




Electroacupuncture Plus Auricular Acupressure for Chemotherapy-Associated Insomnia in Breast Cancer Patients: A Pilot Randomized Controlled Trial

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Abstract

Objective: Chemotherapy-associated insomnia is a highly prevalent complaint in breast cancer patients. This study was undertaken to evaluate the safety, feasibility, and preliminary effectiveness of electroacupuncture plus auricular acupressure for chemotherapy-associated insomnia in patients with breast cancer. **Materials and Methods:** In this randomized, wait-list controlled trial, thirty breast cancer patients under or post chemotherapy with insomnia were randomly allocated to the acupuncture or wait-list control group. Participants in acupuncture group received electroacupuncture plus auricular acupressure treatment twice weekly for 6 weeks. Participants in wait-list group received the same regimen of treatment after 6-week of waiting period. Insomnia Severity Index (ISI) served as the primary outcome measurement. Secondary outcomes were sleep parameters recorded with sleep diary and actiwatch, as well as the scores of Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS), and Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B). **Results:** Twenty-eight participants completed study (13 in the acupuncture group vs 15 in the wait-list control group). At week-6 post-intervention, ISI score change from baseline showed significant between-group difference favoring acupuncture group of -2.9 points (95% CI: -5.2 to -0.6 , $P=.014$). The acupuncture group showed greater improvements in the total sleep time recorded by sleep diary ($P=.026$), scores of PSQI ($P=.012$), HADS-depression ($P=.020$), and FACT-B ($P<.001$) compared with the control group. Improvements were maintained at week-10 and week-14 follow-ups. **Conclusions:** Acupuncture is safe, feasible, and effective for chemotherapy-associated insomnia in breast cancer patients under or post chemotherapy. A larger sample size randomized clinical trial is warranted to confirm the present findings.

Clinical Trial Registration: NCT03762694.

Keywords

electroacupuncture, auricular acupressure, chemotherapy-associated insomnia, breast cancer, wait-list controlled

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Introduction

Insomnia is a highly prevalent and distressing sleep disorder in breast cancer patients with incidence rate of 42% to 69%.¹ It is defined as difficulty initiating or maintaining sleep, or early morning awakenings with inability to fall back to sleep.² Chemotherapy plays an important role in the development and aggravation of insomnia in cancer patients.^{3,4} The proportion of patients undergoing chemotherapy reporting insomnia is 3 times higher than that of the general population.⁵ Over 36% of breast cancer patients

develop insomnia post chemotherapy.⁶ Precipitating factors for the development of insomnia under chemotherapy include the psychological stress related to the cancer diagnosis and treatments, impact of chemotherapy pre-medications (eg, corticosteroids), and the occurrence of menopause and neurotoxicity symptoms induced by chemotherapy.⁷ Negative consequences of cancer related insomnia include depression, anxiety, fatigue, aggressive pain, impaired immune functioning, decreased quality of life, and even increased cancer mortality.^{4,8,9} If not appropriately treated, it can persist for years after completion of chemotherapy.¹⁰



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Acupuncture has been increasingly introduced into the management and treatment of cancer treatment-related side effects.¹¹ It involves acupuncture point stimulation using needles and possibly electricity on the surface of body, scalp, or ears. Numerous studies have proved the safety and effectiveness of acupuncture for managing insomnia.^{12,13} Electroacupuncture (EA) and auricular acupressure (AA) have shown promising efficacy in improving sleep quality and decreasing depressive symptoms.^{14,15} EA has been demonstrated to be well-tolerated and effective for treating chemotherapy-induced side effects such as cognitive impairment in breast cancer patients.¹⁶ This study aimed to determine the feasibility, preliminary effectiveness and safety of EA plus AA for chemotherapy-associated insomnia in breast cancer patients under or post chemotherapy. We hypothesized that EA plus AA would be feasible and show superior effectiveness for insomnia as compared to the wait-list control.

Materials and Methods

Participants

This was a randomized, wait-list controlled, assessor and data analyst-blinded, pilot clinical trial. The trial was approved by the Institutional Review Board of University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 18-526). This study was conducted in accordance with the Standards for Reporting Interventions in Clinical Trials of Acupuncture recommendations.¹⁷

The study was conducted between March 2019 and October 2020. Participants were recruited from Department of Oncology, Queen Mary Hospital. Participants provided written informed consent after the study procedures were fully explained. Assessments and interventions were conducted at the outpatient clinics of School of Chinese Medicine, University of Hong Kong. No subjects were paid for participation. Acupuncture was provided free of charge.

The inclusion criteria were (1) female patients aged 18 to 75 years; (2) diagnosis of stage I to IV breast cancer; (3) undergoing or have completed chemotherapy ≤ 6 months; (4) insomnia occurs at least 3 nights each week and presents ≥ 1 month, with the fulfillment of diagnostic criteria for brief insomnia disorder of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; (5) insomnia severity as defined by Insomnia Severity Index score ≥ 10 points in the past 2 weeks; (6) expected survival time > 6 months.

Subjects were excluded if they had (1) other sleep disorders (eg, obstructive sleep apnea); (2) irregular sleep pattern or shift work; (3) severe hearing, visual, or language defects; (4) severe hematological dysfunction (hemoglobin < 8 g/dL, platelet count $< 60\,000/\mu\text{L}$, absolute neutrophil count $< 1000/\mu\text{L}$); (5) pacemakers or other electronic implants that could interfere with electroacupuncture; (6) received acupuncture in the past 3 months; (7) participated in other clinical trials in the past 3 months.

