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Original Article

Electroacupuncture frequency for chemotherapy-induced neuropathy in breast cancer: a randomized controlled trial

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Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent dose-limiting toxicity in breast cancer patients. Electroacupuncture (EA) shows promise but optimal stimulation parameters remain undefined. We conducted a randomized trial comparing EA frequencies for CIPN.

Methods: This single-center, single-blind trial randomized patients to 2, 100, and 2/100 Hz EA, or mecobalamin (Mecbl). The primary outcome was the patient neurotoxicity questionnaire (PNQ) response rate at Week 4. Secondary outcomes included PNQ scores, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grades at Weeks 4/8, and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20) and Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) scales.

Results: 2/100 Hz EA achieved the highest overall response rate. Both 2 and 2/100 Hz EA improved PNQ sensory scores at Week 4. Sensory scores improved across groups, while motor scores decreased with 2 and 2/100 Hz EA. Only 2 Hz EA improved autonomic function. For quality-of-life, 2 Hz EA enhanced physical function, fatigue, pain and insomnia, while 2/100 Hz EA improved nausea/vomiting, constipation, appetite and global health with additional pain relief at Week 4. The 100 Hz EA group showed no significant benefits in these domains.

Conclusions: This study preliminarily explored EA's potential benefits for CIPN, with 2/100 Hz showing the highest response rate and 2 Hz demonstrating sensory improvement advantages. Different frequencies produced distinct therapeutic profiles. Further research should evaluate frequency-specific effects of EA for CIPN.

Key words: electroacupuncture; breast cancer; chemotherapy-induced peripheral neuropathy.

Implications for Practice

We report an exploratory investigation of different EA frequencies for managing peripheral neuropathy in breast cancer patients. Our observations suggest that frequency selection should be individualized based on symptom profiles. The data indicate that while 2/100 Hz EA demonstrated the most comprehensive effects, 2 Hz EA appeared particularly beneficial for sensory improvement, and 2/100 Hz EA showed relevance for gastrointestinal symptoms and overall well-being. These clinical observations, though preliminary, may guide practitioners in tailoring EA frequency selection when addressing CIPN in this patient population.

Introduction

Breast carcinoma constitutes the second most prevalent malignancy worldwide and represents the most frequently diagnosed oncologic condition in female populations.[1] The current therapeutic armamentarium encompasses surgical resection, radiation therapy, cytotoxic chemotherapy, endocrine modulation, and molecularly targeted agents.[2] Chemotherapeutic interventions maintain a pivotal role in systemic disease control due to their demonstrated efficacy, however, the widespread clinical utilization of platinum-derived compounds and taxane-based protocols has been associated with a 67% incidence of chemotherapy-induced peripheral neuropathy (CIPN) during initial treatment cycles.[3] This iatrogenic complication significantly impairs therapeutic compliance and functional capacity, while persistent neuropathic manifestations frequently precipitate psychological comorbidities including anxiety disorders and

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depressive syndromes, thereby substantially compromising patients' health-related quality of life.[4]

CIPN represents a prevalent and dose-limiting drug reaction characterized by progressive, often irreversible neurotoxic damage affecting sensory, motor, and autonomic neural pathways.[5] The clinical phenotype typically includes distal paresthesia, dysesthesia, thermal allodynia, and progressive motor impairment. Epidemiologic investigations have documented CIPN incidence rates ranging from 60% to 68% during the initial 1-3 month treatment period, with approximately 30% of patients demonstrating persistent symptomatology at 6-month follow-up intervals.[6] Numerous antineoplastic agents demonstrate neurotoxic potential, including platinum coordination complexes, taxane derivatives, vinca alkaloids, epothilones (exemplified by ixabepilone), proteasome inhibitors (notably bortezomib), and immunomodulatory compounds (such as thalidomide). Among these, platinum-based agents, taxanes, ixabepilone, and thalidomide exhibit particularly pronounced neurotoxic profiles.

Contemporary management strategies for CIPN remain constrained by limited therapeutic options. Current clinical practice guidelines endorse duloxetine as the sole pharmacologic intervention with established efficacy for neuropathic pain mitigation.[7,8] However, this approach fails to address the predominant clinical manifestations of sensory loss and motor dysfunction, for which evidence-based interventions remain conspicuously absent. Adjunctive therapies including mecobalamin (Mecbl) supplementation are frequently employed empirically,[9,10] notwithstanding the paucity of robust clinical evidence supporting their efficacy. While dose reduction or therapeutic discontinuation represent common clinical responses, these measures inevitably compromise antineoplastic efficacy while providing incomplete symptomatic relief.

Electroacupuncture (EA), a fundamental therapeutic modality within traditional Chinese medical paradigms, has emerged as a potential intervention for oncotherapy-associated complications,[11,12] including CIPN.[13] The ESMO-published guidelines recommend acupuncture as an intervention for CIPN, but with a Level II E recommendation based on small-sample studies and expert consensus, indicating the evidence base remains limited.[14] Emerging evidence suggests EA may ameliorate CIPN symptoms.[15–17] However, current research lacks robust methodological quality in evaluating its therapeutic efficacy. Notably, existing studies exhibit significant heterogeneity in stimulation parameters, particularly regarding frequency selection,[18,19] a critical factor that may substantially influence treatment outcomes. Optimizing stimulation parameters may represent a critical step in establishing therapeutic efficacy. Therefore, we conducted a randomized controlled trial to preliminarily evaluate the effects of frequency-specific EA interventions on CIPN in breast cancer patients.

Methods

Study design and participants

This single-center, randomized, controlled trial was conducted from January 2022 to January 2024 at Zhejiang Cancer Hospital. The trial followed the principles of the Declaration of Helsinki[20] and was approved by the Medical Ethics Committee of Zhejiang Cancer Hospital (Approval no: IRB-2021-458). The registration number was No. ChiCTR2100054458 (https://www.chictr.org.cn/showproj.html? proj=144615). The trial protocol has been published previously.[21] All patients provided written informed consent before participation. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guideline.[22]

Women with breast cancer 18-70 years of age were screened for the following: diagnosis of CIPN, grade I or higher occurred after taxanes containing drugs chemotherapy, such as nab-paclitaxel, paclitaxel liposome, paclitaxel, and docetaxel (used alone or in combination). Additional eligibility details see Table S1.

