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Original Article

Acupuncture May Help to Prevent Chemotherapy-Induced Peripheral Neuropathy: A Randomized, Sham-Controlled, Single-Blind Study

Ming-Cheng Huang[1,2], Sheng-Chi Chang[3], Wen-Ling Liao[4,5], Tao-Wei Ke[3,12], Ai-Lin Lee[6], Hwei-Ming Wang[13], Che-Pin Chang[2], Hung-Rong Yen[2,7,8,9], Hen-Hong Chang [*,2,4,8], William Tzu-Liang Chen[*,3,10,11]

[1]Graduate Institute of Chinese Medicine, School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
[2]Department of Chinese Medicine, China Medical University Hospital, Taichung, Taiwan
[3]Division of Colorectal Surgery, Department of Surgery, China Medical University Hospital, Taichung, Taiwan
[4]Graduate Institute of Integrated Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
[5]Center for Personalized Medicine, Department of Medical Research, China Medical University Hospital, Taichung, Taiwan
[6]All Ease Traditional Chinese Medicine Clinic, Taichung, Taiwan
[7]School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
[8]Chinese Medicine Research Center, China Medical University, Taichung, Taiwan
[9]Department of Biotechnology, Asia University, Taichung, Taiwan
[10]School of Medicine, Department of Surgery, China Medical University, Taichung, Taiwan
[11]Division of Colorectal Surgery, Department of Surgery, China Medical University Hsinchu Hospital, Zhu-Bei, Taiwan
[12]College of Chinese Medicine, China Medical University, Taichung, Taiwan.
[13]Department of Surgery, China Medical University Hospital, Taichung, Taiwan

[*]Corresponding author: Hen-Hong Chang, PhD, Graduate Institute of Integrated Medicine, College of Chinese Medicine, China Medical University, 91 Xueshi Rd, Taichung City 40402, Taiwan, ROC. Tel: +886 4 22053366 ext. 3609; tcmchh55@gmail.com; or, William Tzu-Liang Chen, MD, China Medical University Hospital, 2 Yude Rd, Taichung City 404332, Taiwan, ROC. Tel: +886 4 22052121 ext. 1638; Email: golfoma22@gmail.com

Abstract

Objective: This study investigated the efficacy of acupuncture in preventing chemotherapy-induced peripheral neuropathy (CIPN) in patients with colorectal cancer (CRC).

Methods: This single center, randomized, controlled, single-blind clinical trial randomly assigned patients with stage 3 CRC attending outpatient clinics in China Medical University Hospital to either verum or sham acupuncture treatment concurrently with chemotherapy. Primary outcomes were nerve conduction velocity (NCV) and touch thresholds of limb terminals. Secondary outcomes were total and subdomain scores on the Functional Assessment of Cancer Therapy-General (FACT-G), and scores on the FACT/GOG-Ntx subscale and the Brief Pain Inventory-Short Form (BPI-SF), at baseline, weeks 12, 36, and follow-up (week 48).

Results: Thirty-two patients met the inclusion criteria and received verum acupuncture (N = 16) or sham acupuncture (N = 16). Under the intent-to-treat principle, 26 participants were analyzed. Significant changes from baseline for questionnaire scores and sensory NCV were observed in both study groups. Sham acupuncture was associated with significant reductions from baseline in motor NCV and sensory touch thresholds; no such changes were observed with verum acupuncture. No serious adverse events were reported.

Conclusion: Prophylactic acupuncture may exert neuroprotective effects on mechanical or tactile touch thresholds during chemotherapy regimens in patients with CRC, with evidence of this protectiveness persisting at 6 months' follow-up. The lack of change in motor NCV values with verum acupuncture indicates neuroprotective effects. Sensory NCV values and patient-reported outcomes did not differ significantly between the study groups.

Key words: acupuncture; chemotherapy; peripheral neuropathy; prevention; colorectal cancer; oxaliplatin.

Implications for Practice

The results of this clinical trial indicate that acupuncture given concurrently with oxaliplatin protects against the often-debilitating chemotherapy-induced peripheral neuropathy (CIPN) in stage 3 colorectal cancer. Verum acupuncture was more protective than sham acupuncture upon touch thresholds in the prevention of CIPN. The beneficial effect of acupuncture upon the touch threshold endured for at least 6 months after completion of the intervention.

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Introduction

Oxaliplatin is a third-generation platinum-based chemotherapeutic that is commonly used in the treatment of metastatic colorectal cancer (CRC). The large multinational MOSAIC trial reported that 92.1% of the FOLFOX4 recipients had CIPN during treatment; these neuropathies were classified as grade 3 in 12.4% of the patients and were still present in 5 patients after 1 year.[1] At 48 months of follow-up, grades 1, 2, and 3 CIPN was present in 11.9%, 2.8%, and 0.7% of the FOLFOX4-treated patients.[2]

Symptoms of CIPN affect quality of life, including daily life functioning and sleep quality, causing distress, and depression in severe cases.[3-5] Data from a large population-based sample of CRC survivors 2-11 years after diagnosis found that not only were neuropathy-related symptoms still being reported, but oxaliplatin recipients more frequently reported tingling (29% vs. 8%; $P = .001$), numbness (17% vs. 5%; $P = .005$), and aching or burning pain (13% vs. 6%; $P = .03$) in the toes/feet compared with those who did not receive chemotherapy.[6] The prevalence of oxaliplatin-induced peripheral neuropathy (OXLIN) varies according to the cumulative dose of oxaliplatin, chemotherapy regimens, and dose administration schedules, as well as pharmacogenetic susceptibility.[7]

Of concern is the fact that cancer treatment is hampered when chemotherapy doses are reduced, delayed, or discontinued in response to severe acute peripheral neuropathy.[8-10] Thus, new, effective preventive and treatment strategies are crucial for the management of CIPN. Insufficient evidence supports any pharmacotherapy options for preventing CIPN.[11] One study has indicated that duloxetine, a serotonin-norepinephrine reuptake inhibitor (SSRI), can alleviate peripheral neuropathy in oxaliplatin-treated patients.[8] At a dose of 60 mg per day for 5 weeks, duloxetine can reduce neuropathic pain in patients with cancer.[12] However, almost a third (28.1%) of patients have reportedly discontinued duloxetine because of adverse events including dizziness, nausea, drowsiness, irritability, and insomnia.[13] Data also support another SSRI, venlafaxine, for the treatment and secondary prevention of OXLIN-associated acute neuropathy, while the antiepileptic pregabalin reportedly reduces the sensory symptoms of peripheral neuropathy in patients with CIPN.[14] The 2020 American Society of Clinical Oncology (ASCO) guidelines for the prevention and management of CIPN in survivors of adult cancers failed to find any evidence in support of pharmacological agents for the prevention of CIPN; there was moderate evidence in support of duloxetine for patients with established painful CIPN and the guidelines could not make any recommendations on the use of antiepileptics gabapentin or pregabalin, or tricyclic antidepressants, outside a clinical trial.[15]

