers. Wilcoxon matched pairs signed-rank tests were conducted to determine change scores of outcomes at pre- vs. post- and pre- vs. 1-month follow-up. Spearman's rho correlation coefficient was used to examine the linear association of score changes of all objective study outcomes.
Results: Comparing pre-and-post APA, (1) the mean score of the monofilament for all lower extremity sites tested decreased after APA, indicating sensory improvement; (2) the suprathreshold pinprick stimuli mean scores on the upper extremities increased, except the scores from the index finger and thumb; (3) the pain tolerance of thumb and trapezius areas increased; (4) decreasing IL1β ($p = .05$), IFNγ ($p = .02$), IL-2 ($p = .03$), IL-6 ($p = .05$), IL-10 ($p = .05$), and IP10/CXCL10 ($p = .04$) were observed pre-post APA. Conditional pain modulation was significantly ($p < .05$) associated with pain intensity ($r = 0.55$), tingling ($r = 0.59$); and IL1β concentration ($r = 0.53$) pre-post APA. The sustained effects of 4-week APA were observed at the 1-month follow-up.
Conclusions: Our study findings demonstrated the promising effectiveness of APA in the management of CIN, and these treatment effects can be assessed using reliable and valid objective measures.
Clinical Implications: If the efficacy of APA to manage CIN is confirmed in a larger sample, APA has the potential to be a scalable treatment for CIN because it is a reproducible, standardized, and easy-to-perform intervention.

The continued high prevalence of chemotherapy-induced neuropathy (CIN) and the limited effectiveness of current CIN treatment options highlight the critical need to identify ways to better manage CIN. To date, no effective treatment for CIN has

This study was supported by a grant to Dr. Yeh from the Johns Hopkins Discovery Award.
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https://doi.org/10.1016/j.pmn.2019.04.004
1524-9042/

been established (Hershman et al., 2014). In a systematic review of 48 randomized controlled trials (RCTs) for the treatment of CIN—although the findings of CIN outcomes were inconclusive because of the small sample size and heterogeneous instruments used at different time point—we included 47 studies for analysis (Hershman et al., 2014). Self-report measures are the most common methods used to assess CIN in research and clinical settings, although many questionnaires do not assess the distribution of sensation lost according to specific locations on the body where symptoms are present. Additionally, patients are often asked to rate their severity of pain, numbness, or tingling as a single question on the following self-reported measures: the European Organization for Research and Treatment of Cancer (Fayers et al., 2001), Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy Scale (Postma et al., 2005), Functional Assessment of Cancer Therapy/Gynecologic Oncology Group—Neurotoxicity Subscale 11 questionnaire (Cella, 1997), the Eastern Cooperative Oncology Group Neuropathy Scale (Cavaletti et al., 2003), or the National Cancer Institute Common Toxicity Criteria (Trotti et al., 2003).

Patients are often not able to accurately interpret the intended meaning of the items in these instruments, causing problematic assessment and interpretation. It is known that these self-report clinical assessments lead to a significant degree of interrater variability between patient and clinician rating variations (Brewer, Morrison, Dolan, & Fleming, 2016). The insensitive or unreliable measures may be the reason these failed trials were not able to adequately assess the effectiveness of CIN treatment (Albers, Chaudhry, Cavaletti, & Donehower, 2014; Gewandter, Dworkin, Finnerup, & Mohile, 2017).

Quantitative sensory testing (QST) is a standardized, comprehensive, objective assessment of somatosensory function (Rolke et al., 2006a; Rolke et al., 2006b). It has been used to evaluate a participant's perception of detection and pain threshold generated through touch (A-β fibers), warmth (C fibers), cold (A-δ fibers), and heat (C fibers; Campbell et al., 2015). CIN is characterized as a sensory dysfunction that affects peripheral nerves, with specific functional alterations in A-δ and C sensory nerve fibers (Seretny et al., 2014). Thus QST can be used noninvasively to quantify the pain and sensory nerve function of CIN in a detailed and standardized manner (Woolf, 2011).

QST has been responsive to pharmacologic and nonpharmacologic interventions. Along with clinical tools such as pain inventory, QST has been used to evaluate body acupuncture effects by quantifying stimulus-evoked negative and positive sensory phenomena to determine peripheral and central mechanisms of pain (Baeumler et al., 2014; Campbell et al., 2015; Kong, Schnyer, Johnson, & Mackey, 2013; Lang, Stoer, Schober, Audette, & Irnich, 2010; Starkweather et al., 2016). Studies have identified changes in heat, pressure, and mechanical pain thresholds immediately after acupuncture (Baeumler et al., 2014; Kong et al., 2013; Lang et al., 2010). In the only published auricular point acupressure (APA) QST study, conducted on 16 healthy adults, 2-minute APA increased the pain threshold at 24 hours after APA compared with sham treatment (Santoro et al., 2015). These findings strongly suggest that APA may alter pain processing in the central nervous system; however, Santoro's study was conducted on healthy participants with a single treatment, which may not be generalizable to CIN patients because pain processing may differ between participants with chronic pain versus healthy individuals (Peyron, Laurent, & Garcia-Larrea, 2000).

The exact pathophysiology of CIN remains unknown (Sisignano, Baron, Scholich, & Geisslinger, 2014). Several hypotheses have been proposed, including inflammation (Lees, Duffy, & Moalem-Taylor, 2013; Sisignano et al., 2014) and damage to mitochondria in peripheral sensory neurons (Flatters & Bennett, 2006). The majority of the signs and symptoms of CIN arise from damage to dorsal root ganglion neurons or their axons, leading to pain, sensory loss, and sometimes sensory ataxia (Costigan, Scholz, & Woolf, 2009), which might exacerbate symptoms of peripheral nerve damage (Janes et al., 2014). The inflammatory component results from the activation of microglia, astrocytes, and satellite glial cells in the dorsal horn of the spinal cord that leads to the production and release of proalgesic mediators, such as tumor necrosis factor (TNF) and interleukin-1β (IL-1β) (Ji et al., 2013; Peters, Jimenez-Andrade, Kuskowski, Ghilardi, & Mantyh, 2007).

How does APA work to relieve CIN? The underlying mechanisms of the analgesic effects of APA are not well understood. One theoretical explanation is that pain and neuronal excitability are relieved by APA by normalizing pathologic, hypersensitive reflex pathways—the neuroimmune pathway, the particular area of interest in the proposed study—that interconnect the ear microsystem and the somatotopic brain (Huang, 2005; Oleson, 2013). The neurophysiologic connections between ear acupoints and the human central nervous system have been supported by functional magnetic resonance imaging (Alimi, Geissmann, & Gardeur, 2002). Studies suggest that stimulation of ear points from chronic low back pain after 4 weeks of APA causes a broad spectrum of systemic effects, such as neuroimmune (i.e., decreased proinflammatory cytokines; IL-1α, IL-12, eotaxin) and increased anti-inflammatory cytokines (IL-13 in serum), suggesting that APA affects neuroimmune signaling (Lin et al., 2015; Yeh et al., 2014a,b, 2017). These data suggest that APA may relieve CIN symptoms through downregulating proinflammatory cytokines, chemokines, and neuropeptides or upregulating anti-inflammatory cytokines. These responses explain how APA may be able to regulate the inflammatory biomarkers to achieve CIN relief.