Randomization and blind

Patients eligible for this study were randomized to receive 2, 100, and 2/100 Hz EA, and Mecbl treatment in a ratio of 1:1:1:1 by the envelope randomization method. Patients in the 3 EA groups were kept blinded to their group assignment. Although acupuncturists were not blinded to the group assignments, they were not involved in the outcome assessments or data analyses. Other researchers, including the statisticians, outcome assessors, and data analysts, were all blinded to the group assignments. To achieve blinding of patients in the 3 EA groups, we chose the same type of disposable acupuncture needles, selected the same acupoints and skin disinfection process. The only difference was the frequency of EA, while the patients did not know which frequency they used.

Interventions

Patients in the 3 EA groups received 12 30-minute sessions of EA, once every other day (3 times a week) for 4 consecutive weeks. All treatments were performed by 4 licensed acupuncturists with at least 5 years of clinical experience.

Patients with CIPN in the upper limbs were selected acupoints at Quchi (LI11), Waiguan (SJ5), Hegu (LI4), Houxi (SI3), and Baxie (EX-UE9) bilaterally, and EA was connected Hegu (LI4) with Waiguan (SJ5) points. In the lower limbs, acupoints selected as Yanglingquan (GB34), Zusanli (ST36), Yinglingquan (SP9), Sanyinjiao (SP6), Taichong (LR3), and Bafeng (EX-LE10) points bilaterally, and EA was connected Zusanli (ST36) with Sanyinjiao (SP6) points (Figure 1). In all limbs, select both the upper and lower limb acupoints and EA treatment mentioned above were given. The location of all selected acupoints followed the national standards of China (GB/T 123456-2021). The EA frequencies of the 3 EA groups were 2, 100, and 2/100 Hz separately, which were consistent with the group name. The stimulation intensity was 0.5-4 mA, mainly based on the patient's tolerance, with clear feeling, but no discomfort. All the patients were followed up for 4 weeks after the last intervention. (The acupuncture needles were adopted Huatuo brand needle produced by Suzhou Medical Apparatus Plant, with the model of 0.25 * 40 MM. The EA equipment adopted the HANS acupoint nerve stimulator, the model was HANS-200E, produced by Nanjing Jisheng Medical Technology Co., Ltd.).

Patients in the Mecbl group were treated with Mecbl tablets orally (produced by Misato Plant of Eisai Co., Ltd), 1 tablet at a time, 3 times a day for 4 weeks, and followed up for 4 weeks.

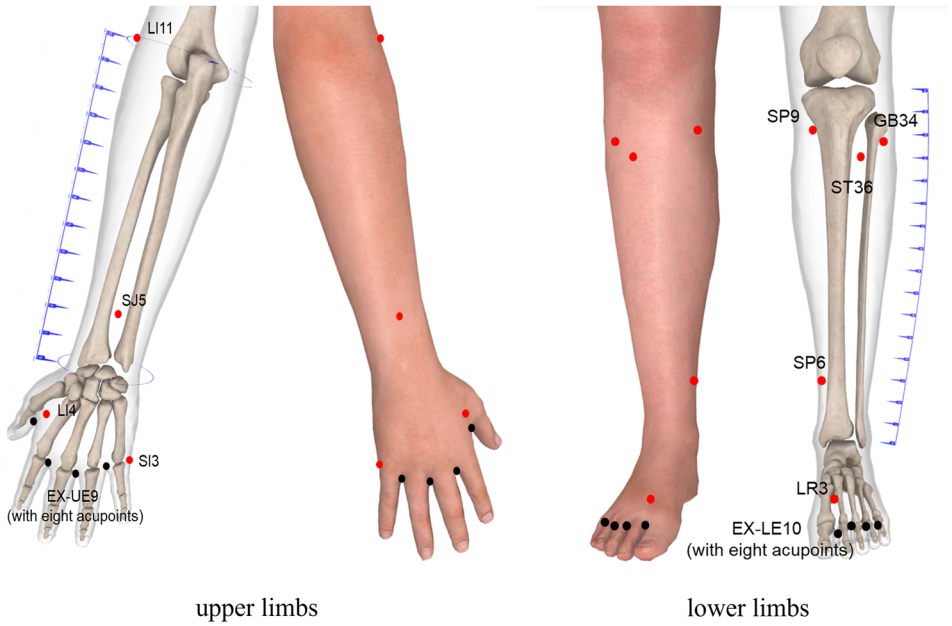

Figure 1. Acupoint. Upper limbs including Quchi (LI11), Waiguan (SJ5), Hegu (LI4), Houxi (SI3), and Baxie (EX-UE9) bilaterally. Lower limbs including Yanglingquan (GB34), Zusanli (ST36), Yinglingquan (SP9), Sanyinjiao (SP6), Taichong (LR3), and Bafeng (EX-LE10) points bilaterally.

Outcomes

The primary outcome was the response rate based on the PNQ overall score at Week 4, defined as at least a one-grade reduction in either sensory or motor subscales compared with baseline. The PNQ, a validated instrument for diagnosing and quantifying CIPN in breast cancer patients.[23] demonstrates robust psychometric properties with particular sensitivity in detecting neuropathy-related functional impairment. This comprehensive tool evaluates sensory symptoms (including numbness, tingling, and pain) and motor dysfunction, where a one-grade change in subscale scores constitutes a clinically meaningful threshold.[24] Sustained response was additionally evaluated as maintenance of at least one-grade improvement from baseline through Week 8.

Secondary outcomes comprised response rates for PNQ sensory and motor subscales, along with National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0) neuropathy grading, all measured as ≥1-grade improvements from baseline to Weeks 4 and 8. Trained assessors performed all neurotoxicity grading using standardized NCI-CTCAE criteria.[25] Quality of life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20)[26] and Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[27] instruments at baseline, Week 4, and Week 8, with raw scores linearly transformed to 0-100 scales following established methodology.[28]

We implemented comprehensive adverse event monitoring throughout the study period, systematically documenting event onset, clinical manifestations, management strategies, outcomes, and potential associations with trial discontinuation. Concomitant analgesic usage, including medication type and dosage, was prospectively recorded during all study visits.