Clinical evidence in support of the use of acupuncture therapy for reducing symptoms of CIPN and improving the outcomes of patients receiving chemotherapy has encouraged the use of acupuncture in the integrative oncology setting.[16-19] No effective pharmacotherapeutic strategies are available for preventing or improving CIPN, which can result in chemotherapy dose reductions, delays in treatment, and even discontinuation of chemotherapy. These limitations greatly affect patient outcomes and overall survival. This randomized, sham-controlled, single-blind study investigated the efficacy of acupuncture in the prevention of CIPN.

Materials and Methods

This trial used a single center, randomized, controlled, and single-blind study design. The Institutional Review Board of China Medical University Hospital reviewed and approved the study protocol in 2015 (CMUH104-REC1-076). The protocol registration number of this study is NCT02744274 and is accessible from the ClinicalTrials.gov website (https://clinicaltrials.gov/ct2/show/NCT02744274). Prior to enrollment, the study coordinator fully explained the study procedures to the participants, who were enrolled into the trial after signing informed consent forms.

Participants

The study physician invited patients with CRC attending the clinics of the Department of Chinese Medicine or Division of Colorectal Surgery in China Medical University Hospital between January 1, 2016 and April 30, 2019 to enroll in this study. The study coordinator explained the details of the trial to each patient. Inclusion and exclusion criteria were defined as follows:

Inclusion Criteria

1. Patients diagnosed with stage 3 CRC.
2. Patients scheduled to receive oxaliplatin-based chemotherapy.
3. Patients were willing to cooperate with physicians and receive a full course of chemotherapy.
4. Patients were willing to receive acupuncture treatments and follow-up assessments.
5. Adults aged between 20 and 70 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Exclusion Criteria

1. Were currently receiving chemotherapy or radiotherapy, or had undergone tumor resection surgery in the past month.
2. Had undergone chemotherapy with neuropathic agents including taxanes, platinum compounds, vinca alkaloids, bortezomib, or thalidomide in the past 6 months.
3. Local infection at or near the acupuncture site meant that the patient was not suitable for acupuncture, as determined by a physician's examination.
4. Concurrent use of alternative medicines such as herbal agents, high-dose vitamins, and minerals.
5. Patients with known coagulopathy or were taking anticoagulants.
6. Platelets <50,000/μL.
7. White blood cells <3000/μL.
8. Known active central nervous system (CNS) involvement.
9. Cardiac pacemaker.
10. Psychological or behavioral disorders including schizophrenia.
11. Were pregnant or breastfeeding.
12. History of diabetic neuropathy or neuropathy related to HIV infection.
13. Previous acupuncture treatment for any indication within 30 days of enrollment.

14. Current medications that could affect symptoms related to CIPN.
15. Grade III lymphedema or more severe situation, ie, systematic edema arising from cardiogenic or nephrogenic disease.

Randomization

Patients eligible for this study were all assigned the same chemotherapy schedule and were randomly allocated to the verum acupuncture group or sham acupuncture group in a 1:1 ratio using a permuted block design with a computer random number generator. The allocation was sealed in the opaque envelope and kept by the study coordinator. Prior to the first intervention, the coordinator opened the envelope and informed the acupuncturist of the patient's assignment.

Blinding

The study participants, assessor, and statistician were all blinded to the treatment assignments; only the acupuncturist and study coordinator were aware of these details.

Safety Assessments

The study coordinator monitored treatment-related adverse events via standard adverse event (AE) reporting throughout the study. The surgeons administered physical examinations including body weight, ECOG, and blood biochemical examinations that included a complete blood count and differential count, absolute neutrophil count, aspartate aminotransferase, alanine aminotransferase, creatinine, erythrocyte sedimentation rate, and C-reactive protein (CRP) values prior to each chemotherapy treatment.

Interventions

All verum and sham acupuncture sessions were performed by one acupuncturist with more than 3 years of clinical experience and licensed by central government health authorities. The acupuncturist could answer questions from the participants about management of CIPN-related symptoms during daily life, but not identify which acupuncture intervention the participant was receiving. The patients received bi-weekly verum or sham acupuncture within the weeks that they were scheduled to receive standard oxaliplatin-based chemotherapy chemotherapeutic agents. The interventions were administered before and 2 days after the chemotherapy session. If the chemotherapy was stopped, the acupuncture intervention was also discontinued. In addition to exercise, all the participants were asked to avoid the acupuncture, herbs, vitamin/mineral supplements, medication for CIPN such as duloxetine in the follow-up period (Supplementary Fig. S1).

Verum Acupuncture Group

Participants were in the supine position. The acupuncturist disinfected the skin of the selected acupoints with alcohol, then vertically penetrated the skin with disposable stainless steel needles (0.30 mm × 40 mm, Yuguang, Taiwan) to the depth predetermined for each point (between 8 mm and 25 mm, depending on the location of the acupoint) and achieved a "*de qi*" response, usually described as a pressure or achiness feeling around the acupoints. The selected acupoints for this study were bilateral LI4, LI11, SJ5, LR3, ST36, SP6, GB34, Baxie, and Bafeng. The acupuncture treatment regimen was decided by consensus between 2 of the study authors (H.-H.C. and M.-C.H.) according to their expertise in traditional Chinese medicine based on Chinese medicine theory, personal experience, and the published literature. Needle retention time was 30 minutes, during which the acupuncturist twisted needles every 10 minutes for the *de qi* sensation.

Sham Acupuncture

This study used a sham acupuncture needle, the Streitberger device, with a blunt tip. When the acupuncturist positioned the needle onto the skin, the needle failed to penetrate the skin and instead retracted into the handle of the device. This device has been designed to mimic the sensation of needling pricking the skin at the relevant treatment acupoints and thus persuade recipients to believe that they are receiving acupuncture treatments. The needles were fixed with a plastic ring and micropore on the body of the participants for 30 minutes without manipulation to avoid the sensations other than the initial contact on the skin. The selected acupoints, retention time of the needle, number of treatment sessions, treatment frequency, and duration were the same as those for the verum acupuncture group.