Based on the conceptual framework of APA to reduce CIN symptoms (Yeh et al., 2019), we explored the reliable and valid laboratory-assessed objectives measures to assess CIN outcomes after 4 weeks of APA. Specifically, we reported the following: (1) the effects of a 4-week APA intervention on sensory and pain threshold, motor function such as grip strength and pinch test, and inflammatory biomarkers; and (2) the preliminary correlations among clinical outcomes such as CIN symptoms and physical function, sensory function, motor function, and inflammatory biomarkers.

Material and Methods

A detailed description of the participants and recruitment methods are explained in Yeh et al., 2019. The study outcomes for this Part II study include sensory function measured by QST battery, motor function (i.e., grip strength and pinch test), and inflammatory biomarkers. They are discussed in detail next. All of the study outcomes except blood were collected before the APA treatment (pre-APA, T1), once a week for the 4 weeks of APA treatment (T2, T3, and T4), after the 4-week APA treatment (T5), and at 1-month follow-up (T6). Blood (10 milliliters [mL]) was collected in an EDTA vacutainer, using standard phlebotomy procedures. Blood was drawn by a trained nurse at pre-APA (T1), post-APA (T5) and 1-month follow-up (T6).

Measures

Quantitative Sensory Testing

The QST battery consisted of the following: (1) mechanical QST (i.e., mechanical detection threshold and mechanical pain threshold), (2) pressure pain threshold, and (3) cold pressor testing and conditional pain modulation. Two research nurses who received comprehensive training performed the QST battery; the inter-rater reliability was examined to ensure consistency.

Mechanical detection threshold. We used Semmes-Weinstein monofilament tests (SWMT) (Bell-Krotoski, Fess, Figarola, & Hiltz, 1995; Weinstein, 1993), also called "light touch threshold," to examine cutaneous sensation threshold levels. Specifically, we used Touch-Test Sensory Evaluators Six-Piece Foot Kit (North Coast Medical, Inc., Morgan Hill, CA, USA) to assess the foot sensation threshold (Bell-Krotoski et al., 1995; Weinstein, 1993). Each nylon monofilament was attached to a rod and had different weights: 2.83 (0.07 grams [g]), 3.61 (0.4 g), 4.31 (2 g), 4.56 (5 g), 5.07 (10 g), and 6.65 (300 g; Hunter, Callahan, & Mackin, 1995). Before use, each monofilament was inspected and replaced if the rod was bent. We recorded the score of SWMT from 1 (2.83 nylon monofilament) to 6 (5.07 nylon monofilament). SWMT were administered to 9 locations on the dorsal and plantar surfaces of the foot (i.e., Foot Screening Form, Hunter et al., 1995). Testing began from distal to proximal foot locations and from small to large monofilaments. Participants were instructed to close their eyes during the test. Starting from the smallest monofilament, the research nurses applied a monofilament at a 90-degree angle against the skin until it bowed for 1.5 seconds, up to three times, to elicit a sensation perceived by the participant. If a participant was able to detect the sensation of the monofilament on a test location, the specific thickness of the filament detected was then converted to a corresponding score and therefore recorded as the participant's sensory score. If the participant did not perceive the sensation, the next monofilament in rank was used until a monofilament was detected. Participants were kept unaware of the measurement sequence and were not informed as to whether they identified a monofilament correctly. SWMT has good interrater reliability and validity when applied correctly (Bell-Krotoski et al., 1995; Carrer et al., 2018; Feng, Schlosser, & Sumpio, 2011). SWMT has been used to measure sensory abnormalities in cancer patients (da Silva Simao, Teixeira, Souza, & de Paula Lima, 2014The interrater reliability between the two raters was 86%.

Mechanical pain threshold. We used Weighted PinPrick stimulators (MRC Systems, GmbH, Heidelberg, Germany) to measure cutaneous sensation threshold on the hand. PinPrick stimulators are a custom-made set of seven pinprick stimulators, ranging from 8 to 512 millinewton (mN). For purposes of this study, the forces of 32, 64, 128, 256, and 512 mN were used. Each stimulator had a flat contact surface of 0.2 mm so that it did not break the skin, and forces of 32, 64, 128, 256, and 512 mN were used to deliver a single pinprick stimulus. The testing procedure was similar to SWMT. After each pinprick stimulus, participants were asked about their pain intensity (0-10 rating). The mechanical pain threshold has been used to measure clinical pain and CIN with established reliability and validity (Nahman-Averbuch et al., 2011). The interrater reliability between the two raters in this study was 100%. Each pinprick device was inspected and calibrated before each testing session to ensure the tip was not bent.

Pressure pain thresholds (PPT). We used a digital force gauge (FDIX; Wagner Instruments, Greenwich, CT, USA) to determine the PPT in the trapezius and thumb (i.e., distal interphalangeal joints) areas on both sides of the body. The digital force gauge device was purchased in new condition and used solely for the duration of the study, with each participant using the same device to ensure that the device remained calibrated and retained reliability. FDIX included a pressure gauge and a 1 square centimeter (cm^2) rubber plunger tip with a digital display of force in increments of 0.01 kilopascal (kPa). The pressure at the site was gradually increased at a steady rate and stopped when the participant indicated that the stimulus was first perceived as painful. Thirty-second interstimulus intervals were maintained to let the muscle rest. The threshold was then determined as the arithmetic mean of the two series in kPa. The PPT has been used to as a clinical examination method to assess small fiber neuropathy with established reliability and validity (Themistocleous, Ramirez, Serra, & Bennett, 2014) and for cancer patients with CIN (van den Heuvel et al., 2017). The interrater reliability between the two raters was 82%.

Cold pressor testing and conditional pain modulation (CPM). A series of procedures designed to elicit and measure endogenous inhibition of pain were applied to assess CPM. Participants underwent a series of cold pressor tasks (i.e., conditioning stimuli) consisting of immersion of the hand in a circulating cold-water bath. During hand immersion, PPT on the trapezius were reassessed while the participants' hands remained in the cold water. Participants were allowed to remove their hand at any time. Two minutes after finishing the first immersion, participants reimmersed their hand in the water for the second evaluation, with each immersion separated by 2 minutes. The tasks administered to the participants were conducted in random order. A CPM Index was quantified as the average percentage change between two trials in PPT during the cold pressor tasks relative to baseline ratings. This was measured at above PPT at the trapezius (Edwards et al., 2013). One final cold-water immersion was performed at the conclusion of the CPM procedures. This involved a typical cold pressor task, using immersion of the hand until the participant's tolerance was reached, within a 5-minute time limit, unknown to the participant. The CPM has been used to measure pain modulation on CIN (Nahman-Averbuch et al., 2011). The interrater reliability between the two raters was 82%.