Statistical analysis

De-identified outcome data were analyzed by a statistician blinded to group allocations using the SPSS statistical software (Version 24.0, IBM, USA). For baseline characteristics, continuously distributed variables were described using mean (standard deviation [SD]) or median (interquartile range [IQR]), and discrete variables were described by frequencies and percentages. The analysis was based on the modified intention-to-treat (MITT) principle and included all randomized patients with baseline data. The response rate of PNQ and NCI-CTCAE, the use of analgesics, and the incidence of adverse events were evaluated with the χ^2 test, non-parametric test, or Fisher exact test described by frequencies and percentages. Continuous variables from the EORTC QLQ-CIPN20 and EORTC QLQ-C30 were compared between groups using the Mann–Whitney *U* test, a non-parametric test for independent samples. Multiple comparisons between groups were adjusted using the Bonferroni correct into control for Type I error. For within-group comparisons across all measurement time points, the Wilcoxon signed-rank test was applied to assess longitudinal changes. Blind evaluation using the BANG Bling index, performed by R, version 4.2.3 (R Foundation for Statistical Computing). All statistical analyses were 2-sided tests and the level of significance was established at 0.05.

Sample size

This study is a pilot trial. Based on data from similar studies, the primary outcome was defined as the proportion of patients achieving at least a 1-unit improvement on the PNQ scale, with an anticipated rate of 65% in the EA group and 35% in the conventional treatment group.[23] Sample size calculation (2-sided test $\alpha = 0.05$, power = 80%) indicated a requirement of 40 participants per group. Furthermore, existing methodological studies suggest that a feasible sample size for pilot trials

ranges from 10 to 40 cases per group,[29] while another study based on medium effect size prediction recommends 35 cases per group.[30] Accounting for a 15% dropout rate, 40 participants were enrolled per group, totaling 160 participants.

Results

This study enrolled patients who visited the outpatient or inpatient departments of Zhejiang Cancer Hospital between January 2022 and October 2023. A total of 853 patients were screened, of whom 693 were excluded, primarily due to lack of interest in the study or participation in other clinical trials. We randomized 160 patients (40 per group) and analyzed 152 with baseline data in the MITT population (Figure 2).

Table 1 presents the baseline characteristics of patients in each group. No significant differences were observed in age, body mass index (BMI), or disease duration. The proportions of patients with metastatic neoplasms, chemotherapy cycles, chemotherapy protocols used, and KPS scores were also similar between groups. Furthermore, subdomain scores on the PNQ, NCI-CTCAE, EORTC QLQ-CIPN20, and EORTC QLQ-C30 showed no significant intergroup differences.

In the primary outcome the 2/100 Hz EA group demonstrated significantly greater improvement in the overall response rate of PNQ compared to the Mecbl group at Week 4 ($P < .05$). No statistically significant differences were observed among other groups. Regarding PNQ sensory response rates at Week 4, both the 2 and 2/100 Hz EA groups showed superior outcomes compared to the Mecbl group (all $P < .05$). However, no significant between-group differences were detected in motor or autonomic subscale scores of PNQ, nor in NCI-CTCAE grade assessments at Week 4 (Figure 3).

At Weeks 4 and 8 of assessment, no significant differences were observed in any subscale scores of EORTC QLQ-CIPN20 (all $P > .05$) (Figure 4). Among the domain scores of EORTC QLQ-C30, only appetite loss in the 2/100 Hz EA group at Week 8 showed differences compared with both the 2 Hz EA group and Mecbl group, while no statistical significance was found in other domains (all $P > .05$) (Figure 5).

In comparisons with baseline, all 4 intervention groups demonstrated significant differences in total EORTC QLQ-CIPN20 scores (all $P < .05$). However, at the Week 8 follow-up, only the EA groups (2, 2/100, and 100 Hz) showed significant differences compared with baseline (all $P < .05$). For EORTC QLQ-CIPN20 sensory scores, all groups exhibited statistically significant differences compared with baseline at both Weeks 4 and 8. In motor scores, both the 2 and 2/100 Hz EA groups showed significantly lower scores than baseline at Weeks 4 and