Participants screening and recruitment were conducted by a research assistant. Eligible participants were sequentially randomly assigned to 2 groups according to a randomization list (at 1:1 ratio), which was generated by an independent research assistant with block randomization prior to recruitment. Randomization information was concealed in sequentially numbered opaque envelopes. Envelopes were opened by acupuncturist after participants completed baseline assessments. Except acupuncturists, other researchers including statisticians and assessors were blinded to group assignments.

Intervention

All participants received routine care provided by the oncologists for symptom management. All acupuncturists had over 5-year practice experience and received a brief training session before study initiation. Participants in acupuncture group received 12 sessions of EA plus AA treatment twice each week for 6 weeks. A brief introduction of treatment procedures was given by acupuncturist during the first treatment. Treatment protocol (see Figure 1 and Supplemental Appendix Table 1 for point locations) were developed based on neurobiological rationales,^{18,19} previous clinical trials,^{14,16} and clinical experience of acupuncture experts. For EA, a semi-standardized prescription was used. The prescription included 10 points, with 6 basic points that were frequently used to treat insomnia,²⁰ and 4 additional points to address participants' particular constitutions. The 6 fixed points included: EX-HN1 (Sishencong), GV20 (Baihui), GV24 (Shenting), PC6 (Neiguan; bilateral), KI3 (Taixi; bilateral), and SP6 (Sanyinjiao; bilateral). Four additional points were selected from: EX-HN3 (Yintang), CV4 (Guanyuan), LI4 (Hegu; bilateral), HT7 (Shenmen; bilateral), ST25 (Tianshu; bilateral), ST36 (Zusanli; bilateral), LR3 (Taichong; bilateral), KI6 (Zhaohai; bilateral), or any other points if necessary. After cleansing of the skin on acupoint with

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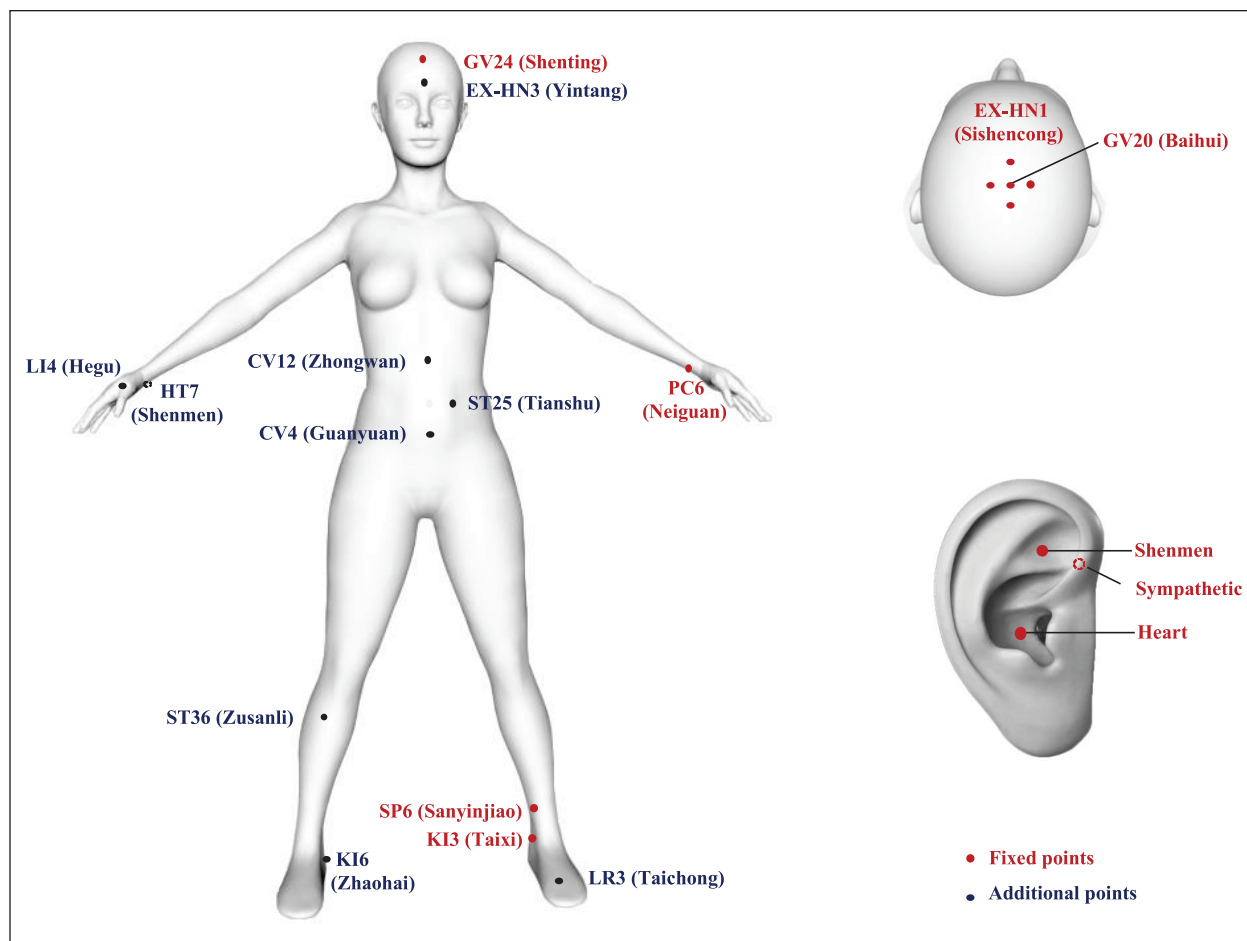


Figure 1. Acupuncture points and auricular points.

alcohol swab, a sterilized, disposable filiform needle (0.2 mm × 25/40 mm) with a guiding tube, was inserted into each point. “De qi” sensation was achieved. Four pairs of electrodes from EA apparatus (AWQ-104L, Electro Therapeutic Devices Inc.; 2-5 Hz, continuous wave) were connected to Baihui (+) and Shenting (−), left and right Sishencong (L+, R−), and other 2 pairs of points based on individual syndromes. Needles were remained for 25 minutes. For AA, *Vaccaria* seeds were embedded on surface of 3 auricular points (Heart, Shenmen, and Sympathetic) and maintained between 2 treatments. Participants were suggested to press each point gently for 1 minute thrice daily. Participants in the wait-list group did not receive acupuncture during the first 6 weeks, and would receive 12 sessions of acupuncture after waiting period (Figure 2a).