Motor function. The assessment of motor function included hand grip and pinch strength. Hand grip strength was assessed using a hand dynamometer (Jamar Plus+; Sammons Preston, Rolyon, Bolingbrook, IL, USA). Pinch strength was assessed using a digital pinch gauge (Sammons Preston Jamar Digital Pinch Gauge), which has been used in previous studies assessing hand strength (Mathiowetz et al., 1985). The same hand dynamometer and digital pinch gauge device were consistently used to conduct the study. Both instruments were in new condition and used for the sole purpose of the study.

Participants were instructed to exert maximum strength during each test while they were seated with their arms by their sides, elbows flexed 90°, with the forearm and wrist in neutral position, based on the recommendations from the American Society of Hand Therapy (Fess & Moran, 1981). Each participant's grip strength was measured three times on each hand, alternating sides. The strongest value was retained for analysis for each hand. For the pinch test, key pinch, tip-pinch (i.e., thumb and index fingers), key pinch (i.e., thumb pad, lateral aspect of the index finger), and palmar pinch (i.e., thumb and index finger) were conducted. The examiner held onto the distal portion of the gauge to help the participant maintain steadiness. The pinch gauges were positioned with the readout area face down so that participants had no visual feedback during testing. Two consecutive readings were taken with each pinch gauge, and a 1-minute rest was given between devices. The average of the two readings was used for data analysis. The grip strength has been used to measure sensory nerve function in CIN (Griffith et al., 2014). The interrater reliability between the two raters in this study was 81%.

Inflammatory biomarker. Plasma samples were diluted in the sample diluent human blood at a 1:4 dilution. A panel of 40 cytokines and chemokines were measured in diluted samples using the Bio-Plex Pro-Human Chemokine Panel (Catalog no.

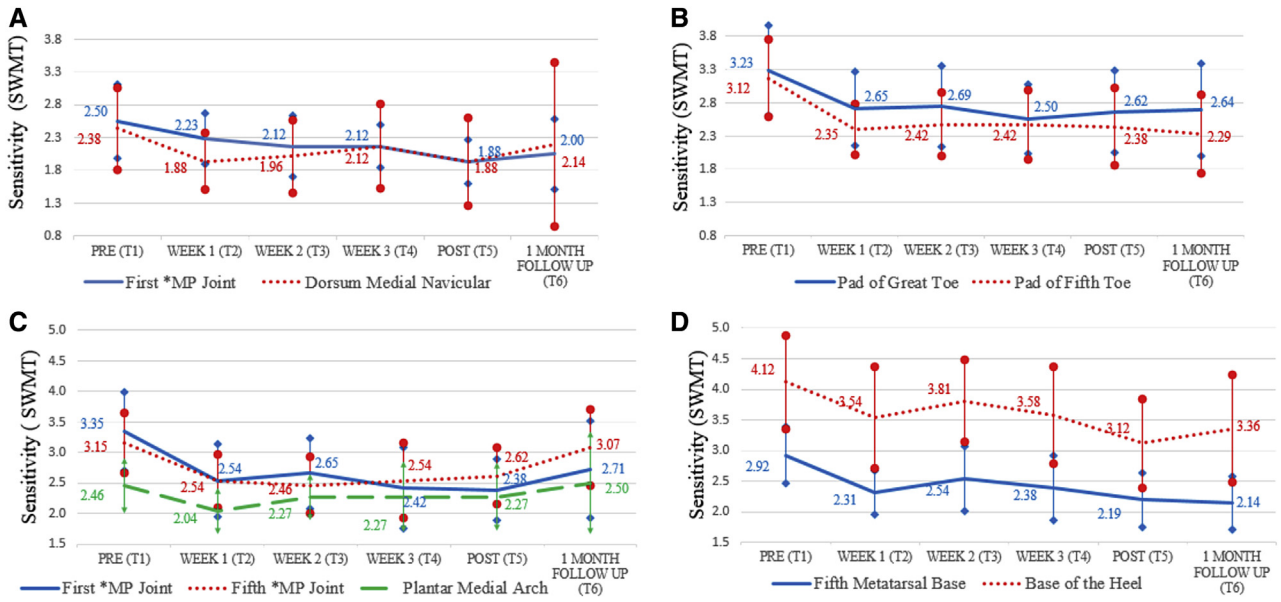

Figure 1. Mean light touch threshold changes on the dorsal surface of lower extremities. (A) The change in SWMT score for first MP joint and dorsum medial navicular. (B) The change in SWMT score for Pad of Great Toe and Fifth Toe. (C) The change in SWMT score for first MP joint, fifth MP joint, and planta medial arch. (D) The change in SWMT score of Fifth Metatarsal base and base of the heel at preintervention (T1), weekly during intervention (T2, T3, and T4), post- (T5), and 1-month follow-up (T6). The diagram shows means ± 1 standard error. CIN = Chemotherapy-Induced Neuropathy; SWMT = Semmes-Weinstein Monofilament tests; APA = Auricular Point Acupressure; MP joint = Metacarpophalangeal joint.

171AK99MR2 Lot no. 64189581, BioPlex, BioRad, Hercules, CA. USA) at the Johns Hopkins Human Immunology Monitoring Core by a blinded technician who was not aware of the data collection time points. Luminex bead-based immunoassays were performed following the manufacturer's protocol and concentrations were determined using five-parameter log curve fits, using Bio-Plex Manager 6.0, with vendor-provided standards and quality controls. The standards and controls were in duplicate, but the samples were run in single wells. The coefficient of variability values were ≤10. The fluorescence values were taken from the median channel fluorescence of many individual beads for each target and all were multiplexed in the same well.