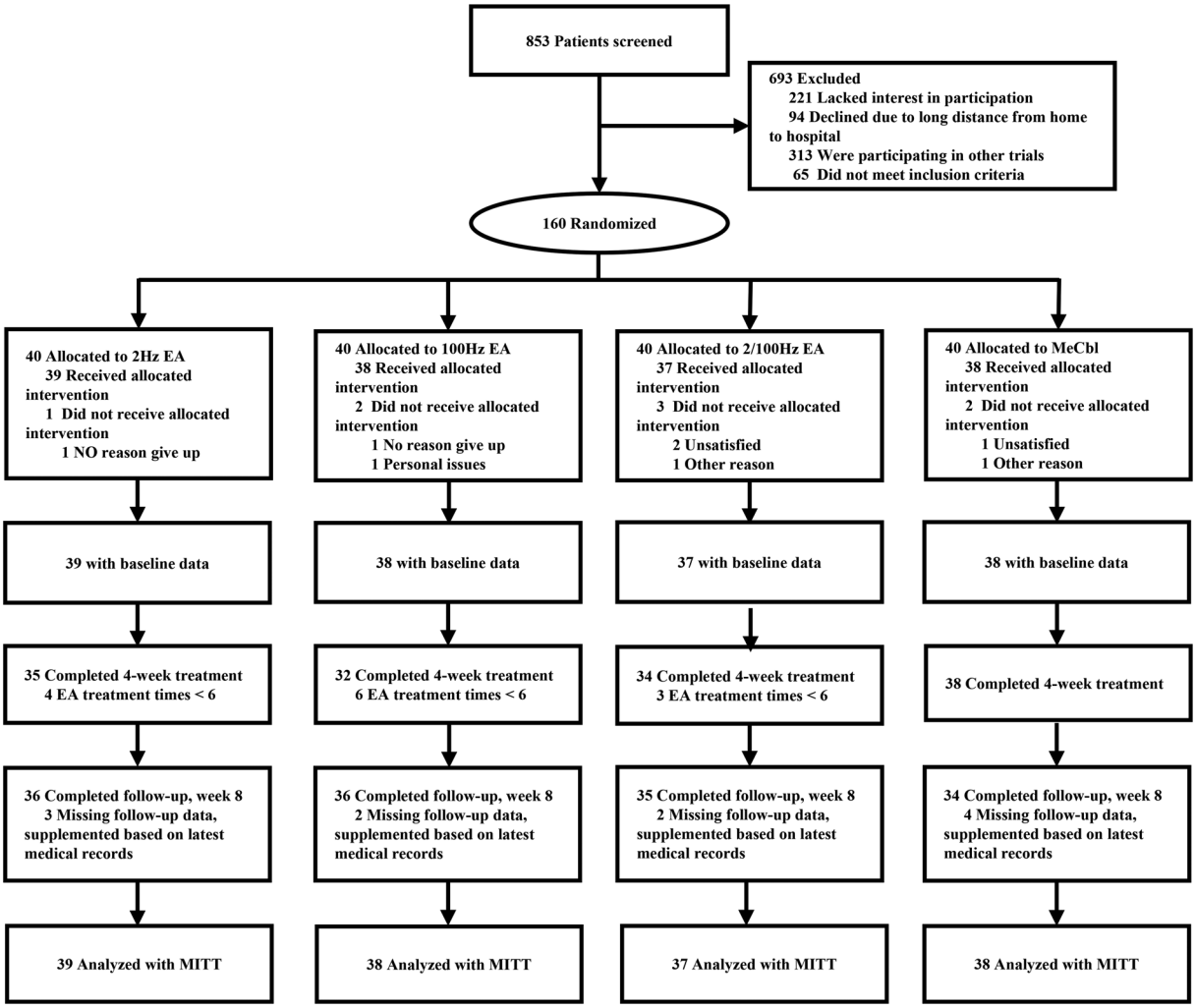

Figure 2. Flow chart of the study process. Abbreviations: EA: electroacupuncture; Mecbl: mecobalamin; MITT: modified intention-to-treat.

Table 1. Baseline characteristics of patients in MITT analysis.

Characteristic	Patients, No. (%)				
	2 Hz EA (n=39)	100 Hz EA (n=38)	2/100 Hz EA (n=37)	Mecbl (n=38)	Total (n=152)
Age, mean (SD), years	53.74 (8.44)	54.39 (8.25)	52.02 (9.62)	53.02 (9.61)	53.30 (8.94)
BMI, mean (SD)	21.68 (3.71)	21.65 (3.55)	23.28 (3.10)	23.01 (3.19)	22.39 (3.45)
Duration of illness, mean (SD), month	5.85 (4.35)	5.37 (3.91)	5.64 (3.80)	5.56 (3.96)	5.61 (3.98)
Neoplasm metastasis, years	29 (74.36)	31 (81.58)	29 (78.39)	33 (86.84)	122 (80.26)
Chemotherapy cycles, mean (SD)	13.79 (8.75)	12.89 (9.17)	12.83 (8.16)	12.13 (7.54)	12.92 (8.37)
Single chemotherapy protocol, years	10 (25.64)	14 (36.84)	13 (35.14)	11 (28.95)	48 (31.58)
KPS, mean (SD)	88.71 (5.46)	89.60 (4.84)	88.78 (6.16)	89.34 (4.52)	89.11 (5.24)
PNQ sensory grade[a]					
Grade A	0	0	0	0	0
Grade B	8 (20.51)	10 (26.32)	9 (24.32)	8 (21.05)	35 (23.03)
Grade C	13 (33.33)	7 (18.42)	11 (29.73)	20 (52.63)	51 (33.55)
Grade D	16 (41.03)	19 (50.00)	16 (43.24)	10 (26.32)	61 (40.13)
Grade E	2 (5.13)	2 (5.26)	1 (2.70)	0	5 (3.29)
PNQ motor grade					
Grade A	6 (15.38)	6 (15.79)	1 (2.70)	3 (7.89)	16 (10.53)
Grade B	11 (28.21)	14 (36.84)	16 (43.24)	20 (52.63)	61 (40.13)
Grade C	15 (38.46)	12 (31.58)	14 (37.84)	13 (34.21)	54 (35.53)
Grade D	6 (15.38)	6 (15.79)	5 (13.51)	2 (5.26)	19 (12.50)
Grade E	1 (2.56)	0	1 (2.70)	0	2 (1.32)
NCI-CTCAE grade[b]					
Grade I	9 (23.08)	13 (34.21)	11 (29.73)	13 (34.21)	46 (30.26)
Grade II	21 (53.85)	19 (50.00)	19 (51.35)	21 (55.26)	80 (52.63)
Grade III	7 (17.85)	6 (15.79)	6 (16.22)	4 (10.53)	23 (15.13)
Grade IV	2 (5.13)	0	1 (2.70)	0	3 (1.97)
EORTC QLQ-CIPN20, median (IQR)[c]					
Total score	27.78 (16.67)	23.15 (16.67)	27.78 (16.67)	21.3 (14.81)	24.07 (17.59)
Sensory score	29.63 (12.96)	22.22 (14.81)	25.93 (14.81)	25.93 (17.59)	24.07 (17.59)
Motor score	23.81 (23.81)	23.81 (23.81)	23.81 (23.81)	23.81 (23.81)	23.81 (20.24)
Autonomic score	16.67 (33.33)	16.67 (33.33)	16.67 (33.33)	16.67 (33.33)	16.67 (33.33)
EORTC QLQ-C30, median (IQR)[d]					
Physical function	66.67 (40.0)	63.33 (45.0)	73.33 (33.33)	86.67 (36.67)	73.33 (40.0)
Role function	50.00 (33.33)	58.33 (33.33)	66.67 (33.33)	66.67 (33.33)	66.67 (33.33)
Emotional function	83.33 (20.83)	75.00 (25.00)	75.00 (25.00)	91.67 (25.00)	83.33 (25.0)
Cognitive function	66.67 (16.67)	66.67 (16.67)	66.67 (16.67)	75.00 (16.67)	66.67 (16.67)
Social function	33.33 (66.67)	33.33 (16.67)	33.33 (50.0)	33.33 (45.83)	33.33 (50.0)
Fatigue	66.67 (33.33)	55.56 (33.33)	55.56 (33.33)	44.44 (30.56)	44.44 (33.33)
Nausea and vomiting	0.00 (0.00)	0.00 (0.00)	0.00 (16.67)	0.00 (0.00)	0.00 (0.00)
Pain	33.33 (33.33)	16.67 (29.17)	33.33 (33.33)	25.0 (33.33)	25.0 (33.33)
Dyspnea	0.00 (33.33)	0.00 (33.33)	0.00 (33.33)	0.00 (33.33)	0.00 (33.33)
Insomnia	33.33 (33.33)	33.33 (33.33)	33.33 (33.33)	33.33 (33.33)	33.33 (66.67)
Appetite loss	33.33 (33.33)	33.33 (33.33)	33.33 (33.33)	33.33 (33.33)	33.33 (33.33)
Constipation	0.00 (33.33)	0.00 (33.33)	0.00 (33.33)	0.00 (33.33)	0.00 (33.33)

(Continued)

Table 1. Continued.