Outcome Measures

Primary outcome was the score change of Insomnia Severity Index (ISI) between baseline and the end of week-6

treatment. ISI is a 7-item self-reported questionnaire devised to evaluate insomnia severity,²¹ which is well-validated in diagnosing cancer-associated insomnia.²² Secondary outcomes were sleep parameters including sleep onset latency (SOL), wake time after sleep onset (WASO), total sleep time (TST), and sleep efficiency (SE) recorded by actiwatch (Spectrum Plus, Philips Respironics; USA)²³ and sleep diary²⁴ for a week at baseline and week-6, score changes of Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS), Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) from baseline to week-3, 6, 10, and 14. PSQI is 19-item self-reported questionnaire for assessing sleep dysfunction, with a higher score indicating poorer sleep quality.²⁵ HADS is a 14-item questionnaire with 2 subscales to assess the severity of anxiety and depression.²⁶ FACT-B is a 37-item questionnaire devised to evaluate multidimensional health-related quality of life (QoL) in patients with breast cancer, with a higher score indicating better QoL.²⁷ Feasibility are commonly assessed by recruitment rate, attrition rate, and the frequency of use of

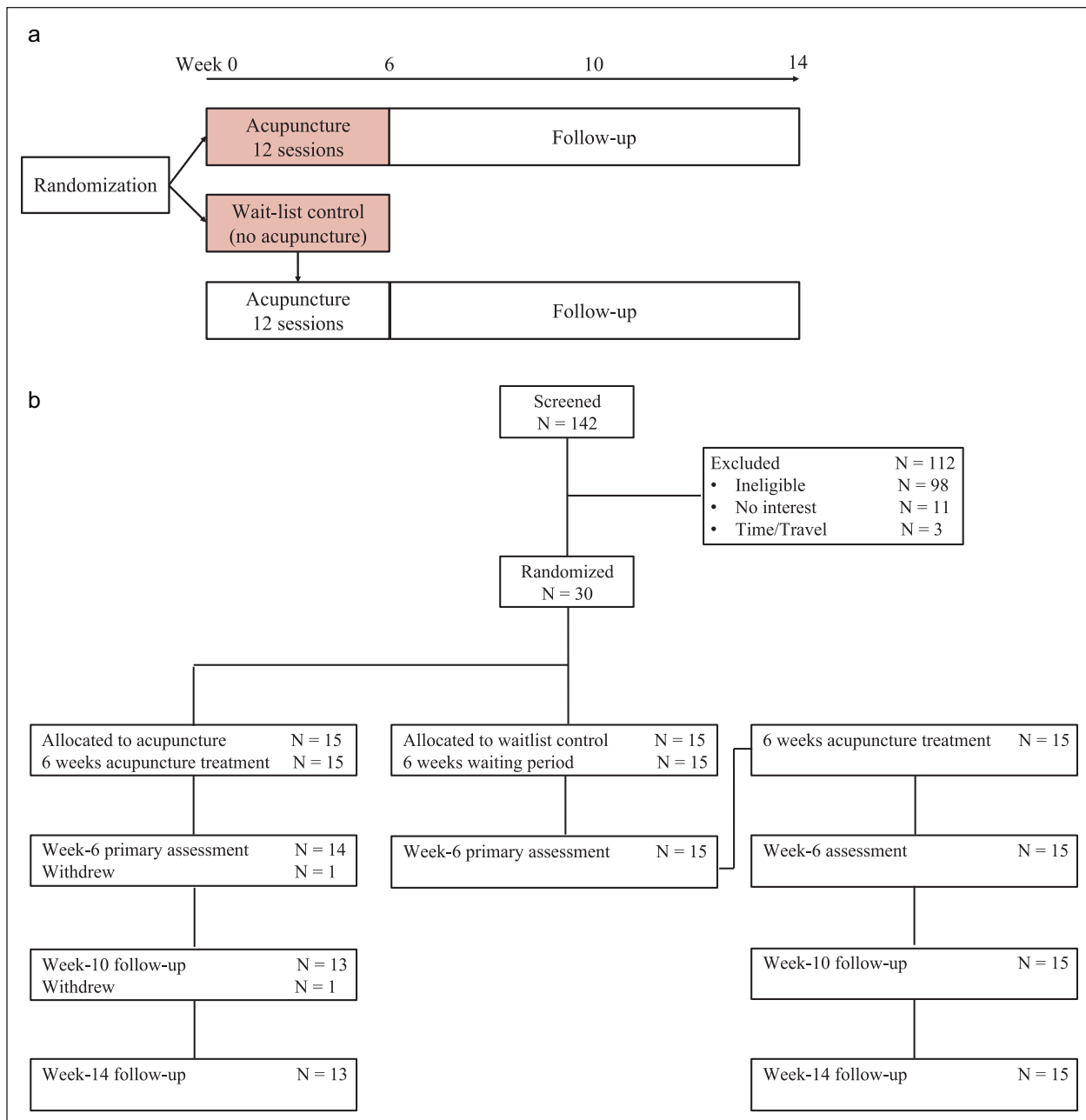


Figure 2. Study design (a) and flow diagram (b).

the intervention.²⁸ Participants' expectancy for clinical outcomes of acupuncture treatment is assessed by the 4-item Acupuncture Expectancy Scale (AES),²⁹ with a higher score indicating greater expected outcome for treatment.