Table 1
Objective Outcomes of Chemotherapy-Induced Neuropathy at Pre-post and 1-Month Follow-Up After Auricular Point Acupressure

Objective Outcomes	Study Visits (Mean ± SD)			Change (T5-T1)		Change (T6-T1)	
	Pre (T1)	Post (T5)	1-M FU (T6)*	%	Effect Size	%	Effect Size
Light touch threshold (Semmes-Weinstein Monofilament Tests)							
First MTP Joint—dorsal	2.50 ± 0.94	1.88 ± 0.55	2.00 ± 0.58	−25	−0.66	−20	−0.53
Dorsum Medial Navicular	2.38 ± 1.02	1.88 ± 1.10	2.14 ± 1.35	−21	−0.49	−10	−0.24
Pad of great toe	3.23 ± 1.13	2.62 ± 1.02	2.64 ± 0.75	−19	−0.54	−18	−0.52
Pad of fifth toe	3.12 ± 0.96	2.38 ± 0.96	2.29 ± 0.64	−24	−0.77	−27	−0.86
First MTP Joint—plantar	3.35 ± 1.07	2.38 ± 0.82	2.71 ± 0.86	−29	−0.91	−19	−0.60
Fifth MTP Joint—plantar	3.15 ± 0.83	2.62 ± 0.77	3.07 ± 0.67	−17	−0.64	−3	−0.10
Plantar Medial arch	2.46 ± 0.75	2.27 ± 0.93	2.50 ± 0.91	−8	−0.25	2	0.05
Fifth Metatarsal base	2.92 ± 0.76	2.19 ± 0.72	2.14 ± 0.48	−25	−0.96	−27	−1.03
Base of the heel	4.12 ± 1.26	3.12 ± 1.21	3.36 ± 0.94	−24	−0.79	−18	−0.60
Weighted PinPrick Stimulators Test							
Index finger	3.14 ± 1.81	3.00 ± 1.74	2.43 ± 1.83	−4	−0.08	−23	−0.39
Thumb	1.76 ± 1.05	1.71 ± 0.97	1.43 ± 1.30	−3	−0.05	−19	−0.31
Middle finger	3.62 ± 1.66	3.79 ± 2.37	3.26 ± 3.00	5	0.10	−10	−0.22
Hypothenar	2.74 ± 1.78	3.23 ± 2.39	3.1 ± 2.61	18	0.28	16	0.25
Dorsum	2.63 ± 2.09	3.13 ± 2.97	2.67 ± 2.92	19	0.24	2	0.02
Conditioned Pain Modulation (cold)	−0.01 ± 0.34	0.03 ± 0.22	−0.19 ± 0.25	−400	0.12	1,800	−0.53
Pressure Pain Thresholds							
Thumb	11.13 ± 4.10	11.91 ± 3.70	12.34 ± 2.80	7	0.19	11	0.30
Trapezius	13.56 ± 7.70	15.05 ± 7.50	16.42 ± 6.81	11	0.19	21	0.37
Grip strength	54.01 ± 15.75	55.84 ± 16.44	55.94 ± 16.88	3	0.12	4	0.12
Pinch Test							
Key pinch	4.92 ± 2.02	5.21 ± 2.00	5.58 ± 1.19	6	0.14	13	0.33
Tripod pinch	4.22 ± 1.60	4.51 ± 1.75	5.05 ± 1.42	7	0.18	20	0.52
Tip-to-tip pinch	3.10 ± 1.00	3.74 ± 2.25	4.35 ± 2.85	21	0.64	40	1.25

SD = standard deviation; 1-MFU = 1-month follow-up; (−%) = decreasing; (%) = mean increasing; MTP = metatarsophalangeal; pad of great toe (i.e., plantar side of hallux or big toe); pad of fifth toe (i.e., plantar side of most lateral toe); middle finger (i.e., anterior side of third phalange).
* Repeated measures one-way analysis of variance.

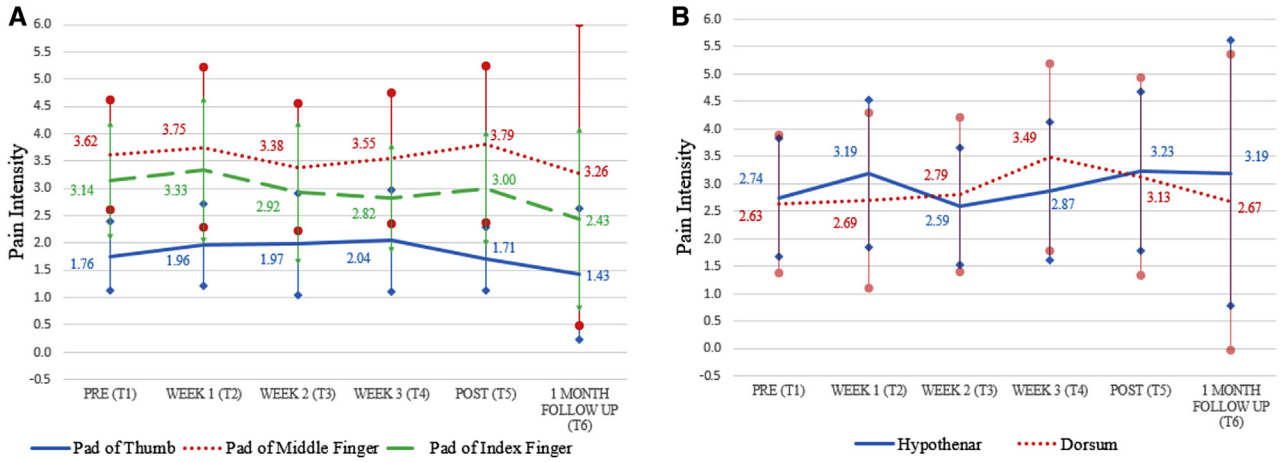

Figure 2. Mean perceived pain intensity score changes during the suprathreshold pinprick stimuli testing on hand. (A) The change in pain intensity for pad of thumb and pad of middle finger. (B) The change in pain intensity in hypothenar and dorsum at preintervention (T1), weekly during intervention (T2, T3, and T4), postintervention (T5), and 1-month follow-up (T6). The diagram shows means ± 1 standard error. CIN = Chemotherapy-Induced Neuropathy; APA = Auricular Point Acupressure.

Procedure

At each study visit for APA, participants completed the self-reported questionnaires (see part 1 of this report), sensory testing procedures, grip strength, and pinch test. Participants' peripheral blood samples, approximately 15 mL, were collected using standard phlebotomy procedures at pre-APA (T1), post-APA (T5), and 1-month follow-up (T6). Tubes containing blood samples were labeled with the participant's ID number and time of collection. After collection, the tubes were centrifuged at 3,000 revolutions per minute for 10 minutes, and the plasma was transferred into 0.5 mL polypropylene microcentrifuge tubes and stored at −70 °C until batch assayed. Participants received the APA treatment, which was provided by the first author (C.H.Y.).

Analysis

Descriptive analyses were used to describe the data collected from the study outcomes measures. Such variables included cytokines, neuropeptide, pain intensity, and physical functions. The percentage change scores were also calculated by dividing the raw change score by the prescore and multiplying by 100. We used a cutoff point of 30% improvement in primary outcomes to determine whether the mean score change reached clinical significance (Dworkin et al., 2008). A Wilcoxon matched pairs signed-rank test was conducted to determine the biomarker level differences between pre-APA (T1), post-APA (T5) and pre-APA (T1), and 1-month follow-up (T6). We used Spearman's ρ correlation coefficient to examine the linear association of the changes score of cytokines and clinical outcomes from pre–APA treatment to post–APA treatment. Because of the small sample size, statistical significance was not examined, but the *p* value was presented. We performed all data analyses using SPSS software Version 24 (IBM Corp., Armonk, NY, USA).