Characteristic	Patients, No. (%)				
	2 Hz EA ($n=39$)	100 Hz EA ($n=38$)	2/100 Hz EA ($n=37$)	Mecbl ($n=38$)	Total ($n=152$)
Diarrhea	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Financial difficulties	66.67 (66.67)	66.67 (66.67)	66.67 (66.67)	66.67 (66.67)	66.67 (66.67)
Global QOL	58.33 (16.67)	66.67 (22.92)	58.33 (16.67)	66.67 (8.33)	66.67 (16.67)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EA: electroacupuncture; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-CIPN20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN 20-item; Mecbl: mecobalamin; MITT: modified intention-to-treat; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events (Version 5.0); PNQ, patient neurotoxicity questionnaire; QOL: quality of life.
[a]PNQ grades symptoms from grade A (no neuropathy) to grade E (very severe neuropathy).
[b]NCI-CTCAE grades symptoms from grade I (slight) to grade IV (sensory).
[c]EORTC QLQ-CIPN20 contains 20 items, including 9 items in the sensory subscale, 8 items in the motor subscale and 3 items in the autonomic subscale. The higher scores indicate a worse quality of life. All items are scored with 4 levels, "no, a little, quite, and very" respectively, with 1-4 points. Each subscale is linearly transformed from a 0 (no neuropathy) to 100 (severe neuropathy) point scale (the formula standard score was SS = [(RS-1)/R] × 100).
[d]EORTC QLQ-C30 includes 5 functional subscales (body, function, cognition, emotion, and Society), 3 symptom subscales (fatigue, pain, nausea, and vomiting), 6 single symptom measurement items (dyspnea, loss of appetite, insomnia, constipation, diarrhea, and economic difficulties), and 1 overall health subscale. To enable the scores of various fields to be compared with each other, a range-based method was further used for linear transformation, converting the coarse scores into standardized scores with values ranging from 0 to 100. The 5 functional subscales (the formula standard score was SS = [1-(RS-1)/R] × 100) and 1 overall health subscale (the formula standard score was SS = [(R-1)/R] × 100) with higher scores indicate better functional status and quality of life. The 3 symptom subscales and 6 single symptom measurement items (both the formula standard score was SS = [(R-1)/R] × 100) with higher scores indicate worse quality of life.

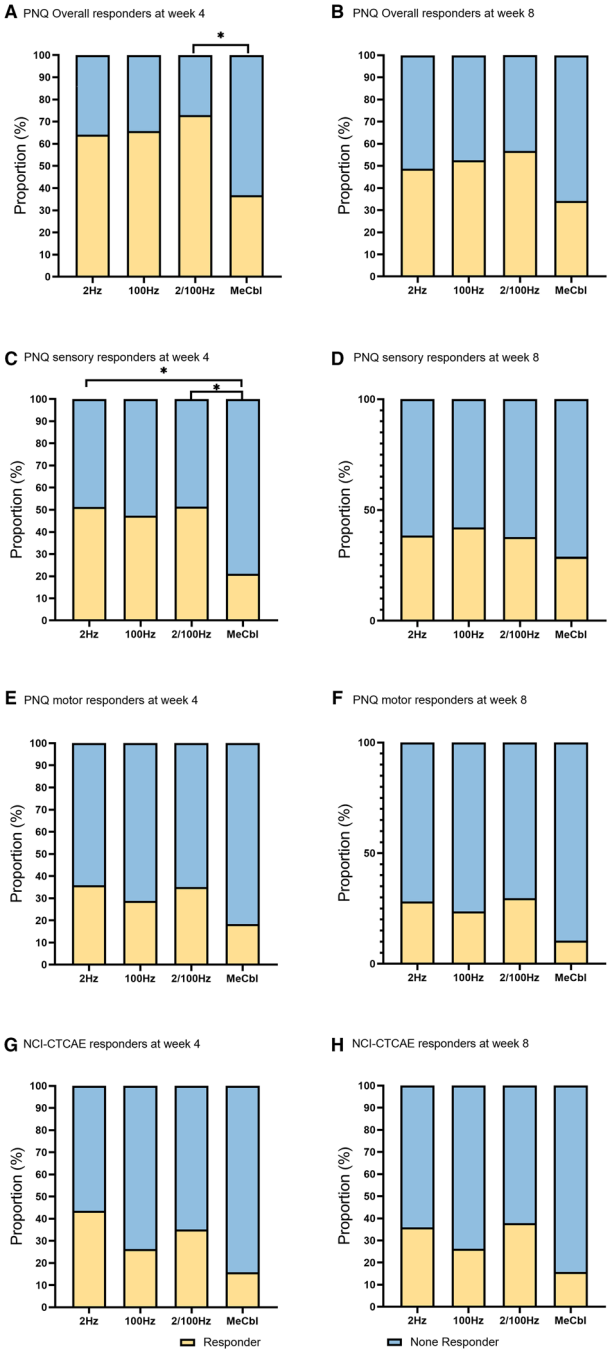

Figure 3. The response rate of PNQ and NCI-CTCAE. Abbreviations: EA: electroacupuncture; Mecbl: mecobalamin; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events (Version 5.0); PNQ, participant neurotoxicity questionnaire. Response rate defined as at least a one-grade reduction compared with baseline. Bonferroni was used for multiple comparisons and adjusted *P*-values. *Implies a statistical difference between the two groups in the proportion of responders ($P<.05$).

8 (all $P<.05$), while the 100 Hz EA group only demonstrated differences at Week 4 ($P<.05$). Regarding autonomic function, only the 2 Hz EA group showed differences compared with baseline at both Weeks 4 and 8 (all $P<.05$) (Table S2).

