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Original article

Acupuncture relieves menopausal discomfort in breast cancer patients: A prospective, double blinded, randomized study

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ABSTRACT

Background: This study evaluates the effect of acupuncture on hot flashes and disturbed night sleep in patients treated for breast cancer. The effect of acupuncture was tested against a sham-acupuncture group and a no-treatment control group. Plasma estradiol was measured to rule out this as cause of effect. Side effects of the treatment were registered.
Methods: We randomized 94 women into the study: 31 had acupuncture, 29 had sham acupuncture and 34 had no treatment.
Findings: In the acupuncture group, 16 patients (52%) experienced a significant effect on hot flashes compared with seven patients (24%) in the sham group ($p < 0.05$). The effect came after the second acupuncture session and lasted for at least 12 weeks after last treatment. A statistically significant positive effect was seen on sleep in the acupuncture group compared with the sham-acupuncture and no-treatment groups. The effect was not correlated with increased levels of plasma estradiol. No side effects of acupuncture were registered.
Interpretation: We find that acupuncture significantly relieves hot flashes and sleep disturbances and is a good and safe treatment in women treated for breast cancer.
The project is registered at Clinical Trials.gov (no: NCT00425776).

Introduction

Breast cancer patients have a higher incidence of bothersome hot flashes and sleep disturbances than other women do.[1–4] The reasons for this high incidence of postmenopausal symptoms might be because most women with breast cancer are between 50 and 70 years, where the incidence of hot flashes is already high. Furthermore, prior to the breast cancer diagnosis, some women would have used hormone replacement therapy and would have subsequently withdrawn from this therapy. Adjuvant therapy often aggravates hot flashes, ultimately leading to poor quality of life.[5] Consequently, there is a need for better rehabilitation, especially when the disease has been treated and is under control.

The exact pathophysiological background for the vasomotoric symptoms in postmenopausal women is unclear; nevertheless, it is undoubtedly multi-factorial and might include dysfunction of the thermoregulation center.[6,7] The pathophysiology of acupuncture and how it works is unknown. A hypothesis suggests that the hormone endorphin increases during acupuncture, thereby moderating the thermoregulatory mechanism in the hypothalamus.[7,8] Calcitonin gene-related peptide level, a powerful vasodilator released during hot flashes, is shown to decrease during periods with acupuncture.[6] Although several clinical trials have shown an effect of acupuncture on vasomotoric symptoms,[6,8–13] others have not.[14,15] Two reviews from 2009 conclude that the evidence is not sufficiently convincing to suggest acupuncture as an effective treatment of menopausal symptoms in patients with breast cancer and call for further studies to investigate the effects of acupuncture for treating hot flashes.[16,17] Some studies suggest that acupuncture can increase plasma hormone levels.[18–20] Accordingly, it is important to investigate whether there is an undesirable increase in plasma estradiol during and after acupuncture because of the possible increased risk of recurrence of cancer.[21]

In addition to the lack of evidence of the effect of acupuncture on hot flashes, there is also a lack of systematic, well-conducted research investigating the possible side effects of this treatment. The aim of the present study was to investigate the therapeutic effect of acupuncture on hot flashes and disturbed sleep in breast cancer patients, the possible side effects of this treatment, and the effect on plasma estradiol levels.

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Material and methods

The study included 94 women, mean age 61 years (45–76 yr). The inclusion criterion was women treated for breast cancer with self-estimated troublesome hot flashes and disturbed night sleep. Exclusion criteria were treatment with hormone replacement therapy or known metastatic disease. Only the women's own perception of symptoms was registered. There were used no further selection criteria. The patients were recruited by advertisement at the breast center waiting room for mammography control and in the outpatient clinics. Inclusion was done by the investigator at the breast center where oral and written information was given, and before entering all the participants signed an informed consent. All patients were in the postoperative period from 6 months to 5 years. Two patients had chemotherapy but their treatment had ceased at the time of acupuncture. For all patients who had antihormone-treatment, it was given during the whole study period. The randomization was done by the acupuncturist. The participant personally drew a sealed envelope from a plastic bag and was randomly allocated to either of three groups. Group 1 included 31 patients who had acupuncture; Group 2 included 29 patients who had sham acupuncture; and Group 3 included 34 women with no treatment. Group 1 and 2 were both patient- and investigator blinded.