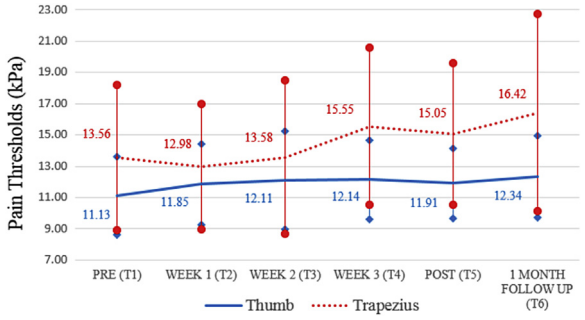

Figure 3. Mean pressure pain thresholds on thumb and trapezius changes. Diagram shows the mean change ±1 standard error of the pressure pain thresholds measured by the digital force gauge in the trapezius and thumb (distal interphalangeal joints) and trapezius areas at preintervention (T1), weekly during intervention (T2, T3, and T4), postintervention (T5), and 1-month follow-up (T6). CIN = Chemotherapy-Induced Neuropathy; APA = Auricular Point Acupressure; kPa = kilopascal.

Results

Participants

Our sample included 15 participants, although 2 participants dropped out of the study because of new medical issues after they received the first APA treatment (see Part 1 of this report). Data from the remaining 13 participants were used for analysis.

QST Results

Light Touch Sensation

Figure 1 presents the weekly change patterns of feet sensations after APA. Compared with pre-APA, the mean score of the monofilament for each tested site all decreased, indicating that the participants had better sensations in their feet (Table 1). At the two dorsal sites tested on the foot, the mean percentage change was 25% in the first metacarpophalangeal joint and 21% in the dorsum medial navicular. On the plantar side of the foot, the first metacarpophalangeal joint had the largest decreased score (29%) at post-APA. In general, the effects of APA on both feet were sustained at 1-month follow-up.

Mechanical Pain Threshold

The suprathreshold pinprick stimuli mean scores were increased from pre-APA to post-APA, except the scores from the index finger and thumb, indicating increased pain threshold (Table 1). After the 4-week APA, the mean percentage change scores decreased by 19% at the dorsum, 18% at the hypothenar, and 5% at the pad of the middle finger compared with the pre-APA intervention. Figure 2 presents the mean change patterns for the weekly change patterns of pain threshold on the hand after APA.

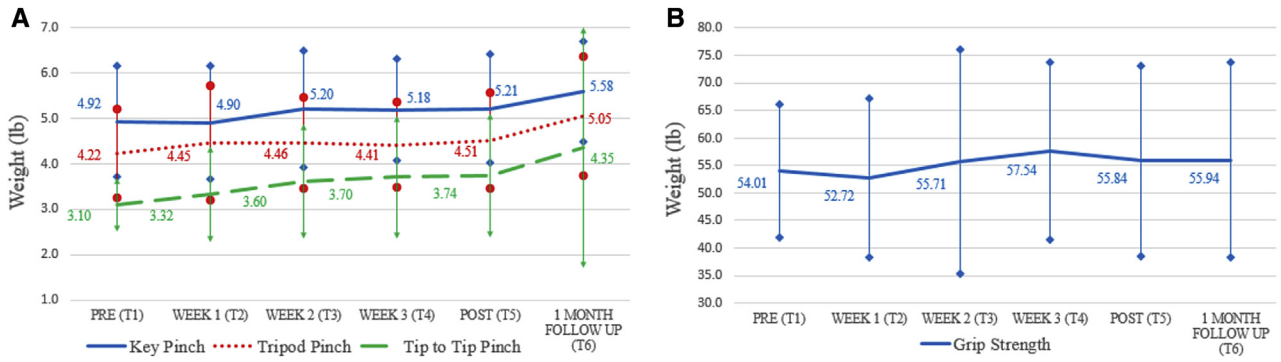

Figure 4. Mean patterns of grip strength and pinch score changes. (A) The mean change ± 1 standard error in weight forces (lb) of the key pinch, tripod pinch, and tip to tip pinch strength. (B) The mean change ± 1 standard error in weight forces (lb) of the hand grip strength at preintervention (T1), weekly during intervention (T2, T3, and T4), post-intervention (T5), and 1-month follow-up (T6). CIN = Chemotherapy induced Neuropathy; APA = Auricular Point Acupressure.

Pressure Pain Thresholds

The pressure pain thresholds for thumb and trapezius increased after 4 weeks of APA, indicating increased pain threshold in the thumb and trapezius (Table 1). The effects of APA lasted at the 1-month follow-up. Figure 3 presents the weekly change patterns of PPT on the thumb and trapezius areas.

Grip and Pinch Strength

Grip strength increased after 4 weeks of APA and was sustained at the 1-month follow-up (Table 1). Pinch tests (key pinch, tripod pinch, tip-to-tip pinch) increased after 4 weeks of APA and continued to improve at the 1-month follow-up (Fig. 4).

Inflammation

Compared with pre-APA (T1), there was a significant decrease in IL-1β.

($Z = -1.96$, $p = .05$), interferon-γ ($Z = -2.33$, $p = .02$), IL-2 ($Z = -2.19$, $p = .03$), IL-6 ($Z = -1.96$, $p = .05$), IL-10 ($Z = -1.96$, $p = .05$), and IP10/CXCL10 ($Z = -2.07$, $p = .04$) after 4 weeks of APA (T5) (Table 2). There was a significant decrease in eotaxin/CCL11 ($Z = -2.07$, $p = .04$), fractalkine/CX3CL1 ($Z = -2.07$, $p = .04$), and MIP1aCCL3 ($Z = -1.96$, $p = .05$) at the 1-month follow-up (T6) compared with pre-APA (T1).

Correlations of Score Changes Between Outcomes

The maximum score of CIN symptoms was chosen in order to examine the correlations of score changes between self-reported and laboratory-assessed outcomes. Toes' intensity, including pain, numbness, tingling, and stiffness, had the highest score compared with other body parts, so they were used to examine the correlations with QST and inflammatory cytokines (Table 2).

At the mean change of pre-APA (T1), compared with post-APA (T5; Table 3), moderate correlations ($0.3 \leq r \leq 0.7$) were found between CPM and pain, $r = 0.55$; CPM and tingling, $r = 0.59$; CPM and pain intensity, $r = 0.48$; foot sensory and tinging, 0.61; CMP and IL-1β, $r = 0.53$ using the mean change in scores, pre-APA (T1) to post-APA (T6; Table 3).