Outcome Measurements

The nerve conduction velocity (NCV) and von Frey monofilament tests served as primary outcome measurements in the assessment of nerve impairment along motor and sensory fibers. Questionnaires included the Functional Assessment of Cancer Therapy-General (FACT-G, used to assess a patient's general condition) and 2 specific questionnaires on CIPN symptoms, the FACT/GOG (Gynecologic Oncology Group) Neurotoxicity (Ntx) subscale and Brief Pain Inventory-Short Form (BPI-SF), as secondary outcome measurements. The questionnaires, NCV, and von Frey monofilament examinations were completed at baseline (visit 1), week 12 (visit 2), week 24 (visit 3), week 36 (visit 4), and week 48 (visit 5) after initiation of the study intervention.

No gold standards exist for the assessment of CIPN, although clinicians commonly use nerve conduction studies (NCS) to grade CIPN.[20,21] Skin surface electrodes were used to record motor and sensory nerve conduction. Motor conduction velocity was studied in the bilateral median, ulnar, peroneal, and tibial nerves. Sensory conduction velocity was tested in the bilateral median, ulnar, radial, and sural nerves.

To determine touch-detection thresholds, we used von Frey monofilaments (Semmes-Weinstein) in an up/down manner,[22] beginning with a bending force of 0.02 g. Each von Frey monofilament was applied to the skin for approximately 1 s. If the participant failed to detect the stimulus, the next higher force monofilament was applied to the same location. When the patient detected the stimulus given, the next lower von Frey was applied to the skin. Monofilaments were administered in this manner until the same filament was detected for 3 consecutive applications and assigned as the touch-detection threshold.

Data Analysis

Data analysis was conducted using SPSS software v. 21.0 for Windows (IBM, Armonk, NY, USA). Patients' clinical characteristics were evaluated by descriptive analysis using mean values and standard deviations for continuous outcomes, and frequencies and percentages for categorical data. Categorical variables were compared between the 2 groups using the chi-square test or Fisher's exact test. Continuous variables such as between-group differences between responses on the

questionnaires, NCS measurements, and von Frey monofilament values were compared using the Mann-Whitney *U* test, while baseline comparisons across all measurement points were examined with the Wilcoxon signed-rank test. A *P*-value of < .05 was considered statistically significant. The intention-to-treat (ITT) analysis was performed in all statistical analyses.

Results

The study recruited 106 patients attending CMUH Colorectal Surgery outpatient clinics from January 2016 to April 2019. Seventy-four patients were excluded majorly because of diabetes neuropathy, herbs use, vitamin/mineral supplements use, neoadjuvant chemotherapy, or rejection of participation. Thirty-two patients satisfied all inclusion criteria and were enrolled. In the verum acupuncture group, 3 patients did not receive the assigned intervention: 1 withdrew because of the commuting distance from home to hospital; 1 withdrew because of the time schedule; and 1 withdrew to receive cancer-related therapy at another hospital. Three patients in the sham control group did not have the allocated intervention: 1 withdrew because of the commuting distance; 1 rejected the chemotherapy; and 1 refused to comply with study procedures. Two patients in the verum acupuncture group were lost to follow up due to death after rapid disease deterioration. In the sham acupuncture group, 1 patient was lost to follow up after receiving other treatment for tumor metastasis. Finally, 26 patients were included in the ITT analysis (see Fig. 1).

Table 1 shows the baseline characteristics of patients in each study group. The median age was 52 years for each group; gender ratios did not differ significantly. Vital signs (body temperature, heart rate, systolic, and diastolic blood pressure) were similar between the groups. Administered oxaliplatin dosages did not differ significantly between the groups. Subdomain scores on the FACT-G questionnaire and FACT/GOG-Ntx subscale were not significantly different between the groups. Scores for the BPI-SF domains assessing the interference of pain on functioning and the severity of pain were not notably different between the 2 groups.

Administered chemotherapy cycles for each acupuncture group are shown in Table 2. The majority (92.3% of sham acupuncture recipients and 84.6% of verum acupuncture recipients) had 8 or more cycles of chemotherapy; approximately half of each group received 12 cycles.

No significant between-group differences were observed for the changes from baseline in FACT questionnaire subdomain scores at weeks 24, 36, or 48 (all $P > .05$). At weeks 24, 36, or 48, FACT/GOG-Ntx scores were not significantly different from baseline in either group (all $P > .05$). Changes from baseline in scores on the BPI-SF domains assessing the interference of pain on functioning and the severity of pain did not differ markedly between the study groups at weeks 24, 36, or 48 (all $P > .05$) (Supplementary Table S1).

As shown in Supplementary Table S2, no significant between-group differences were observed in the median changes from baseline at weeks 24, 36, and 48 in NCV values

