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Effect of Acupuncture vs Sham Procedure on Chemotherapy-Induced Peripheral Neuropathy Symptoms
A Randomized Clinical Trial

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common and debilitating long-term adverse effect of neurotoxic chemotherapy that significantly worsens cancer survivors' quality of life. Well-tolerated, evidence-based interventions for CIPN are needed.[1]

Methods

This pilot randomized clinical trial compared the effect of 8 weeks of real acupuncture vs sham acupuncture or usual care to treat CIPN. The trial protocol (Supplement 1) was approved by the institutional review board of Memorial Sloan Kettering Cancer Center and follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline (**Figure**). Written informed consent was obtained from all study participants. Patients with solid tumors with persistent moderate to severe CIPN (symptoms of numbness, tingling, or pain rated ≥4 on a numeric rating scale [NRS]) who had completed 3 or more months of chemotherapy prior to study enrollment and were not taking stable neuropathic medication were eligible. Patients were allocated 1:1:1 to real acupuncture, sham

+ Supplemental content

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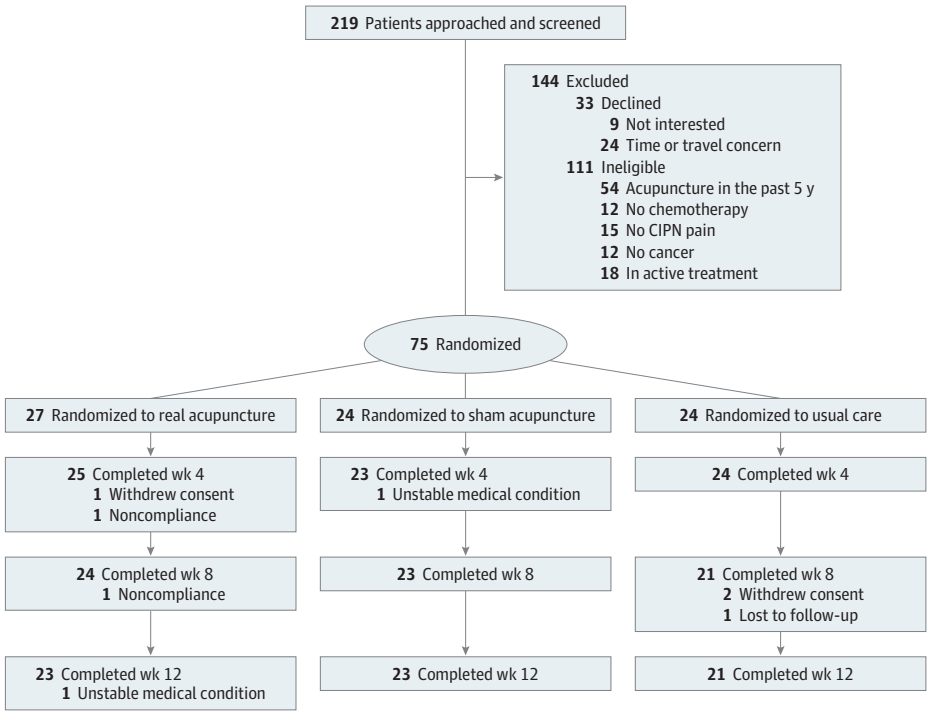
Figure. CONSORT Diagram of Participant Flow Through the Study



The number of participants who completed treatment at weeks 8 and 12 were included in the analysis for those weeks. CIPN indicates chemotherapy-induced peripheral neuropathy.

acupuncture, or usual care through computer-generated randomization conducted by the Clinical Research Database in randomly permuted blocks.

The real acupuncture group received ear and body acupuncture at Shen Men, point zero, and a third electrodermal active point,[2] and bilateral body: LI-4, PC-6, SI-3, LR-3, GB-42, ST-40, Bafeng 2, and Bafeng 3. Electrical acupuncture was also applied bilaterally from LR-3 (negative) to GB-42 (positive) at 2 to 5 Hz for 20 minutes. The sham acupuncture group received a noninsertion procedure on nonacupoints. The usual care group did not receive any interventions throughout the study period. Investigators, study coordinators, and the statistician were blinded to the treatment assignments.