At pre-APA, compared with the 1-month follow-up (T6; Table 4), moderate correlations ($0.3 \leq r \leq 0.7$) were found in the fingers' pain threshold and pain interference ($r = 0.44$); CPM with numbness, tingling, stiffness; interferon-γ with pain interference ($r = 0.90$); IL-2 with numbness ($r = 0.59$), tingling ($r = 0.72$), and stiffness ($r = 0.51$); and IL-6 with pain ($r = 0.57$), numbness ($r = 0.47$), and tingling ($r = 0.59$).

Discussion

To our knowledge, this is the first study to use laboratory measures, including QST, inflammatory biomarkers, grip strength, and pinch strength, to evaluate the effectiveness of APA on CIN. The strength of our study is the use of both subjective, such as self-report measures, presented in Part 1, and laboratory data to complement and enhance our understanding of CIN measurements to evaluate APA treatment outcomes. The study findings indicate that the use of APA to manage CIN is promising. After 4 weeks of APA, CIN patients had improved sensation in their lower extremities, improved pain threshold on their upper extremities, increased pressure pain thresholds, and increased grip as well as pinch strength. Interpretation of our study findings is limited by the small sample size, lack of a sham control group, and the inability to control for treatment-related or psychological placebo effects.

Our QST findings suggest that APA may activate neuronal signaling at the peripheral and central nervous system. Based on our SWMT findings, the lower extremity testing sites appeared to regain sensory discrimination after the first week of APA, from data on weekly assessments, after 4 weeks of APA, and at the 1-month follow-up, indicating that APA may reduce numbness—a prime characteristic of neuropathic pain. At the same time, concurring with a previous study (Santoro et al., 2015), both pain tolerance and clinical outcomes, as reported in Part 1 study, improved after 4 weeks of APA. These effects lasted through a 1-month follow-up assessment, indicating that APA may modulate nerve sensitivity, transmitting APA stimuli into neuronal signals to modulate CIN pain and symptoms within the central nervous system.

Consistent with previous pilot studies (Lin et al., 2015; Yeh et al., 2014a,b, 2017), APA altered the inflammatory response, potentially mediating CIN symptom relief. CIN is believed to be caused by the activation of the innate immunity orchestrated by various proinflammatory mediators such as TNF-α, IL-1β, IL-2, IL-10, and monocyte chemoattractant protein 1 (MCP-1) after chemotherapy (Zhang et al., 2016). These inflammatory cytokines can directly stimulate and sensitize A and C fibers, leading to spontaneous discharge from these fibers, causing allodynia and hyperalgesia in CIN (Zhang et al., 2016). Evidence indicates that signal blockade of TNF-α, IL-1β, IL-6, MCP-1/C-C motif chemokine ligand 2 (CCL2), and macrophage inflammatory protein-1 α (MIP-1a)/CCL3 can reverse the CIN hypersensitivity mechanism (Li et al., 2014). Similar to other studies, acupuncture and acupressure can reduce inflammation (Qi et al., 2014; Yeh et al., 2017). The significant reductions

Table 2
Inflammatory Cytokines and Chemokines Level in Plasma Pre-post and 1-Month Follow-Up After Auricular Point Acupressure

	Study Visits (Mean ± SD)			Change (T5-T1)*		Change (T6-T1)*	
	Pre (T1)	Post (T5)	1-M FU (T6)	%	Effect Size	%	Effect Size
Proinflammatory Cytokines							
IL-1β	2.35 ± 0.92	2.14 ± 0.67	2.08 ± 0.69	−9	−0.23	−11	−0.29
IL-2	26.62 ± 6.13	15.43 ± 10.67	20.61 ± 5.96	−42	−1.83	−23	−0.98
IL-6	21.47 ± 6.18	14.66 ± 9.18	19.12 ± 7.02	−31	−1.10	−11	−0.38
TNF-α	23.07 ± 4.70	19.88 ± 4.19	19.58 ± 3.74	−14	−0.68	−15	−0.74
IFN-γ	65.29 ± 14.82	56.11 ± 13.76	50.71 ± 23.63	−14	−0.62	−22	−0.98
Anti-inflammatory Cytokines							
IL-4	15.53 ± 7.07	12.91 ± 6.62	22.53 ± 10.85	−17	−0.37	45	0.99
1L-10	67.14 ± 16.52	42.93 ± 20.85	46.17 ± 16.61	−36	−1.47	−31	−1.27
Chemokines							
6Ckine/CCL21	4,533.30 ± 1,534.87	3,667.93 ± 1,159.38	3,604.09 ± 1,149.34	−19	−0.56	−21	−0.61
BCA-1/CXCL13	25.72 ± 35.18	15.72 ± 5.13	14.83 ± 4.51	−39	−0.28	−42	−0.31
CTACK/CCL27	1,143.69 ± 654.30	910.34 ± 193.71	898.95 ± 209.49	−20	−0.36	−21	−0.37
ENA-78/CXCL5	696.12 ± 474.88	784.75 ± 515.19	765.67 ± 482.48	13	0.19	10	0.15
Eotaxin/CCL11	38.03 ± 13.52	29.01 ± 4.65	28.66 ± 4.32	−24	−0.67	−25	−0.69
Eotaxin-2/CCL24	277.63 ± 209.77	224.62 ± 168.89	222.45 ± 162.51	−19	−0.25	−20	−0.26
Fractalkine/CX3CL1	284.44 ± 169.62	218.15 ± 108.80	212.94 ± 111.09	−23	−0.39	−25	−0.42
GCP2/CXCL6	65.23 ± 37.39	65.93 ± 33.86	63.99 ± 36.19	1	0.02	−2	−0.03
GM-CSF	35.16 ± 26.51	55.72 ± 14.94	59.53 ± 25.95	58	0.78	69	0.92
Gro-a/CXCL1	185.93 ± 79.96	165.31 ± 67.01	158.89 ± 66.67	−11	−0.26	−15	−0.34
Gro-b/CXCL2	856.86 ± 363.76	779.69 ± 330.59	738.55 ± 335.34	−9	−0.21	−14	−0.33
I-309/CCL1	28.25 ± 16.94	36.23 ± 2.56	36.44 ± 3.15	28	0.47	29	0.48
IL-8/CXCL8	11.16 ± 6.34	7.32 ± 5.01	8.95 ± 3.27	−34	−0.61	−20	−0.35
IL-16	759.92 ± 539.18	919.99 ± 1,078.92	611.52 ± 359.85	21	0.30	−20	−0.28
IP-10/CXCL10	188.34 ± 141.30	121.19 ± 41.57	122.06 ± 41.45	−36	−0.48	−35	−0.47
I-TAC/CXCL11	54.21 ± 36.61	38.03 ± 24.07	35.37 ± 23.50	−30	−0.44	−35	−0.51
MCP-1/CCL2	32.55 ± 15.03	24.91 ± 2.25	24.83 ± 2.36	−24	−0.51	−24	−0.51
MCP-2/CCL8	29.72 ± 14.29	24.37 ± 9.06	24.33 ± 10.53	−18	−0.37	−18	−0.38
MCP-3/CCL7	80.98 ± 30.04	75.91 ± 22.34	73.39 ± 18.99	−6	−0.17	−9	−0.25
MCP-4/CCL13	92.69 ± 25.38	91.24 ± 39.21	89.62 ± 37.27	−2	−0.06	−3	−0.12
MDC/CCL22	753.34 ± 332.47	809.66 ± 356.06	798.36 ± 357.61	7	0.17	6	0.14
MIF	4,271.93 ± 4,091.51	3,766.61 ± 1,745.27	3,536.12 ± 1,835.52	−11	−0.12	−17	−0.18
MIG/CXCL9	322.86 ± 8.61	208.70 ± 104.66	204.59 ± 104.53	−35	−0.47	−37	−0.49
MIP-1a/CCL3	8.61 ± 1.42	7.50 ± 1.08	7.41 ± 1.06	−13	−0.78	−14	−0.85
MIP-1d/CCL15	3,460.50 ± 1,304.23	2,799.28 ± 503.62	2,761.65 ± 493.03	−19	−0.51	−20	−0.54
MIP-3a/CCL20	22.31 ± 32.60	10.24 ± 4.42	9.98 ± 4.53	−54	−0.37	−55	−0.38
MIP-3b/CCL19	298.21 ± 182.24	254.96 ± 131.43	246.50 ± 132.78	−14	−0.24	−17	−0.28
MPIF-1/CCL23	271.34 ± 273.49	253.67 ± 114.30	243.80 ± 109.12	−7	−0.06	−10	−0.10
SCYB16/CXCL16	532.35 ± 281.58	418.58 ± 87.46	412.92 ± 93.73	−21	−0.40	−22	−0.42
SDF-1a+b/CXCL12	1,837.28 ± 745.45	1,540.19 ± 291.23	1,535.87 ± 290.18	−16	−0.40	−16	−0.40
TARC/CCL17	190.73 ± 181.69	140.89 ± 123.60	133.51 ± 125.77	−26	−0.27	−30	−0.31
TECK/CCL25	381.55 ± 147.72	336.88 ± 97.74	331.12 ± 96.84	−12	−0.30	−13	−0.34