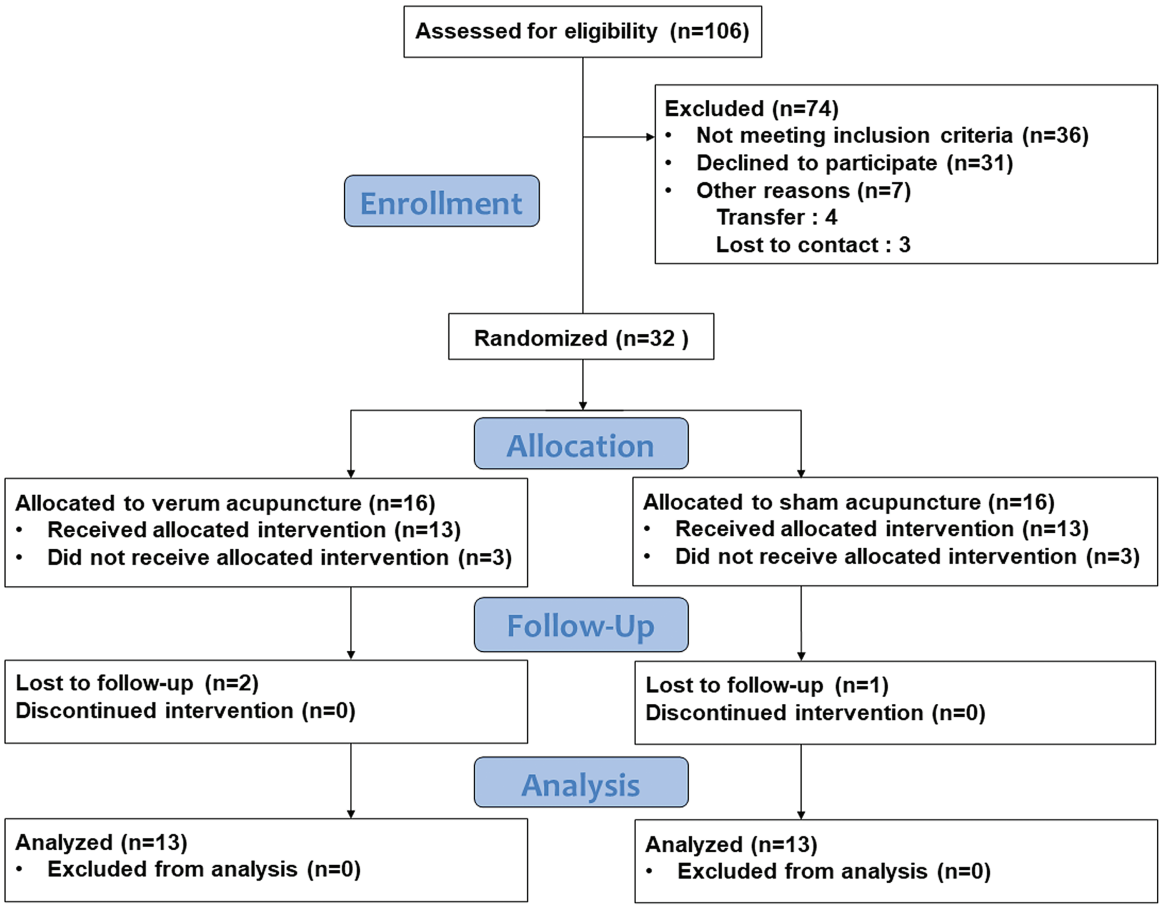

Figure 1. Flow diagram of the study participants.

Table 1. Clinical characteristics of colorectal cancer patients in the verum and sham acupuncture groups.

	Sham (*N* = 13)	Verum (*N* = 13)	*P*-value
Age	52.0 (40.0, 57.0)	52.0 (36.5, 53.0)	.487
Gender			.420
Male	6 (46.2%)	4 (30.8%)	
Female	7 (53.8%)	9 (69.2%)	
Vital sign			
Body temperature	36.6 (35.9, 36.9)	36.4 (36.3, 36.7)	.877
Heart rate	86.0 (75.0, 98.5)	83.0 (70.5, 88.5)	.182
SBP	114.0 (102.5, 123.0)	127.0 (104.0, 137.5)	.112
DBP	76.0 (66.5, 86.0)	75.0 (64.5, 85.5)	.817
Oxaliplatin dosage			
Times	12.0 (8.0, 12.0)	10.0 (8.0, 12.0)	.783
Dose	146.0 (130.0, 160.0)	138.5 (125.5, 149.8)	.367
FACT-G			
Physical well-being score	1.0 (0.0, 2.0)	0.0 (0.0, 4.0)	.828
Social/family well-being score	35.0 (31.5, 47.8)	45.5 (29.8, 50.8)	.778
Emotional well-being score	5.0 (5.0, 7.5)	7.0 (4.5, 7.5)	.568
Functional well-being score	18.0 (12.0, 22.5)	17.0 (13.0, 22.5)	.980
Total	69.3 (55.2, 77.7)	74.2 (52.3, 79.0)	.720
FACT/GOG			
Neurotoxicity score	0.0 (0.0, 1.0)	0.0 (0.0, 2.5)	.428
BPI			
Pain interference score	0.0 (0.0, 0.5)	0.0 (0.0, 1.1)	.551
Pain severity score	0.0 (0.0, 1.1)	0.0 (0.0, 1.8)	.900

Values are presented as *N* (%) or medians with interquartile ranges (IQRs). *P*-values are from the chi square test or Mann-Whitney *U* test.
Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; DBP, diastolic blood pressure; FACT, The Functional Assessment of Cancer Therapy; SBP, systolic blood pressure.

Table 2. Numbers of chemotherapy cycles administered in each acupuncture study group.

Chemotherapy cycles	Sham (*N* = 13)	Verum (*N* = 13)
5	1 (7.7%)	0 (0.0%)
6	0 (0.0%)	1 (7.7%)
7	0 (0.0%)	1 (7.7%)
8	3 (23.1%)	2 (15.4%)
9	1 (7.7%)	1 (7.7%)
10	1 (7.7%)	2 (15.4%)
12	7 (53.8%)	6 (46.2%)

(all $P > .05$), including conduction of motor and sensory nerves. Sensory NCV of the left median nerve was clearly decreased from baseline at week 48, but was not statistically significant between groups ($P = .056$).

No significant between-group differences were observed for the median changes from baseline at weeks 24, 36, and 48 in the touch thresholds on von Frey testing (all $P > .05$) (Supplementary Table S3). The only values that were significantly different from baseline were the mean touch thresholds for the right big toe and index toe at week 48 in both groups ($P = .049$).

Median FACT-G Physical well-being scores were significantly increased from baseline at week 24 (visit 3) in both study groups (both $P < .01$); Social/family well-being scores were significantly decreased from baseline in both groups at visits 3, 4 (week 36) and 5 (week 48) (all $P < .01$)(Fig. 2). Emotional well-being scores were not significantly different from baseline at any time point in either group. Functional well-being scores were significantly increased from baseline at visit 4 in the sham acupuncture group ($P < .05$); no significant changes from baseline were observed for this score in the verum acupuncture group. Neurotoxicity scores were significantly increased from baseline at visits 3 and 4 in both study groups (all $P < .05$). Median total FACT-G scores were significantly decreased from baseline at visit 5 in the sham acupuncture group and at visit 2 in the verum acupuncture group (both $P < .05$).

Sham acupuncture group exhibited significant decreases from baseline in motor NCV of the right ulnar nerve at visit 3 (week 24) and of the right tibial and peroneal nerves at visit 4 (both $P < .05$) (Fig. 3). No significant changes from baseline in NCV of the left median, right median, left ulnar, left peroneal, and left tibial nerves were observed with sham acupuncture at any time point (all $P > .05$). No significant changes from baseline in motor NCV were observed at any time point with verum acupuncture (all $P > .05$).