Participants were asked whether they had experienced any adverse events (AEs) at each visit. The severity of AEs were graded according to the Common Terminology Criteria for Adverse Events V5.0 criteria.³⁰ AEs were appropriately managed within 24 hours. Serious AEs, if any, would be immediately reported to project investigators and Ethics Committee.

Data Monitoring

A data and safety monitoring board was established,³¹ which included independent experts of a statistician, an oncologist and a researcher of insomnia. They were not involved in the conduct of the trial. Regular meetings were scheduled to review the trial progress.

Statistical Analysis

The sample size was estimated depended on the anticipated change of ISI score. Previous trial for primary insomnia

showed a significant reduction in ISI of 5 points in acupuncture group as compared with sham control.¹⁴ Since there was not previous related study using wait-list control, to be conservative, we used the result of sham acupuncture group and pooled sample standard deviation of 4.05 for calculation. Therefore, 12 participants per group had a power of 80% and an alpha level of 0.05 to reject the null hypothesis. Given an estimated 20% dropout rate, 30 subjects were required.

Outcomes were analyzed using intention-to-treat principle. For descriptive statistical analysis, comparisons between groups were explored with *t* test or Chi-Square test or Wilcoxon rank-sum test. Changes of outcomes from baseline were analyzed employing a linear mixed-effect model with repeated-measures with baseline outcomes as covariates; treatment, visit, and treatment \times visit interaction were set as fixed-effects; and individual was set as random-effect. Meanwhile, to detect the effect of participants' expectancy for acupuncture or wait-list, baseline expectancy was adjusted in the additional analysis. Post-hoc analysis was performed with a mixed-effect model with repeated measures to determine impact of waiting period on acupuncture effect. This model included baseline, treatment, and follow-up as response variables, with time as fixed-effect. All statistical tests were conducted with SAS V9.4 with a 2-sided *P*-value of less than .05 was considered as statistically significant.

Results

Recruitment, Baseline Characteristics, and Feasibility

Between March 26, 2019 and June 9, 2020, we screened 142 participants for eligibility. Thirty eligible participants were randomly allocated either acupuncture ($n=15$) or wait-list group ($n=15$). Baseline characteristics were similar between 2 groups (Table 1). Two participants from acupuncture group withdrew due to time commitments (Figure 2b). No participant withdrew from wait-list group (6.7% total attrition rate across 2 groups). Twenty-eight participants completed 12 sessions of treatment: 13 (86.7%) in acupuncture group and 15 (100%) in wait-list group.

Primary Outcome

After 6 weeks of treatment, the change from baseline in ISI score was -6.6 (95% CI: -8.3 to -5.0) in the acupuncture group and -3.7 (95% CI: -5.3 to -2.1) in the wait-list group, with a between-group difference of -2.9 (95% CI: -5.2 to -0.6 , $P=.014$) favoring acupuncture group (Table 2 and Figure 3a). The results did not show deviations after the adjustment of baseline expectancy for acupuncture or wait-list.

Secondary Outcomes

After 3 weeks of treatment, participants in the acupuncture group showed a greater reduction in ISI compared to the wait-list group ($P=.001$; Table 2 and Figure 3a). After 6 weeks of treatment, the acupuncture group had greater improvement in PSQI ($P=.012$), TST recorded by sleep diary ($P=.026$), HADS-depression ($P=.020$), and FACT-B scores ($P<.001$). Two groups showed similar improvements in other sleep parameters and anxiety (Table 2). The number of participants used sleep medications in the acupuncture group decreased after acupuncture treatment (baseline: $n=3$; week-6: $n=2$; week-14 follow-up: $n=1$). After acupuncture treatment, the number of participants took sleep medications in the wait-list control group also decreased (baseline: $n=2$; week-6 at waiting period: $n=3$; week-6 at acupuncture treatment period: $n=0$; week-14 follow-up after acupuncture: $n=0$).

Long-Term Effects of Acupuncture

In the acupuncture group, 6 weeks of treatment led to 5.3-point reduction in ISI score as compared with pre-treatment (95% CI: -6.9 to -3.7 , $P<.001$; Figure 3b and Table 3). Participants in the wait-list group showed reduction in ISI score of 6.6 (95% CI: -8.1 to -5.0 , $P<.001$; Figure 3b and Table 3) after completing 6 weeks of acupuncture treatment. Significant reductions in PSQI and HADS, and increase in FACT-B were observed in both groups after 6 weeks of acupuncture treatment (each $P<.05$; Table 3). These improvements in both groups were maintained at week-14 follow-up (each $P<.01$; Table 3), indicating significant improvements in sleep quality, anxiety, depression, and QoL after acupuncture were maintained for at least 2 months. For post-hoc analysis, there was no statistically significant between-group differences at week-3, 6, and 14 in all outcomes (each $P>.05$; Table 3), indicating that participants benefit from acupuncture regardless of receiving waiting period or not.

Adverse Events

One subject in acupuncture group developed skin allergic reaction on auricular point, 1 experienced mild pain at needle site, and 1 experienced slight bruising at needle site. Subjects from wait-list group reported skin allergic reaction on auricular point ($n=1$), bruising ($n=1$), and palpitations ($n=1$) during acupuncture. All AEs were mild in severity.