In the EORTC QLQ-C30 assessments at Weeks 4 and 8, the 2 Hz EA group showed significant differences from baseline in physical functioning, fatigue, pain, and insomnia symptom

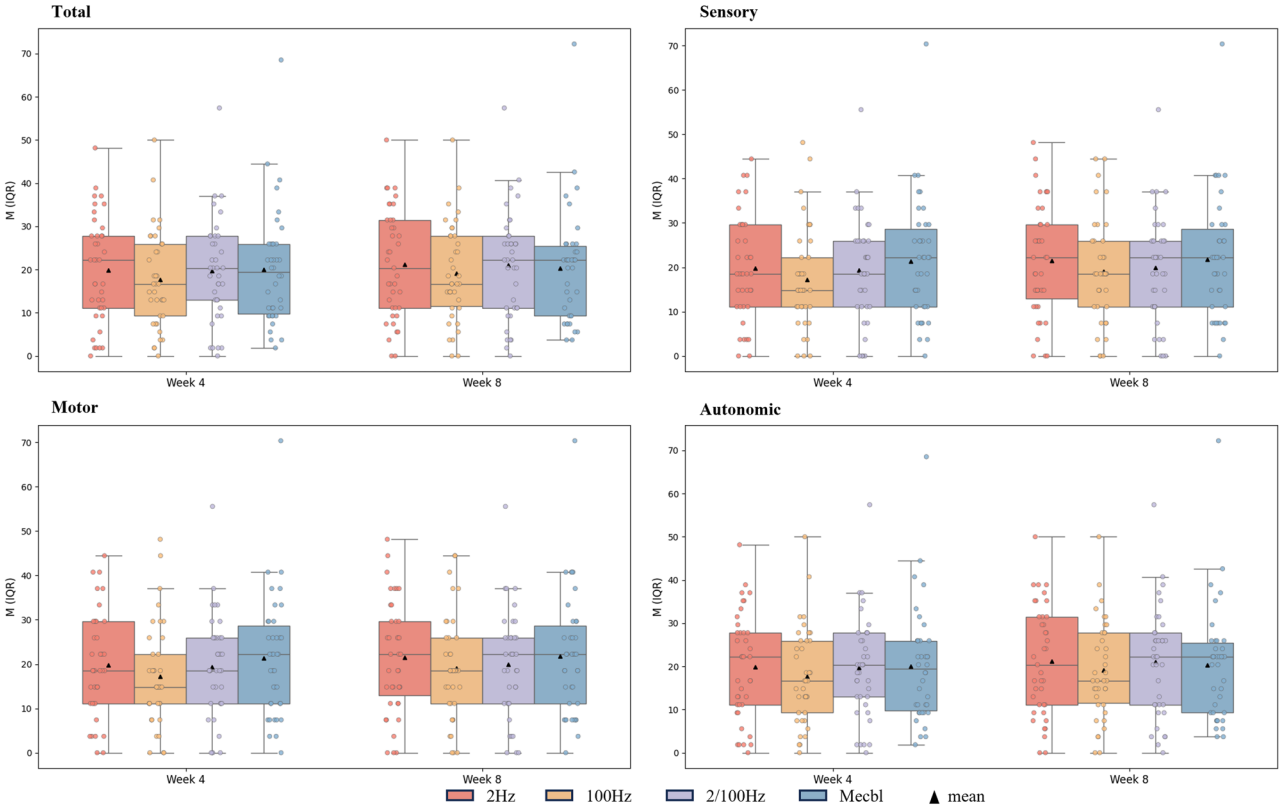

Figure 4. Intergroup comparison of EORTC QLQ-CIPN20 scores across 4 groups at Week 4 and Week 8. Abbreviations: 100 Hz: 100 Hz electroacupuncture; 2 Hz: 2 Hz electroacupuncture; 2/100 Hz: 2 Hz/100 Hz electroacupuncture; EORTC QLQ-CIPN20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN 20-item; Mecbl: mecobalamin. Box plots depict data distribution: boxes span the IQR (25th-75th percentiles) with a horizontal line at the median and a triangle symbol (▲) indicating the mean. All individual observations are overlaid as points. No statistically significant differences were observed between groups by the Kruskal–Wallis test ($P > .05$).

scores (all $P < .05$). The 2/100 Hz EA group demonstrated differences from baseline in nausea/vomiting, constipation, appetite loss, and global health status scores (all $P < .05$). Additionally, the 2/100 Hz EA group showed improvement in pain scores compared to baseline at Week 4 ($P < .05$) (Table S2).

To examine incident use of analgesics during the study, we also evaluated patterns among patients who did not report use at baseline ($n = 28/152$ [18.4%]). Among these patients, new use of analgesics during the study occurred in 15.38% of patients (6/39) in the 2 Hz EA group, 18.42% of patients (7/38) in the 100 Hz EA group, 13.51% of patients (5/37) in the 2/100 Hz EA group, and 26.32% of patients (10/38) in the Mecbl group. Most patients used analgesics occurred during the follow-up period and no differences were observed between groups in assessments (Table S3).

Adverse events occurred similarly frequently in the 4 groups (2 Hz EA, 18/39 [61.5%]; 100 Hz EA, 21/38 [55.3%]; 2/100 Hz EA, 17/37 [45.9%]; Mecbl, 14/38 [36.8%]). EA-related treatment mainly includes pain, subcutaneous bruising, or slight bleeding. The Mecbl group mainly occurs other events (Table 2). At Week 4, 2/39 (BANG'S Bling index = −0.05, 95% CI, [−0.17-0.07]) participants in the 2 Hz EA group guessed their treatment correctly, and 100 Hz EA group, 2/100 Hz EA respectively were 3/38 (BANG'S Bling index = 0.05, 95% CI [−0.09-0.20]), 3/37 (BANG'S Bling index = −0.03, 95% CI [−0.15 to 0.09]) (Table S4).

Discussion

This study was a randomized controlled, four-arm parallel-group, and participant-blinded pilot clinical trial. To our knowledge, it is the first clinical trial specifically designed to investigate the efficacy of different EA frequencies in treating CIPN. Among the 152 patients who completed the study, the results demonstrated that 2/100 Hz mixed-frequency EA yielded significant improvements in overall symptoms, sensory scores. Meanwhile, 2 Hz EA showed clear therapeutic efficacy in improving sensory scores. Consistent with previous studies,[19,31] this trial reaffirms that EA effectively alleviates CIPN symptoms, with superior outcomes compared to Mecbl.