Sham acupuncture was associated with significant decreases from baseline at visit 3 (week 24) in sensory NCV along the right ulnar ($P < .01$), right radial ($P < .01$), left ulnar ($P < .05$) and left sural nerves ($P < .05$); NCV were significantly decreased at visit 4 (week 36) along the right ulnar ($P < .05$), right radial ($P < .01$), right sural ($P < .01$) and left sural nerves

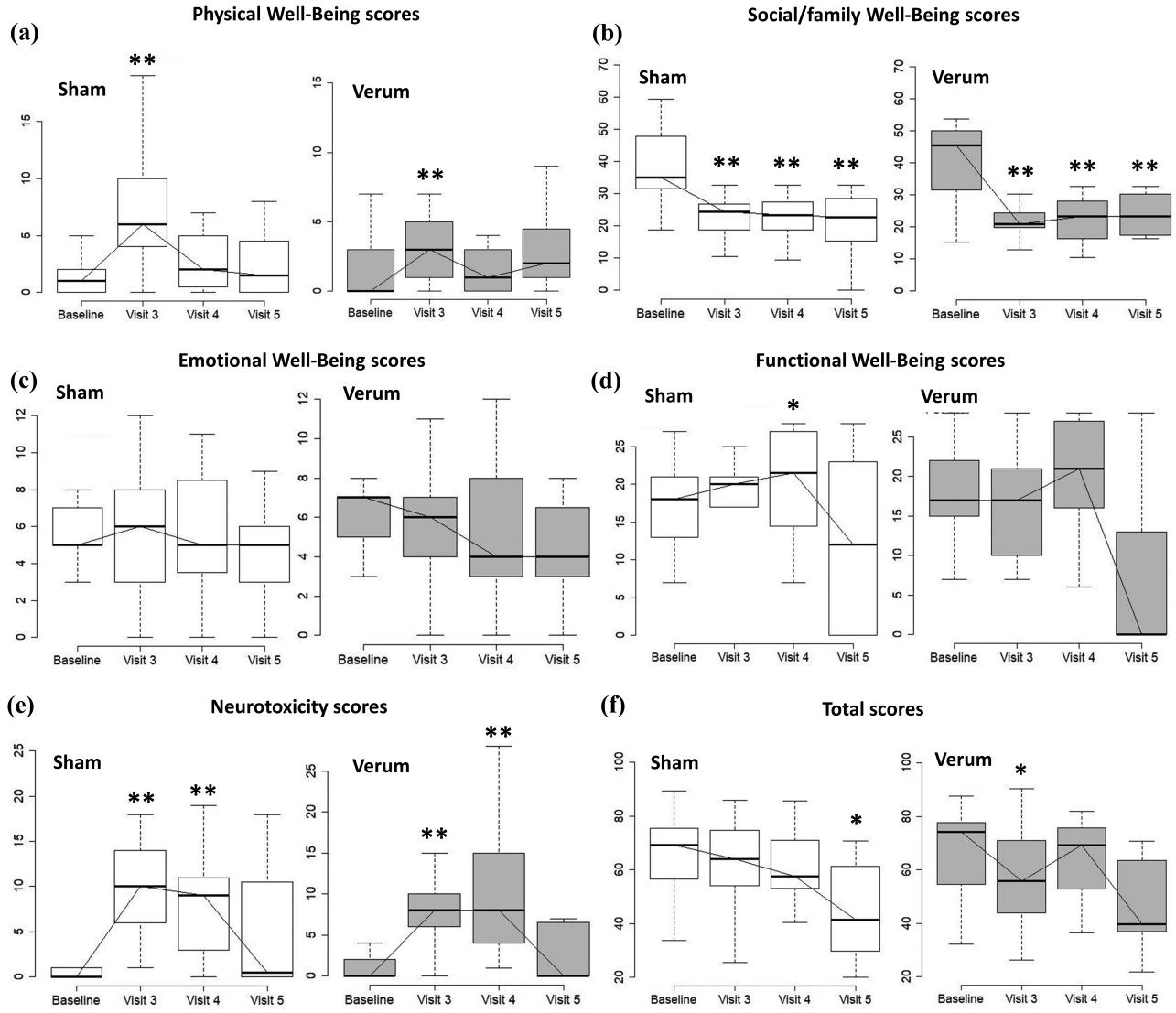

Figure 2. Changes from baseline for both acupuncture study groups at visits 3 (week 24), 4 (week 36), and 5 (week 48) in the median subdomain scores for FACT-G (**a**) Physical well-being, (**b**) social/family well-being, (**c**) emotional well-being, (**d**) functional well-being, (**e**) neurotoxicity, and (**f**) total scores. **P* < .05; ***P* < .01.

(*P* < .05) (Fig. 4). At the end of follow-up (week 48), sham acupuncture was associated with significant decreases from baseline in sensory NCV along the right ulnar (*P* < .05) and right sural nerves (*P* < .05). Verum acupuncture induced significant decreases from baseline at visit 3 (week 24) in sensory NCV along the right median (*P* < .05), left and right ulnar (both *P* < .01), left (*P* < .05) and right radial (*P* < .01), and left sural nerves (*P* < .01); significant decreases from baseline were also observed at visit 4 (week 36) in NCV along the right ulnar (*P* < .05), left (*P* < .05) and right radial (*P* < .01), and left sural nerves (*P* < .01). NCV were significantly decreased from baseline by verum acupuncture at the end of follow-up along the left and right ulnar (both *P* < .05), and left sural nerves (*P* < .05).

Von Frey monofilament assessments revealed significant increases from baseline in the sham acupuncture group at visit 3 (week 24) in mean threshold values of the right 1st, 2nd, 3rd, and 5th fingers (both *P* < .01), as well as the left 1st, 2nd and 3rd fingers (*P* < .01) and bilateral 4th and 5th toes (both *P* < .05); significant increases were also observed at visit 4 (week 36) in mean threshold values of the bilateral 1st, 2nd, 3rd and 5th fingers (all *P* < .05) and 1st, 2nd, 4th and 5th toes (*P* < .05 for left side; *P* < .01 for right side) (Fig. 5). At visit 5 (week 48), sham acupuncture was associated with significantly elevated mean thresholds in the right 1st, 2nd, 4th and 5th toes (both *P* < .05). The only significant change from baseline observed with verum acupuncture was an increase in the right 5th finger at visit 4 (week 36) (*P* < .01).

No serious acupuncture-related AEs were reported. The most frequently reported AE was a residual needling sensation felt immediately after needle removal; this was mild and self-limiting and resolved without any medical interventions.