Two experienced acupuncturists gave either acupuncture in the selected acupuncture points or in the sham points. Group 1 had manual acupuncture in pre-determined bilateral points for 15–20 min once a week for five consecutive weeks. We used true points along the meridians for acupuncture. The points were Hc6, Ki3, Sp6 and Lr3. These points are located on the wrist, ankle and foot. We did not use any extra points as known from Chinese acupuncture. Group 2 had sham acupuncture in four pre-determined bilateral non-acupuncture points outside the meridians, but in the same region as the true points. It was given with the same needles as true acupuncture and inserted superficially in the skin. They were placed with 1 cm distance in the skin of the distal part of tibia in the frontal midline. One needle was given 1 cm cranially from the wrist line at the most ulnar point. The needles were in place for 15–20 min. Treatment was given once a week for five weeks like in the acupuncture group. Group 3: received no acupuncture. The acupuncture points were selected from the textbook Practice of Acupuncture.[22] To our knowledge none of the participants had acupuncture before.

The set-up was tested in a pilot study including 25 women with a history of breast cancer and hot flashes. The study showed that 68% of the women more than halved the nuisance of their hot flashes and 76% had better sleep.

All participants in Group 1 and Group 2 kept a protocol-specific logbook where they rated the extent of their symptoms on a subjective visual analog scale (VAS) from zero to ten. Baseline score was based on a period of two weeks before entering the study. The logbook was filled in three days after each treatment, and six and twelve weeks after the final acupuncture treatment. Their sleep disturbances were rated "yes" or "no" at the same time points. The symptoms were not described in more detail and every patient was her own control. However, any side effects of the acupuncture, the use of adjuvant drugs and alternative medicine were registered at all time points. The participants in the no-treatment group kept a similar protocol-specific logbook filled in at the same time points they were not contacted during that period except for the day at the fifth week where they came for the last blood sample. All participants completed their logbooks. In this study axillary dissection was not a contradiction for acupuncture in the wrists. All the participants were offered acupuncture treatment after the study has ceased.

Plasma estradiol level was measured in blood samples taken just before the first treatment and 30 min after. It was measured again five weeks later, 30 min after the final acupuncture treatment. Blood tests were also drawn from the control group at the allocation and five weeks later. Blood was drawn into Heparin Venous Blood Vacuum Collection Tubes. Plasma aliquots for estradiol testing were stored at −20 °C until analysis was performed using a Roche Modular Immunochemistry®, Electrochemical Luminescent Immuno Assay (ECLIA), Roche Diagnostics GMBA, Mannheim, Germany. The analysis was performed according to the manufactures' instructions.

Approval for the study was obtained from an independent ethics committee on Biomedical Research Ethics, Denmark, (VF-20060112) and Clinical Trials.gov (no: NCT00425776).

Statistics: To detect a 50% decrease in symptoms in more than 50% of the women at a significance level of 5% and with a power of 80%, a total sample size of 93 participants with 31 in each group was needed. The three groups were compared in pairs in terms of each period.

The primary hypothesis was that more than 50% of the women receiving correct acupuncture would significantly halve their distress from hot flashes and night disturbances compared with the women receiving sham acupuncture and those with no treatment.

Comparison of groups was made using the Wilcoxon Rank Sum test and the relative differences were determined using the Kruskal–Wallis test.

Results

Table 1 shows the baseline characteristics of women entering the study. Biologically we have age and adjuvant medical treatment. The area of inclusion consists of Caucasians and no ethnical minorities were represented, no socio-economical data were collected, but the population is known to be very homogeneously.

A significant effect was found on hot flashes in the acupuncture group after the second acupuncture treatment (Fig. 1 and Table 2). The effect lasted for at least 12 weeks after the final acupuncture treatment, when registration was ended. In the sham-acupuncture group no significant effect was seen in comparison with the no-treatment group, but a visual trend of reduced symptoms was noted. A statistically significant positive effect on sleep was shown among those treated with acupuncture compared to those receiving sham acupuncture and no treatment (Table 3).

There was no increase in plasma estradiol level related to acupuncture in any group, as seen in Fig. 2. In three cases, a high level of plasma estradiol was detected. None was acupuncture-related: one case was explained by patient intake; the other two were pre-menopausal, one with too low a dose of antihormone and one with no adjuvant therapy.

During the project period 57 women were treated with adjuvant antihormone therapy (tamoxifen, letrozole or exemestane), two women received adjuvant docetaxel, and 35 women had no adjuvant therapy. Alternative medicine (melbrosia) during the whole

Table 1
Baseline characteristics of women entering the study.

Treatment	Acupuncture $n = 31$	Sham-acupuncture $n = 29$	No treatment $n = 34$
Mean age years	60	62	62
Range	(46–75)	(43–72)	(45–75)
Antihormone treatment	19 (61%)	17 (58%)	21 (61%)
Chemotherapy	0 (0%)	1 (3%)	1 (3%)
Mean VAS score of nuisance of hot flashes before treatment	7.0	7.4	6.4
Number of women with disturbed sleep before treatment	22 (71%)	23 (79%)	28 (82%)