SD = standard deviation; 1-MFU = 1-month follow-up; (−%) = decreasing; (%) = mean increasing; IL = interleukin, TNF = tumor necrosis factor; IFN = interferon; 6Ckine/CCL21 = C-C motif chemokine ligand 21; BCA-1/CXCL13 = C-X-C motif chemokine 13 precursor; CTACK/CCL27 = cutaneous T-cell attracting chemokine; ENA-78/CXCL5 = C-X-C motif chemokine 5 precursor; eotaxin/CCL11 = exotoxin precursor; eotaxin-2/CCL24 = C-C motif chemokine ligand 24; Fractalkine/CX3CL1 = fractalkine isoform 1 precursor; GCP2/CXCL6 = C-X-C motif chemokine 6 precursor; GM-CSF = granulocyte-macrophage colony-stimulating factor precursor; Gro-a/CXCL1 = growth-related protein α/C-X-C motif chemokine ligand 1; Gro-b/CXCL2 = growth-related protein β/C-X-C motif chemokine ligand 2; I-309/CCL1 = C-C motif chemokine ligand 1; IL-8/CXCL8 = C-X-C motif chemokine ligand 8; IP-10/CXCL10 = C-X-C motif chemokine ligand 10; I-TAC/CXCL11 = C-X-C motif chemokine ligand 11; MCP-1/CCL2 = C-C motif chemokine ligand 2; MCP-2/CCL8 = C-C motif chemokine ligand 8; MCP-3/CCL7 = C-C motif chemokine ligand 7; MCP-4/CCL13 = C-C motif chemokine ligand 13; MDC/CCL22 = C-C motif chemokine ligand 22; MIF = macrophage migration inhibitory factor; MIG/CXCL9 = C-X-C motif chemokine ligand 9; MIP-1a/CCL3 = C-C motif chemokine ligand 3; MIP-1 d/CCL15 = C-C motif chemokine ligand 15; MIP-3a/CCL20 = C-C motif chemokine ligand 20; MIP-3b/CCL19 = C-C motif chemokine ligand 19; MPIF-1/CCL23 = C-C motif chemokine ligand 23; SCYB16/CXCL16 = C-X-C motif chemokine ligand 16; SDF-1a + b/CXCL12 = C-X-C motif chemokine ligand 12; TARC/CCL17 = C-C motif chemokine ligand 17; TECK/CCL25 = C-C motif chemokine ligand 25.

* Wilcoxon signed-rank test.

of the inflammatory cytokines and chemokines identified in this study support the mounting evidence that APA may provide CIN symptom relief by downregulating the expression of inflammatory cytokines and chemokines. Although the anti-inflammatory mechanism of APA is still unclear, we speculate that APA may modulate the type 1 helper T cells and macrophages in releasing cytokines and chemokines. The longitudinal pattern of the changes of these biomarkers among different time points during intervention should be further investigated.

In summary, the combination of our clinical self-reported outcomes (see Part 1 of report), QST, and inflammatory markers indicate that APA may activate neuronal signaling at the peripheral and central nervous system by stimulating the sustained release of inflammatory cytokines. In agreement with the acupuncture studies, our findings suggest that APA may produce a broad spectrum of systemic effects such as vasodilation by releasing β-endorphins to elicit short-term analgesic effects or anti-inflammatory cytokines that may explain the long-term effects (Kim et al., 2006; Zhao, 2008; Zijlstra, van den Berg-de Lange, Huygen, & Klein, 2003). Our inflammatory data support the existence of a neuroimmune pathway that interrelates the ear microsystem and somatotopic brain areas. Based on Nogier's somatotopic representation of the human body onto the ear (Nogier, 1981, 1987, 2014), specific points of the ear correspond to specific organs and areas of the body. By stimulating these points, symptomatic parts of the body can be treated. The underlying theory of auricular acupuncture posits that

Table 3
Spearman Correlation Coefficients Among Self-Report and Objective Outcomes, Mean Score Change From Pre (T1) to Post (T5)