Discussion

To the best of our knowledge, this is the first randomized, sham-controlled, single-blind trial to investigate the prophylactic efficacy of acupuncture treatment in CIPN with subjective (ie, questionnaires) and objective measurements (ie, NCV and von Frey monofilament testing). Most previous

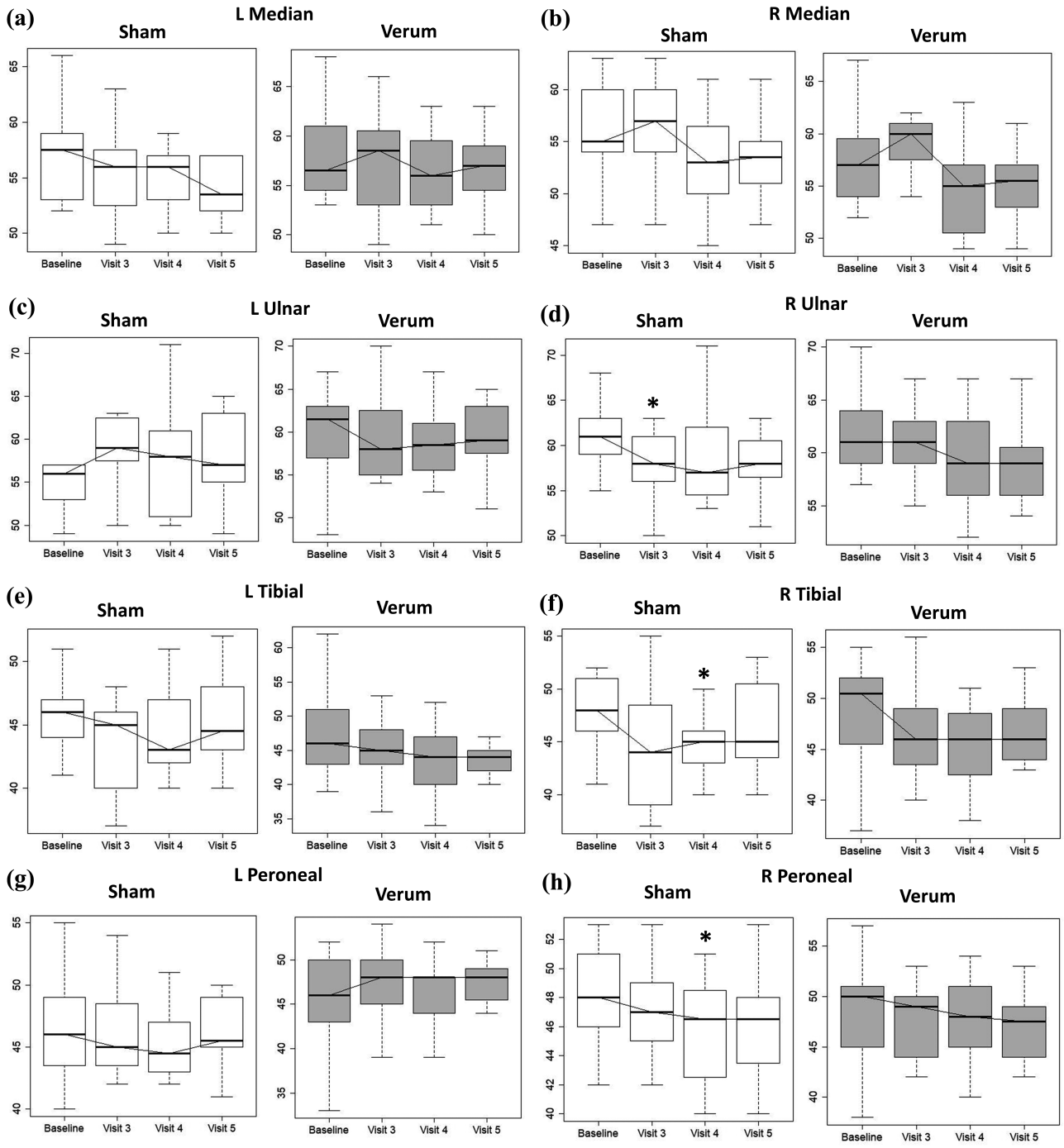

Figure 3. Changes from baseline for both acupuncture study groups at visits 3 (week 24), 4 (week 36), and 5 (week 48) in median motor conduction velocities of (**a**) the left median nerve, (**b**) right median nerve, (**c**) left ulnar nerve, (**d**) right ulnar nerve, (**e**) left tibial nerve, (**f**) right tibial nerve, (**g**) left peroneal nerve, and (**h**) right peroneal nerve. *$P < .05$; **$P < .01$.

randomized controlled trials (RCTs) have examined the efficacy of acupuncture (manual acupuncture or electroacupuncture [EA]) after the occurrence of CIPN.[23-30] Two RCTs that focused on acupuncture efficacy in the prevention of CIPN only used subjective assessments.[31,32]

In our study, 84.6% of participants received at least 8 cycles of chemotherapy and approximately half completed a full course of an oxaliplatin-based regimen, so a greater incidence of CIPN was observed with the increasing accumulation of chemotherapy dose. Patient-reported assessments from both study groups revealed significant increases in the neurotoxicity score of the FACT questionnaire at the end of the intervention and at the third month of the follow-up period, indicating that verum acupuncture was no better than the sham intervention at protecting against neurotoxic symptoms.

As for health-related quality of life, mean total FACT-G scores were significantly decreased from baseline at the end of the study intervention and improved thereafter with verum acupuncture, while the scores remained significantly decreased at the end of the follow-up period (at 48 weeks) in the sham acupuncture group. One previous study that included women