EA has been shown to be superior to Mecbl in treating CIPN.[32] In exploring the efficacy of EA for CIPN, optimizing frequency parameters remains a crucial research direction. The significant work of Weidong Lu's team,[23] which used a 2-10 Hz sparse-dense wave and a similar overall response rate assessment system as in our trial, did not find intergroup differences but observed a trend of improvement in sensory symptoms with 2 Hz sparse wave, corroborating the consistent benefits in the sensory dimension of the 2 Hz group in our study. Notably, both 2 and 10 Hz frequencies are sparse waves. In our study, we changed the frequency to a 2/100 Hz sparse-dense wave and observed a difference in response rate between the 2/100 Hz group and Mecbl. This progress suggests that the addition of high-frequency parameters may be an important variable to

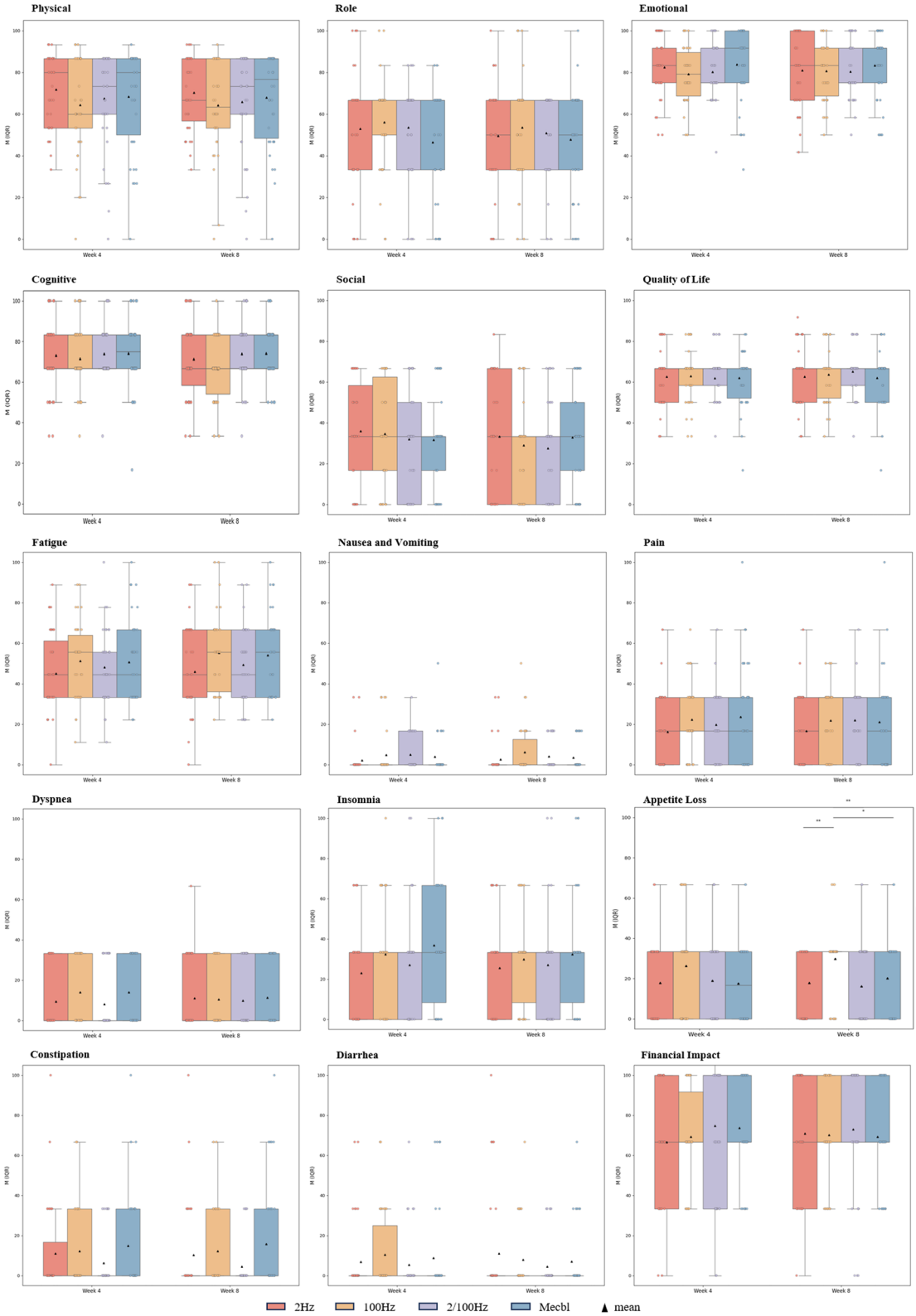

Figure 5. Intergroup comparison of EORTC QLQ-C30 scores across 4 groups at Week 4 and Week 8. Abbreviations: 100 Hz: 100 Hz electroacupuncture; 2 Hz: 2 Hz electroacupuncture; 2/100 Hz: 2 Hz/100 Hz electroacupuncture; EORTC QLQ-CIPN20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN 20-item; Mecbl: mecobalamin. Box plots depict data distribution: boxes span the IQR (25th-75th percentiles) with a horizontal line at the median and a triangle symbol (▲) indicating the mean. All individual observations are overlaid as points. No statistically significant differences were observed between groups by the Kruskal–Wallis test ($P > .05$).

Table 2. Analysis of adverse events.