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1. Pain	–																			
2. Numbness	0.51	–																		
3. Tingling	0.46	0.78*	–																	
4. Stiffness	0.63	0.89*	0.77*	–																
5. Pain Interference	−0.07	−0.04	0.33	0.08	–															
6. FACT-9	−0.08	0.27	0.34	0.09	0.07	–														
7. Index Function	−0.35	−0.65†	−0.31	−0.55	0.34	−0.03	–													
8. Dash	0.32	0.15	0.20	0.15	−0.44	0.60	−0.29	–												
9. Middle Finger	−0.02	0.31	0.27	0.29	−0.43	−0.51	−0.45	0.00	–											
10. CPM Change	0.16	0.40	0.52	0.45	0.00	−0.39	−0.21	−0.18	0.79†	–										
11. Pad of Great Toe	0.36	0.08	−0.14	0.11	−0.16	0.23	−0.20	0.22	−0.66	−0.49	–									
12. Pad of Fifth Toe	0.15	−0.02	−0.02	0.00	0.13	0.75	0.30	0.26	−0.87†	−0.75	0.72	–								
13. First MP Joint- Plantar	0.79†	0.68	0.7†	0.76†	0.13	0.35	−0.19	0.22	−0.09	0.40	0.34	0.20	–							
14. IP-10/CXCL10	−0.11	−0.49	0.14	−0.16	0.29	0.00	0.20	0.36	0.10	−0.30	−0.80	−0.36	−0.71	–						
15. IFN-γ	0.31	0.05	0.05	0.30	−0.90†	−0.10	−0.56	0.70	0.80	0.40	−0.80	−0.60	−0.26	0.50	–					
16. IL-1β	−0.14	−0.37	0.14	−0.10	0.59	0.10	0.03	0.267	0.03	0.09	−0.55	−0.49	−0.39	.96*	0.50	–				
17. IL-2	0.07	0.59	0.72	0.51	0.11	0.29	−0.15	0.107	0.43	0.60	−0.73	−0.41	0.30	0.54	0.50	0.26	–			
18. IL-6	0.57	0.47	0.65	0.59	−0.07	−0.29	−.72†	0.214	0.77	0.77	−0.20	−0.77	0.30	0.43	0.70	0.39	0.43	–		
19. IL-10	0.12	−0.15	0.06	0.15	0.26	0.23	0.67	0.26	−0.10	−0.30	−0.50	0.15	0.00	0.43	0.10	0.31	0.43	−0.49	–	
20. IP-10/CXCL	−0.11	−0.49	0.14	−0.16	0.29	0.00	0.20	0.357	0.10	−0.30	−0.80	−0.36	−0.71	1.0*	0.50	.96*	0.54	0.43	0.43	–

FACT-9 = Functional Assessment of Cancer Therapy-9; CPM = conditional pain modulation; MP = metacarpophalangeal; IP-10 = interferon-inducible protein 10; CXCL = C-X-C motif chemokine ligand; IFN = interferon; IL = interleukin.

* $p \leq .01$.

† $p \leq .05$.

Table 4
Spearman Correlation Coefficients Among Self-Report and Objective Outcomes, Mean Score Change From Preintervention (T1) to 1-Month Follow-Up (T6)

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1. Pain	–																			
2. Numbness	0.55*	–																		
3. Tingling	0.47	0.71†	–																	
4. Stiffness	0.53	0.49	0.58*	–																
5. Pain Interference	0.24	0.17	0.38	0.31	–															
6. FACT-9	0.1	0.34	0.62*	0.27	0.4	–														
7. Index Function	−0.59*	−0.27	−0.1	−0.04	0.14	0.03	–													
8. Dash	0.06	0.09	0.29	0.39	0.26	0.69†	0.11	–												
9. Middle Finger	0.35	0.12	0.01	0.2	−0.17	−0.37	−0.36	0.07	–											
10. CPM Change	0.51	0.27	0.59*	0.19	0.48	0.32	−0.21	0.14	0.12	–										
11. Pad of Great Toe	0.14	−0.14	−0.12	0.09	0.35	0.16	−0.08	0.03	−.59*	0.04	–									
12. Pad of Fifth Toe	0.01	−0.36	−0.09	−0.22	0.22	0.23	0.05	−0.15	−.64*	0.07	0.65*	–								
13. First MP Joint- Plantar	0.22	0.29	0.61*	0.12	0.37	0.34	0.09	0.02	−0.11	0.3	0.02	0.46	–							
14. IP-10/CXCL10	−0.17	0.1	0.3	0.28	−0.39	0.43	0.49	0.46	−0.02	0.01	−0.4	−0.2	−0.08	–						
15. IFN-γ	0.49	0.03	0.03	−0.38	0.03	0.17	−0.41	0.09	0.14	0.37	0.06	0.44	0.46	−0.03	–					
16. IL-1β	0.16	−0.29	0.1	−0.05	0.29	0.1	0.03	0.11	0.08	0.53	0.37	0.38	0.35	−0.07	.89*	–				
17. IL-2	0.44	0.31	0.38	−0.05	−0.35	−0.14	−0.61	−0.38	0.56	0.3	−0.38	−0.01	0.59	−0.14	0.77	0.63	–			
18. IL-6	0.2	0.04	0.2	−0.06	−0.48	−0.21	−0.3	−0.42	0.38	0.12	−0.22	0.15	0.41	0.1	0.6	0.62	0.88†	–		
19. IL-10	0.49	0.06	0.06	−0.17	−0.52	−0.14	−0.6	−0.2	0.5	0.21	−0.08	0.21	0.33	−0.12	0.71	0.85†	0.79†	0.70*	–	
20. IP-10/CXCL	−0.17	0.10	0.3	0.28	−0.39	0.43	0.49	0.46	−0.02	0.01	−0.4	−0.2	−0.08	1.0†	−0.03	−0.07	−0.14	0.1	−0.12	–

FACT-9 = Functional Assessment of Cancer Therapy-9; CPM = conditional pain modulation; MP = metacarpophalangeal; IP-10 = interferon-inducible protein 10; CXCL = C-X-C motif chemokine ligand; IFN = interferon; IL = interleukin.

* $p \leq .05$.

† $p \leq .01$.

nerves in the outer ear correspond to specific areas of the brain and that these areas have a reflex connection with specific parts of the body (Huang, 2005; Oleson, 2014). Thus functional magnetic resonance imaging presents an opportunity to examine this hypothesis as to whether APA can excite specific brain regions to modulate CIN pain/symptoms, which should be included in future studies.

In conclusion, our study findings indicate promising effects of APA in the management of CIN. Different from body acupressure, which usually requires the application of different degrees of pressure on body points between 30-40 minutes per session, auricular points are at a superficial skin level and take less time to stimulate: Patients simply press the seeds for 3 minutes, three times per day (9 minutes total per day) to relieve CIN pain and other symptoms. The characteristics of time efficiency, active participation, and potential for immediate pain relief from APA provides patients a greater sense of control over their pain and other symptoms, allowing them to resume daily tasks that CIPN has prevented them from doing. Teaching patients the skills necessary for APA practice can be completed within 15 minutes (Yeh et al., 2013, 2014a,b). In the future, we envision teaching patients or their caregivers how to do APA treatments in their entirety (applying the seeds and subsequently stimulating them), and that evaluating the effectiveness of this eminently scalable approach will be the focus of future research.

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