The primary end point was CIPN symptom severity measured by NRS (11-point scale; 0 = no symptoms and 10 = worst symptom imaginable) at week 8. In prior studies, the NRS had high reliability and validity.[3,4] We targeted a sample size of 25 participants in each group. This sample size allowed us to estimate the upper bound of a 1-sided 90% confidence interval for the treatment effect on outcome (eg, sham acupuncture vs real acupuncture or usual care vs real acupuncture) to 0.35-unit SDs. Mixed-effects models with an interaction term between group and assessment time (up to 8 weeks) were fit to examine whether temporal changes in a measure differed by group. The threshold for statistical significance was set at 2-sided $P < .05$.

Results

From July 2017 to June 2018, we enrolled 75 patients with solid tumors with moderate to severe CIPN (median [interquartile range] age, 59.7 [36.3-85.9] years; 60 [80%] female; 55 [73%] white; 40 [53%] with breast cancer and 12 [16%] with colorectal cancer). In all, 24 patients were randomized to real acupuncture, 23 to sham acupuncture, and 21 to usual care. Compared with usual care, NRS-measured pain, tingling, and numbness significantly decreased in real acupuncture at week 8 (**Table**). From baseline to week 8, mean absolute reduction in CIPN pain was greatest in real acupuncture (−1.75 [95% CI, −2.69 to −0.81]) and least in usual care (−0.19 [95% CI, −1.13 to 0.75]) (Table). At the 8-week assessment, sham acupuncture had a reduction of −0.91 (95% CI, −2.0 to 0.18). At the longer 12-week follow-up, real acupuncture had a mean absolute reduction in NRS-measured pain of −1.74 (95% CI, −2.6 to −0.83) from baseline, while sham treatment had a reduction of −0.34 (−1.3 to 0.61). Adverse events were few and mild.

Discussion

We found therapeutic benefit of real acupuncture for neuropathic pain that is consistent with previous pilot acupuncture CIPN trials.[5,6] Distinctively, our study is the first, to our knowledge, to incorporate a sham treatment and a nontreatment control to evaluate the efficacy of acupuncture for

Table. Mean Change in Chemotherapy-Induced Peripheral Neuropathy Symptom Scores at Week 8

	Real Acupuncture (n = 24)		Sham Acupuncture (n = 23)		
Symptom	Mean (95% CI)	*P* Value[a]	Mean (95% CI)	*P* Value[a]	Usual Care, Mean (95% CI) (n = 21)
Numeric rating scale pain					
Baseline	4.15 (3.01 to 5.29)		4.12 (2.98 to 5.27)		4.75 (3.42 to 6.08)
Absolute reduction	−1.75 (−2.69 to −0.81)	.05	−0.91 (−2.00 to 0.18)	.31	−0.19 (−1.13 to 0.75)
Numeric rating scale tingling					
Baseline	5.30 (4.25 to 6.34)		5.46 (4.66 to 6.26)		5.50 (4.40 to 6.60)
Absolute reduction	−1.83 (−2.71 to −0.96)	.02	−1.22 (−2.26 to −0.17)	.18	−0.14 (−1.40 to 1.11)
Numeric rating scale numbness					
Baseline	6.59 (5.76 to 7.42)		6.25 (5.62 to 6.88)		6.25 (5.32 to 7.18)
Absolute reduction	−1.54 (−2.40 to −0.68)	.005	−1.52 (−2.56 to −0.49)	.003	0.57 (−0.62 to 1.76)

[a] *P* values are treatment-time interaction terms computed using linear mixed-effects models, comparing with usual care.

CIPN. The addition of a sham acupuncture control in an acupuncture clinical trial is difficult owing to the challenge of incorporating a truly inert placebo. In addition, a sham control limits the ability of a small effect size to elucidate a true difference between real and sham acupuncture. Not only did our study demonstrate the feasibility of conducting a sham-controlled acupuncture trial, it generated sufficient pilot data to inform a definitive sham-controlled efficacy trial. Our trial is limited by its small sample size, single center, and short-term follow-up.

In conclusion, compared with usual care, acupuncture resulted in significant improvement in CIPN symptoms. The effect size observed between real and sham control will inform a rigorous and adequately powered trial to establish the efficacy of acupuncture for CIPN.

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Author Contributions: Dr Bao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Bao was the principal investigator.

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Data Sharing Statement: See Supplement 2.

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SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
Data Sharing Statement