Discussion

The combination of EA plus AA was found to be a feasible and acceptable intervention for chemotherapy-associated insomnia in patients with breast cancer, as supported by the

Table 1. Participants Characteristics.

| Characteristic | Acupuncture (n = 15) | Wait-list (n = 15) | Total (n = 30) | P value* |
|---|----------------------|--------------------|----------------|----------|
| Age, yrs | 52.5 ± 8.9 | 52.7 ± 6.3 | 52.6 ± 7.6 | .944 |
| Body mass index, kg/m ² | 22.6 ± 2.8 | 23.1 ± 3.3 | 22.8 ± 3.0 | .626 |
| Marital status | | | | .143 |
| Married or living with partner | 10 (66.7) | 6 (40.0) | 16 (53.3) | |
| Single, separated, divorced, or widowed | 5 (33.3) | 9 (60.0) | 14 (46.7) | |
| Educational attainment | | | | .342 |
| Primary | 0 (0.0) | 2 (13.3) | 2 (6.7) | |
| Secondary or below | 7 (46.7) | 6 (40.0) | 13 (43.3) | |
| Post-secondary or above | 8 (53.3) | 7 (46.7) | 15 (50.0) | |
| Family monthly income | | | | .737 |
| <HK\$20000 | 5 (33.3) | 7 (46.7) | 12 (40.0) | |
| HK\$20000-HK\$50000 | 7 (46.7) | 6 (40.0) | 13 (43.3) | |
| >HK\$50000 | 3 (20.0) | 2 (13.3) | 5 (16.7) | |
| Menopausal status | | | | .699 |
| Premenopausal | 2 (13.3) | 3 (20.0) | 5 (16.7) | |
| Perimenopausal | 1 (6.7) | 2 (13.3) | 3 (10.0) | |
| Postmenopausal | 12 (80.0) | 10 (66.7) | 22 (73.3) | |
| Cancer stage | | | | .701 |
| I | 2 (13.3) | 2 (13.3) | 4 (13.3) | |
| II | 4 (26.7) | 7 (46.7) | 11 (36.7) | |
| III | 3 (20.0) | 2 (13.3) | 5 (16.7) | |
| IV | 6 (40.0) | 4 (26.7) | 10 (33.3) | |
| Under or post chemotherapy at entry | | | | .690 |
| Under | 10 (66.7) | 11 (73.3) | 21 (70.0) | |
| Post | 5 (33.3) | 4 (26.7) | 9 (30.0) | |
| Adjuvant chemotherapy | | | | .283 |
| Yes | 12 (80.0) | 14 (93.3) | 26 (86.7) | |
| No | 3 (20.0) | 1 (6.7) | 4 (13.3) | |
| Type of chemotherapy | | | | .112 |
| FAC | 3 (20.0) | 0 (0.0) | 3 (10.0) | |
| Paclitaxel | 3 (20.0) | 3 (20.0) | 6 (20.0) | |
| Docetaxel | 9 (60.0) | 9 (60.0) | 18 (60.0) | |
| Others | 0 (0.0) | 3 (20.0) | 3 (10.0) | |
| Insomnia mean duration, months | 6.8 ± 8.4 | 11.9 ± 18.6 | 9.3 ± 14.4 | .345 |
| Usage of sleep medications | | | | .624 |
| Yes | 3 (20.0) | 2 (13.3) | 5 (16.7) | |
| No | 12 (80.0) | 13 (86.7) | 25 (83.3) | |
| ISI | 15.1 ± 3.8 | 15.0 ± 4.8 | 15.1 ± 4.3 | .933 |
| PSQI | 12.5 ± 3.3 | 11.3 ± 3.4 | 11.9 ± 3.4 | .337 |
| Sleep diary | | | | |
| SOL, min | 56.1 ± 27.8 | 38.3 ± 19.4 | 47.2 ± 25.3 | .052 |
| WASO, min | 79.4 ± 40.7 | 67.5 ± 39.0 | 73.4 ± 39.6 | .419 |
| TST, min | 322.7 ± 92.7 | 335.6 ± 66.3 | 329.1 ± 79.4 | .665 |
| SE, % | 63.2 ± 16.7 | 70.6 ± 13.0 | 66.9 ± 15.2 | .186 |
| Actiwatch | | | | |
| SOL, min | 9.8 ± 9.5 | 6.7 ± 5.8 | 8.3 ± 7.9 | .296 |
| WASO, min | 145.3 ± 37.9 | 118.6 ± 36.3 | 132.0 ± 38.9 | .059 |
| TST, min | 341.8 ± 49.5 | 344.7 ± 39.7 | 343.3 ± 44.1 | .862 |
| SE, % | 67.3 ± 8.2 | 72.6 ± 6.0 | 70.0 ± 7.5 | .053 |
| HADS | | | | |
| Anxiety | 7.1 ± 2.0 | 7.8 ± 4.3 | 7.4 ± 3.3 | .552 |
| Depression | 7.9 ± 3.4 | 7.3 ± 4.4 | 7.6 ± 3.8 | .711 |

(continued)

Table 1. (continued)

| Characteristic | Acupuncture (n = 15) | Wait-list (n = 15) | Total (n = 30) | P value* |
|----------------|----------------------|--------------------|----------------|----------|
| FACT-B | 87.6 ± 14.1 | 83.6 ± 22.8 | 85.6 ± 18.7 | .564 |
| AES | 13.8 ± 2.4 | 14.2 ± 2.3 | 14.0 ± 2.3 | .647 |

Note. Data are presented as mean ± standard deviation or number (%).