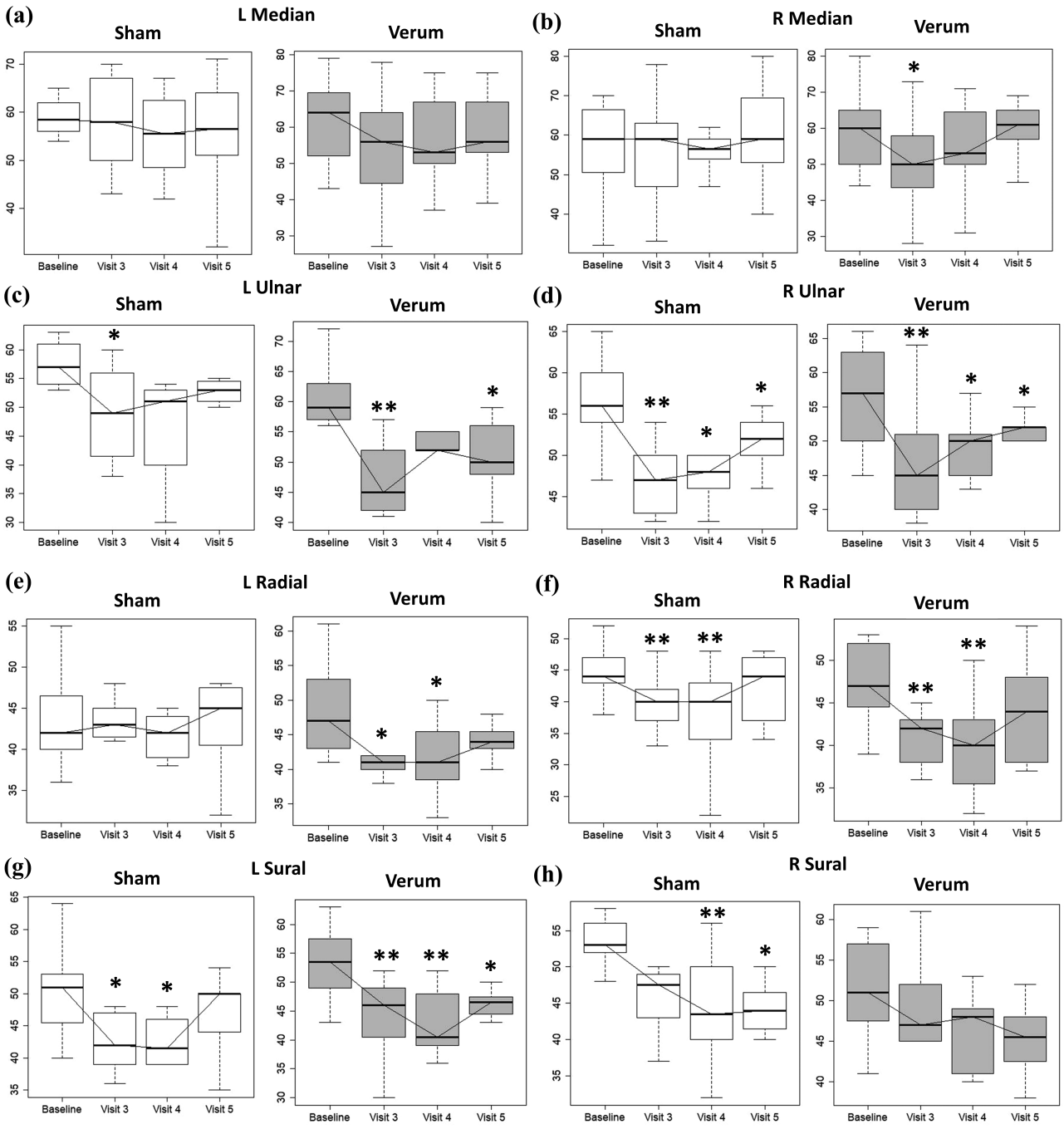

Figure 4. Changes from baseline for both acupuncture study groups at visits 3 (week 24), 4 (week 36), and 5 (week 48) in median sensory conduction velocities of (**a**) the left median nerve, (**b**) right median nerve, (**c**) left ulnar nerve, (**d**) right ulnar nerve, (**e**) left radial nerve, (**f**) right radial nerve, (**g**) left sural nerve, and (**h**) right sural nerve. *$P < .05$; **$P < .01$.

with early-stage breast cancer on taxane-based chemotherapy found that neither EA nor sham EA prevented a worsening in FACT-Ntx scores,[31] whereas in another clinical trial, manual acupuncture administered during weekly paclitaxel chemotherapy did reduce the incidence of high-grade CIPN in stages I–III patients with breast cancer.[29] The discrepant findings of these trials might be due to the different timings of acupuncture intervention and types of acupuncture.[32] Our study also differs from those studies in terms of the cancer diagnosis, chemotherapeutic regimen, and acupuncture treatment, in that in this study, acupuncture was administered concurrently with chemotherapy.

Our study found no significant between-group differences in motor or sensory conduction velocities either during chemotherapy or follow-up. However, similar trends in delayed sensory conduction velocities were observed amongst all the peripheral nerves in both groups, with only the data from the right ulnar, right radial and left sural nerves showing significant between-group differences at weeks 24 and 36 compared with baseline. This may mean that acupuncture given concurrently with chemotherapy does not protect conduction velocities of sensory nerves. Sham acupuncture was associated with significant decreases from baseline in motor nerve conduction velocities of the right ulnar, right tibial, and right