	Patients, No. (%)				
Adverse events[a]	**2 Hz EA (*n* = 39)**	**100 Hz EA (*n* = 38)**	**2/100 Hz EA (*n* = 37)**	**Mecbl (*n* = 38)**	***P***
Pain related to acupuncture or EA treatment[b]	9 (23.1)	14 (36.8)	11 (29.7)	0 (0.0)	<.001
Subcutaneous bruising or slight bleeding related to acupuncture or EA treatment[c]	7 (17.9)	4 (10.5)	5 (13.5)	0 (0.0)	.03
Others: nausea and vomiting, diarrhea, intestinal obstruction, constipation, oral ulcer, insomnia, edema, dizziness, rash, headache, or others[d]	8 (20.5)	9 (23.7)	7 (18.9)	14 (36.8)	.29
Total[e]	18 (61.5)	21 (55.3)	17 (45.9)	14 (36.8)	.46

Abbreviations: EA, electroacupuncture; Mecbl, mecobalamin.
[a]Adverse events were analyzed in all participants who received treatment and counted by type rather than frequency in the same participant. Adverse events with different types occurring in one participant were defined as independent adverse events; an adverse event with multiple occurrences in one participant was defined as one adverse event.
[b]Pain related to acupuncture and EA treatment was common seen, but usually minor and could be accepted by patients. If the same patient expressed needle pain several times during treatment, only one person-time was counted.
[c]Subcutaneous bruising or slight bleeding was also common seen adverse event of acupuncture and EA treatment, mainly related to low platelet count in patients with advanced cancers.
[d]These adverse events were not related to acupuncture and EA treatment and mainly caused by patient's disease itself, anti-tumor drugs, or other therapies. These adverse events were not very serious and could relieve after symptomatic treatment.
[e]In the 2 Hz EA group, 13 patients experienced one adverse event, 4 patients experienced two adverse events, and 1 patient experienced four adverse events. In the 100 Hz EA group, 15 patients experienced one adverse event, 2 patients experienced two adverse events, 3 patients experienced three adverse events, and 1 patient experienced four adverse events. In the 2/100 Hz EA group, 11 patients experienced one adverse event, 4 patients experienced two adverse events, and 2 patients experienced three adverse events. In the MeCbl group, 8 patients experienced one adverse event, and 6 patients experienced two adverse events. There were no differences in adverse events among groups of patients.

break through the efficacy bottleneck. The 2 Hz sparse wave alone can significantly alleviate the sensory symptoms of CIPN, confirming the universality of low-frequency EA in sensory nerve modulation. Therefore, according to our research findings, 2/100 Hz EA is significant in improving overall symptoms (both sensory and motor) in patients with CIPN. However, for patients with CIPN predominantly characterized by sensory manifestations, 2 Hz EA stimulation parameters can be selected to achieve improvement.

While clinical trials evaluating frequency-specific EA effects on CIPN remain limited, preclinical evidence suggests differential neuromodulator properties across frequencies. Animal studies indicate superior efficacy of low-frequency EA in peripheral neuropathy models.[33–35] Meng et al.[36] demonstrated that 10 Hz EA more potently inhibited mechanical allodynia and hyperalgesia than 100 Hz EA in paclitaxel-induced neuropathy rats, mediated through spinal opioid receptors. Similarly, Zhang et al.[37] established that low-frequency EA alleviated paclitaxel-evoked allodynia and hyperalgesia via spinal 5-HT receptor activation and p-CaMKII suppression, effects absent with high-frequency stimulation. The findings of this study provide new evidence regarding the therapeutic effects of 2/100 Hz EA in symptom improvement, which may require further preclinical research to explore its underlying mechanisms.

EA intervention compared to drug treatment not only improves CIPN symptoms but also shows benefits in other aspects of patient quality of life with 2 Hz being superior for fatigue and insomnia improvement while 2/100 Hz works better for nausea vomiting appetite and overall wellbeing and both 2 and 2/100 Hz demonstrate effectiveness for pain symptoms. This conclusion is further corroborated by additional studies. For instance, Chan et al.[38] demonstrated that low-frequency (2 Hz) EA could enhance physical function, role function, and social function in colorectal cancer patients with CIPN. Moreover, Mao et al.[39] found that 2 Hz EA significantly ameliorated symptoms of fatigue, sleep disturbances, and psychological distress in breast cancer patients with aromatase inhibitor-related arthralgia compared to usual care. These findings collectively underscore the multifaceted therapeutic potential of low-frequency EA in improving various dimensions of patient well-being. In the research on pain, previous studies indicated that 2 Hz EA could cause the release of neuropeptides such as endorphins and enkephalins, 100 Hz EA could cause the release of dynorphin, and 2/100 Hz EA could produce a synergistic effect and play a strong analgesic role.[40] Although 2 Hz EA showed a difference compared with Mecbl treatment, we were unable to accurately evaluate the therapeutic effect of EA on pain, due to some patients using analgesic drugs in each group.

Limitations

Our study has several limitations. First, this was a single-center study with a relatively small sample size in each group, these observations are exploratory, which a multi-center and larger sample study should be set up. Second, the current study still has limitations in its control group design. As Mecbl is empirically used in clinical practice to manage non-painful CIPN symptoms, it lacks guideline recommendations. The conclusion that EA demonstrates superior efficacy compared to the control requires validation through more rigorous study designs before definitive claims can be made regarding EA's therapeutic benefits for CIPN. And we did not set up a sham EA group for comparison, and could not quantify the specific effect of EA vs manual acupuncture. Third, acupuncturists were not blinded to the group assignment owing to the treatment procedure. Fourth, the outcomes were based on patient-reported outcome measures, which, while providing direct insights into patients' subjective experiences, remain susceptible to reporting bias.

The original plan was to conduct the nerve conduction velocity as objective data, however, owing to the unwillingness of most patients to undergo the test, even if it was free, therefore, the test was removed.

Conclusions

This randomized clinical trial demonstrated that EA is a beneficial therapy for CIPN. Among patients with breast cancer and CIPN, 2/100 Hz EA exhibited potential advantages in terms of overall response rate, while 2 Hz EA showed superiority in sensory improvement. Both 2 and 2/100 Hz frequencies of EA had potential effects on different symptoms of quality of life. The therapeutic benefits of EA may require personalized treatment protocols tailored to individual symptom profiles. These preliminary results require cautious interpretation and lack generalizability, necessitating well-designed, adequately powered RCTs to generate high-quality evidence for subsequent meta-analyses and systematic evaluations.

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Author contributions

Qiongying Shen (Formal analysis, Writing—original draft), Dehou Deng (Methodology), Guangliang Li (Data curation), Jia Yin Ruan (Formal analysis, Software), Xiying Shao (Investigation, Methodology), Peipei Wang (Methodology), Xiaoyu Li (Validation, Writing—review & editing), Rongrong Li (Methodology), Wenlong Bao (Methodology), Weiji Chen (Conceptualization), and Chao Lu (Conceptualization, Project administration, Supervision)

Supplementary material

Supplementary material is available at *The Oncologist* online.

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Conflicts of interest

The authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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