Abbreviations: FAC, Fluorouracil, Adriamycin, and Cyclophosphamide; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; SOL, sleep-onset latency; WASO, wake after sleep onset; TST, total sleep time; SE, sleep efficiency; HADS Hospital Anxiety and Depression Scale; FACT-B, functional assessment of cancer therapy-breast cancer; AES, Acupuncture Expectancy Scale.

*Comparison between acupuncture group and wait-list group by χ^2 or unpaired t-test.

Table 2. Change in Outcomes from Baseline by Groups.

| Outcomes | Change from baseline | | Between-group difference | |
|------------------------------|------------------------|-----------------------|--------------------------|---------|
| | Acupuncture | Wait-list | Acupuncture vs Wait-list | P value |
| Primary outcome | | | | |
| ISI [†] | | | | |
| Week-3 | -5.4 (-7.1 to -3.7) | -1.6 (-3.2 to 0) | -3.8 (-6.1 to -1.5) | .001 |
| Week-6 | -6.6 (-8.3 to -5.0) | -3.7 (-5.3 to -2.1) | -2.9 (-5.2 to -0.6) | .014 |
| Secondary outcomes | | | | |
| PSQI [†] | | | | |
| Week-3 | -2.4 (-3.7 to -1.1) | -0.7 (-2.0 to 0.5) | -1.7 (-3.5 to 0.1) | .071 |
| Week-6 | -3.9 (-5.2 to -2.6) | -1.6 (-2.9 to -0.3) | -2.3 (-4.1 to -0.5) | .012 |
| Sleep diary, week-6 | | | | |
| SOL, min [†] | -24.2 (-32.4 to -16.1) | -14.1 (-21.6 to -6.3) | -10.1 (-21.2 to 1.0) | .073 |
| WASO, min [†] | -9.1 (-27.5 to 9.3) | -14.8 (-31.9 to 2.3) | 5.7 (-19.4 to 30.8) | .651 |
| TST, min [‡] | 51.7 (31.4 to 72.1) | 20.1 (1.2 to 39.0) | 31.6 (3.9 to 59.4) | .026 |
| SE, % [‡] | 10.4 (6.1 to 14.7) | 5.6 (1.6 to 9.6) | 4.8 (-1.1 to 10.7) | .106 |
| Actiwatch, week-6 | | | | |
| SOL, min [†] | 0.5 (-2.7 to 3.7) | 2.1 (-0.9 to 5.1) | -1.6 (-6.0 to 2.8) | .474 |
| WASO, min [†] | -4.2 (-12.4 to 3.9) | 0.8 (-6.7 to 8.4) | -5.0 (-16.1 to 6.1) | .370 |
| TST, min [‡] | 1.2 (-10.3 to 12.7) | -8.7 (-19.4 to 1.9) | 9.9 (-5.7 to 25.6) | .209 |
| SE, % [‡] | 1.0 (-0.6 to 2.6) | -0.9 (-2.4 to 0.6) | 1.9 (-0.3 to 4.1) | .091 |
| HADS—anxiety [†] | | | | |
| Week-3 | -1.4 (-2.5 to -0.4) | -0.3 (-1.3 to 0.6) | -1.1 (-2.5 to 0.3) | .128 |
| Week-6 | -1.4 (-2.4 to -0.3) | -0.4 (-1.4 to 0.6) | -1.0 (-2.4 to 0.4) | .179 |
| HADS—depression [†] | | | | |
| Week-3 | -1.6 (-2.6 to -0.6) | 0 (-1.0 to 1.0) | -1.6 (-3.0 to -0.3) | .020 |
| Week-6 | -2.2 (-3.2 to -1.2) | -0.6 (-1.5 to 0.3) | -1.6 (-3.0 to -0.3) | .020 |
| FACT-B [‡] | | | | |
| Week-3 | 11.8 (6.1 to 17.5) | 0.5 (-4.9 to 5.9) | 11.3 (3.5 to 19.1) | .005 |
| Week-6 | 14.9 (9.3 to 20.5) | 1.3 (-4.1 to 6.7) | 13.6 (5.9 to 21.3) | <.001 |

Note. Data are presented as mean (95% Confidence Interval).

Abbreviations: ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; SOL, sleep-onset latency; WASO, wake after sleep onset; TST, total sleep time; SE, sleep efficiency; HADS Hospital Anxiety and Depression Scale; FACT-B, Functional Assessment of Cancer Therapy-Breast Cancer.

[†]A greater negative value represents improvement in symptoms.

[‡]A greater positive value represents improvement in symptoms.

high recruitment rate (71%), satisfied adherence rate (87% in the acupuncture group vs 100% in the control group), and low attrition rate (6.7% across 2 arms). After 6 weeks of treatment, subjects in the acupuncture group experienced significantly greater improvements in insomnia, depression, and quality of life relative to the wait-list participants.

The wait-list participants also showed significant improvements in insomnia, depression, anxiety, and quality of life after completing acupuncture treatment. The 6-week twice-weekly course of EA plus AA was safe and well-tolerated. These results support that acupuncture is safe, effective, and feasible for chemotherapy-associated insomnia. Symptom