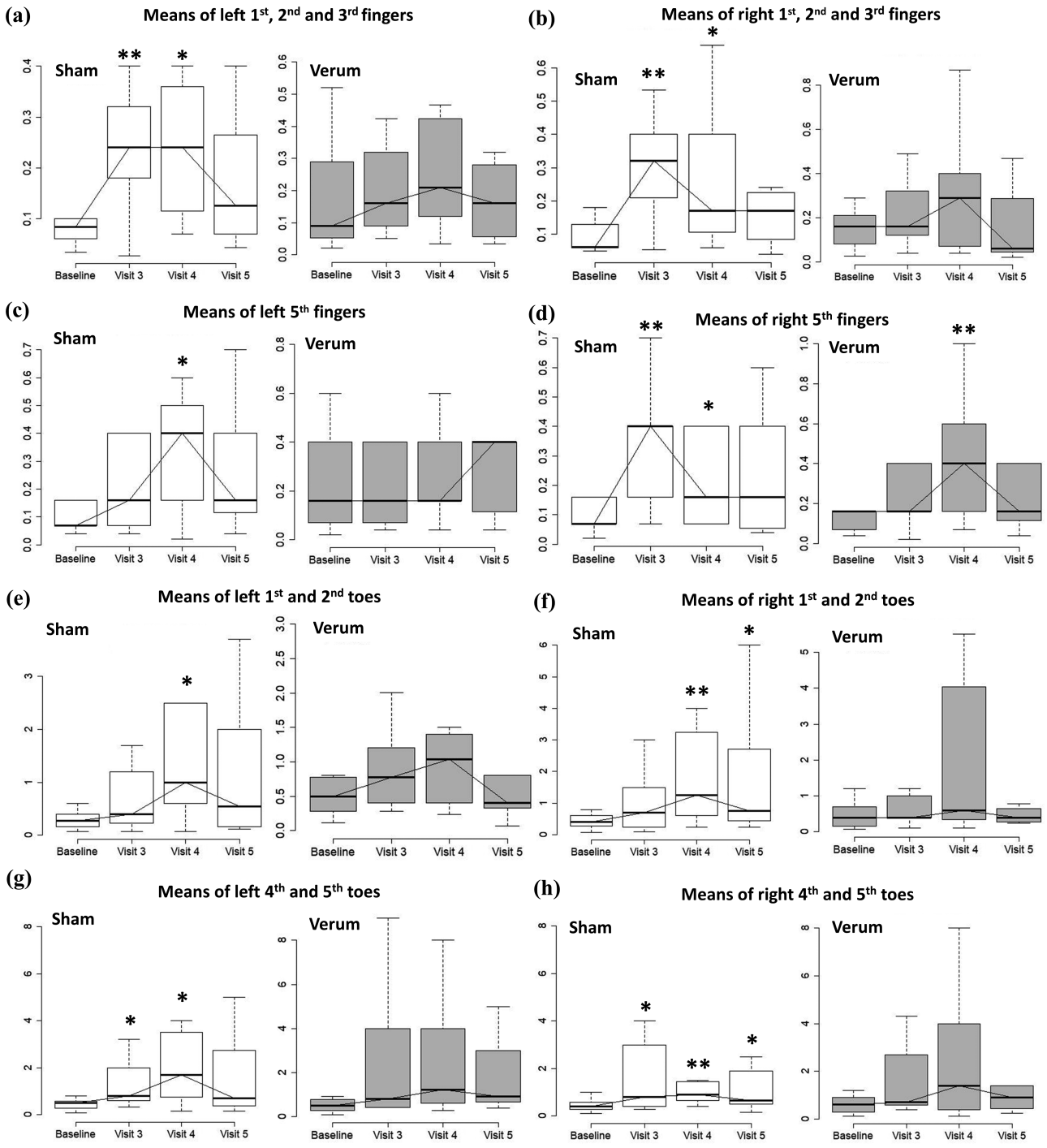

Figure 5. Mean changes from baseline for both acupuncture groups at visits 3 (week 24), 4 (week 36), and 5 (week 48) in von Frey monofilament test values for (**a**) the left 1st, 2nd, and 3rd fingers, (**b**) right 1st, 2nd, and 3rd fingers, (**c**) left 5th finger, (**d**) right 5th finger, (**e**) left 1st and 2nd toes, (**f**) right 1st and 2nd toes, (**g**) left 4th and 5th toes, and (**h**) right 4th and 5th toes. **P* < .05; ***P* < .01.

peroneal nerves at weeks 24 and 36, while verum acupuncture was associated with a delay in motor NCV values that did not reach statistical significance. The limitation posed by the small study sample prevented acupuncture from showing any benefits as to a risk reduction in peripheral neuropathy of the extremities.

We used von Frey monofilament assessments to quantitatively detect touch thresholds. This tool has shown moderate sensitivity and specificity for diagnosing neuropathy in nerve conduction studies.[33] We used medical histories (eg, diabetes) and abnormal NCV values as study exclusion criteria. Recent studies have used von Frey monofilaments to screen for subclinical peripheral neuropathy in patients with cancer prior to chemotherapy.[34,35] One clinical trial that used von Frey monofilaments testing to evaluate the feasibility and effects of laser acupuncture in patients with CIPN demonstrated significant improvements in touch-detection thresholds.[36]

In our study, bilateral touch thresholds of the fingers and toes were significantly worse compared with baseline by the end of the sham intervention and lasted for at least 3

months. Participants given verum acupuncture only experienced a significant increase in the threshold of the right little finger by the third month of follow-up. These findings indicate that verum acupuncture is more protective than sham acupuncture upon touch thresholds in the prevention of CIPN. The beneficial effect of acupuncture upon the touch threshold endured for at least 6 months after completion of the study intervention.

The mechanisms of acupuncture in CIPN are not yet fully understood. Acupuncture needling can increase blood perfusion in the fingertips and thus improve the termini circulation to nourish the neurons and assist with the repair of neural lesions.[37] It has been proposed that acupuncture activates GABAergic, serotoninergic and adrenergic neurotransmission and deactivates hypersensitization of sensory neurons by modulating neurotrophins and nerve growth factors.[38] It is established that acupuncture stimulates nociceptive Aδ and C fibers that transmit sensory signals into spinal cord dorsal horn neurons, which exhibit altered activity after chemotherapy and thus induce peripheral neuropathy symptoms including pain, burning sensations, numbness, hyperesthesia, allodynia, deficits in temperature discrimination, and gait disturbances.[39] The therapeutic response of acupuncture, the *de qi* sensation, also involves the Aδ and C fibers in neural signaling transduction, so this response may be beneficial in the treatment of CIPN.[40]

This study has a few limitations. First, the small sample limited the power to detect significant differences between verum and sham acupuncture. Furthermore, topical cryotherapy reportedly reduces CIPN-induced clinical symptoms and severity,[41] but we were unable to determine whether any of our study participants used cryotherapy. Another important problem is the innate limitations of sham acupuncture controls, which arguably cannot be physiologically inert, because all types of acupuncture techniques stimulate the skin and thus cause afferent nerve activation that may induce reactions including the limbic touch response in the brain.[42] The limitation of truly inert placebo was also proposed in another randomized clinical trial.[28] Interestingly, research suggests that a patient's positive expectations of results from acupuncture treatment predict better outcomes after treatment,[43] but this phenomenon was not evaluated in this study. In addition, lack of a control group without intervention to elucidate the effect of verum and sham acupuncture was another limitation of this study.

Conclusion

Our study found that the prophylactic use of acupuncture exerts neuroprotective effects to touch thresholds of all 4 limbs during chemotherapy and at 6 months of follow-up. Verum acupuncture appeared to exert a protective effect by reducing motor NCV values. Further studies with a larger sample, comprehensive assessments, and appropriate placebo controls are warranted.

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Ethics Statement

The study protocol was reviewed and approved by China Medical University Hospital (CMUH) (CMUH104-REC1-076). The study participants provided their written informed consent to participate in this study.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/design: M.-C.H., S.-C.C., H.-H.C. Provision of study material or patients: S.-C.C., T.-W.K., H.-M.W., W.T.-L.C. Collection and/or assembly of data: M.-C.H., S.-C.C., T.-W.K., A.-L.L., H.-M.W., C.-P.C., H.-R.Y. Data analysis and interpretation: M.-C.H., S.-C.C., A.-L.L., C.-P.C., W.-L.L., H.-H.C. Manuscript writing: M.-C.H., W.-L.L., H.-H.C., W.T.-L.C. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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