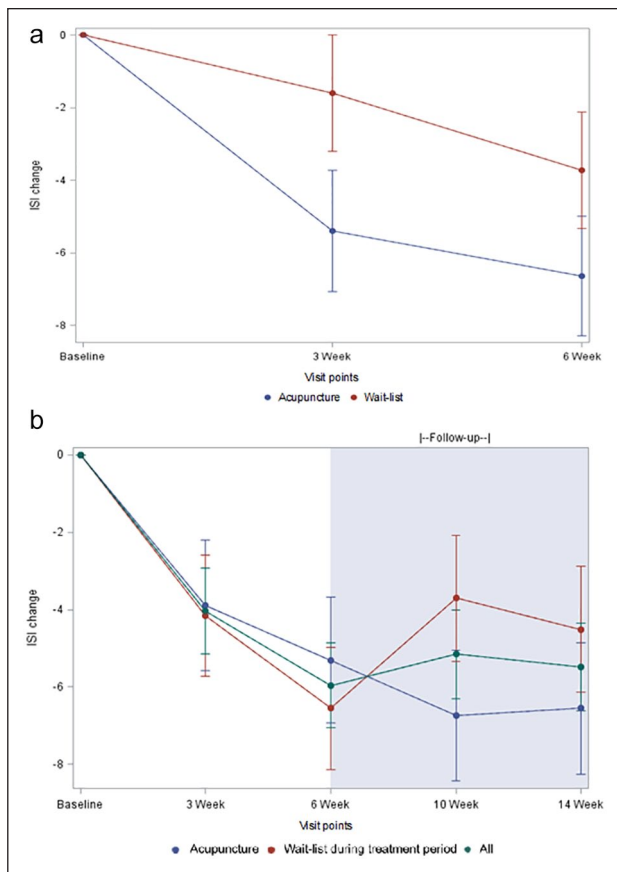


Figure 3. Change of ISI score (a) from baseline to week-6 of groups (b) of participants after acupuncture treatment. Error bar represents 95% Confidence Interval.

improvements were maintained for at least 2 months after acupuncture treatment. This finding provides preliminary support for the long-term effect of acupuncture which is encouraging given the pertinent criticisms of existing pharmacotherapy for insomnia related to questions surrounding its unsatisfying efficacy and undesirable side effects.⁷

The effects observed in this study might be related to the acupuncture regimen used. The study used a combination of auricular, forehead, and body points, with electrical stimulation was applied on forehead and body points, and pressure stimulation was given on auricular points. Forehead acupoints are connected to the trigeminal sensory pathway, which transmits sensory information to trigeminal sensory nuclear complex (TSNC) via monosynaptic connections³² and projects to brain regions that coordinate neurobehavioral engagement with environment and regulate arousal.^{33,34} Electrical stimulation on trigeminal nerve branches is effective in improving sleep quality and reducing stress likely through neuromodulating TSNC activity and functional connectivity to ascending reticular activating system networks.³⁴ EA's modulatory effects on serotonin-producing and noradrenaline-producing neurons from brainstem reticular formation also might be involved into its treatment mechanisms.¹⁶ Auricular points are innervated by the vagus nerve, which exerts effects for insomnia by balancing the hyperactivity of sympathetic nerve.³⁵ Additionally, there is substantial evidence suggesting acupuncture could alleviate insomnia by acting on central and autonomic nervous system, and modulate activities of neurotransmitters including γ -aminobutyric acid and melatonin.³⁶ EA plus AA might produce promising effects by

Table 3. Long-Term Effects of Acupuncture Treatment.

| Outcomes | Acupuncture | Wait-list* | P value ^a | Total | P value ^b |
|------------------------------------|----------------------------------|----------------------------------|----------------------|---------------------|----------------------|
| ISI[†] | | | | | |
| Week-3 | -3.9 (-5.6 to -2.2) [#] | -4.2 (-5.7 to -2.6) [#] | .832 | -4.0 (-5.2 to -2.9) | <.001 |
| Week-6 | -5.3 (-6.9 to -3.7) [#] | -6.6 (-8.1 to -5.0) [#] | .289 | -6.0 (-7.1 to -4.9) | <.001 |
| Week-10 | -6.7 (-8.4 to -5.1) [#] | -3.7 (-5.3 to -2.1) [#] | .014 | -5.2 (-6.3 to -4.0) | <.001 |
| Week-14 | -6.6 (-8.3 to -4.9) [#] | -4.5 (-6.1 to -2.9) [#] | .097 | -5.5 (-6.6 to -4.3) | <.001 |
| PSQI[†] | | | | | |
| Week-3 | -1.8 (-3.3 to -0.3) [#] | -2.5 (-3.9 to -1.0) [#] | .540 | -2.1 (-3.2 to -1.1) | <.001 |
| Week-6 | -3.4 (-4.9 to -1.9) [#] | -4.1 (-5.6 to -2.7) [#] | .495 | -3.8 (-4.8 to -2.8) | <.001 |
| Week-10 | -5.0 (-6.6 to -3.6) [#] | -2.4 (-3.9 to -0.9) [#] | .019 | -3.7 (-4.7 to -2.7) | <.001 |
| Week-14 | -4.7 (-6.3 to -3.2) [#] | -2.4 (-3.9 to -0.8) [#] | .043 | -3.5 (-4.6 to -2.5) | <.001 |
| HADS—anxiety[†] | | | | | |
| Week-3 | -1.6 (-2.7 to -0.5) [#] | -1.5 (-2.5 to -0.5) [#] | .874 | -1.5 (-2.3 to -0.8) | <.001 |
| Week-6 | -1.5 (-2.5 to -0.4) [#] | -1.9 (-2.9 to -1.0) [#] | .493 | -1.7 (-2.4 to -1.0) | <.001 |
| Week-10 | -2.7 (-3.7 to -1.6) [#] | -1.2 (-2.2 to -0.1) [#] | .051 | -1.9 (-2.7 to -1.2) | <.001 |
| Week-14 | -1.8 (-2.9 to -0.7) [#] | -1.5 (-2.5 to -0.4) [#] | .658 | -1.6 (-2.4 to -0.9) | <.001 |
| HADS—depression[†] | | | | | |
| Week-3 | -1.5 (-2.6 to -0.4) [#] | -1.2 (-2.3 to -0.2) [#] | .727 | -1.4 (-2.1 to -0.6) | <.001 |
| Week-6 | -2.1 (-3.2 to -1.1) [#] | -1.5 (-2.5 to -0.5) [#] | .388 | -1.8 (-2.6 to -1.1) | <.001 |
| Week-10 | -2.9 (-4.0 to -1.8) [#] | -0.8 (-1.9 to 0.3) | .009 | -1.8 (-2.6 to -1.1) | <.001 |
| Week-14 | -2.4 (-3.5 to -1.4) [#] | -1.9 (-3.0 to -0.8) [#] | .453 | -2.1 (-2.9 to -1.4) | <.001 |

(continued)

Table 3. (continued)

| Outcomes | Acupuncture | Wait-list* | P value ^a | Total | P value ^b |
|---------------------|----------------------------------|---------------------------------|----------------------|---------------------|----------------------|
| FACT-B [‡] | | | | | |
| Week-3 | 12.4 (6.3 to 18.5) [#] | 7.6 (1.9 to 13.4) [#] | .260 | 9.9 (5.7 to 14.1) | <.001 |
| Week-6 | 15.7 (9.7 to 21.7) [#] | 13.5 (7.7 to 19.2) [#] | .586 | 14.6 (10.4 to 18.7) | <.001 |
| Week-10 | 19.3 (13.2 to 25.4) [#] | 11.2 (5.2 to 17.2) [#] | .065 | 15.1 (10.8 to 19.4) | <.001 |
| Week-14 | 18.8 (12.6 to 24.9) [#] | 10.5 (4.3 to 16.6) [#] | .063 | 14.5 (10.2 to 18.9) | <.001 |

Note. Data are presented as mean (95% Confidence Interval).

Abbreviations: ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; HADS Hospital Anxiety and Depression Scale; FACT-B, functional assessment of cancer therapy-breast cancer.

†A greater negative value represents improvement in symptoms.

‡A greater positive value represents improvement in symptoms.

^aP value was calculated using a mixed-effects model with baseline adjustment to illustrate between-group differences.

^bP value was calculated using a mixed-effects model with baseline adjustment to illustrate pre- and post-acupuncture differences.

*Data from wait-list participants post-waiting period were used.

[#]P < .05, compared with pre-treatment within-group.

broadly modulating multiple brain regions and various neurotransmitters.

The effect of acupuncture for insomnia comorbid with cancer might vary across studies due to the differences in sample characteristics (eg, cancer type, cancer treatment status). Among cancer survivors who had completed active treatment (including surgery, chemotherapy, and radiotherapy), Garland et al¹² found that 8-week of treatment produced 8.3 points reduction in ISI in acupuncture group and 10.9 points in cognitive behavioral therapy group respectively compared to pre-treatment. In our study, 6-week of acupuncture treatment produced 6.6 points reduction in ISI compared to pre-treatment among breast cancer patients undergoing active treatments. In another study, Palesh et al³⁷ investigated the effectiveness of brief behavioral therapy for insomnia among breast cancer patients receiving chemotherapy, and found that 6-week of treatment produced around 5 points reduction in ISI as compared with pre-treatment. Cancer survivors who had completed active cancer treatment seemed to benefit more from acupuncture or behavioral therapy as compared to those who were undergoing active treatment. Active cancer treatments like chemotherapy and radiotherapy are regarded as precipitating factors for insomnia comorbid with cancer.⁷ Even though the effectiveness of acupuncture might be weakened by the persistence of precipitating factors (like active cancer treatments and their side effects), taking the negative health consequences of insomnia comorbid with cancer into consideration, early intervention might play an important role in preventing the aggravation of insomnia.

The findings need to be interpreted with limitations. First, blinding was not possible in this wait-list controlled trial. The sample size of this study was small, which called for larger randomized clinical trials to produce sound conclusions. Furthermore, subjects with insomnia tend to underestimate total sleep time and overestimate sleep-onset latency and wake after sleep onset in self-reported sleep

diary.³⁸ Actiwatch has been reported less sensitive to detect wakefulness and tends to overestimate total sleep time and sleep efficiency.³⁹ The results of sleep diary and actiwatch should be interpreted cautiously. Finally, the waiting period of wait-list group was limited to 6 weeks due to study timeframe and ethical concerns, which led to the lack of comparison of follow-up assessments between groups. The follow-up analysis was based on uncontrolled data due to the study timeframe and therefore should be interpreted with cautions. Despite the limitations, the study has many strengths including using a semi-standardized acupuncture protocol, which allows for addressing individual treatment needs and replicating study findings. Furthermore, recruiting participants with no restrictions on cancer stage nor chemotherapy drugs, adopting validated questionnaires and objective measurement, both enhance the generalizability of the results.

In conclusion, this study provided support for the feasibility, safety, and preliminary effectiveness of EA plus AA for chemotherapy-associated insomnia in patients with breast cancer. Future research should consider statistically controlling for confounding variables (eg, chemotherapy regimens), hence increasing accurate interpretation of causal effects of acupuncture for chemotherapy-associated insomnia. If proven to be effective, acupuncture could be implemented into routine settings to benefit cancer patients suffering from insomnia.

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Author Contributions

JLZ and ZSQ contributed equally to this study. ZJZ, LXL, HYC, JLZ, THS, and WLL were involved in conception and study design. JLZ and ZSQ conducted data analysis. JLZ drafted the manuscript. ZJZ, LXL, JLZ, and ZSQ revised the manuscript. THS referred participants. LLY carried out acupuncture treatments. PYC performed assessments.

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Supplemental Material

Supplemental material for this article is available online.

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