A randomized controlled pilot study of acupuncture for postmenopausal hot flashes: effect on nocturnal hot flashes and sleep quality

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Objective: To assess the effectiveness of acupuncture on postmenopausal nocturnal hot flashes and sleep.
Design: Prospective randomized placebo-controlled study.
Setting: Stanford University School of Medicine and private acupuncture offices.
Intervention(s): Active or placebo acupuncture was administered for nine sessions over seven weeks.
Main Outcome Measure(s): Severity and frequency of nocturnal hot flashes from daily diaries and Pittsburgh Sleep Quality Index (PSQI).
Patient(s): Twenty-nine postmenopausal women experiencing at least seven moderate to severe hot flashes daily, with E_2 <18 pg/mL and FSH 30.0–110.0 IU/L.
Result(s): Nocturnal hot-flash severity significantly decreased in the active acupuncture group (28%) compared with the placebo group (6%), P=.017. The frequency of nocturnal hot flashes also decreased in the active group (47%, P=.001), though it was not significantly different from the placebo group (24%, P=.170; effect size = 0.65). Treatment did not differentially influence sleep; however, correlations between improvements in PSQI and reductions in nocturnal hot flash severity and frequency were significant (P<.026).
Conclusion(s): Acupuncture significantly reduced the severity of nocturnal hot flashes compared with placebo. Given the strength of correlations between improvements in sleep and reductions in nocturnal hot flashes, further exploration is merited. (Fertil Steril® 2006;86:700–10. ©2006 by American Society for Reproductive Medicine.)

Key Words: Acupuncture, hot flashes, hot flushes, night sweats, postmenopause, menopause, sleep, insomnia

Nocturnal hot flashes awaken postmenopausal women frequently throughout the night (1, 2). Compared with menopausal women without hot flashes, those experiencing hot flashes tend to have more disturbed sleep, more frequent awakenings, reduced sleep efficiency, increased stage 4 sleep, shortened first REM period, longer latency until REM, and poorer sleep quality (3–7). Hot flashes have been thought of as a disorder of thermoregulation initiated centrally within the medial preoptic area of the hypothalamus, altered after menopause by changes in central opioid activity (6, 8). Instability in the hypothalamic thermoregulatory set point has the potential to alter sleep (6).

Hormone therapy (HT) has been the standard treatment for reducing nocturnal hot flashes, and some studies documented an associated reduction in sleep disturbance (1, 9, 10). However, many postmenopausal women have discontinued HT use since the risks noted in the Women's Health Initiative trials were published (11), and the clinical effects on sleep disturbance were shown to be milder than previously expected (12). Treatments such as black cohosh and soy have shown promise as effective alternatives to HT, but the data on the safety of these options are still inconclusive (13, 14). Selective serotonin reuptake inhibitors (SSRIs) have also shown promise for reducing hot flashes (15). Although little is known about the effects of SSRIs on sleep in postmenopausal women, SSRI use must be approached with caution, because SSRIs have been shown to worsen insomnia in populations with depression and control populations (16). Hypnotic medication, a standard treatment for insomnia, was recently shown to improve sleep in postmenopausal women, but most sleep medications are indicated only for short-term use (17). Although not specifically tested in postmenopausal samples, cognitive behavioral therapy for insomnia provides equally effective immediate improvement in sleep, yet data on its effects on hot flashes are still preliminary (18).

We found four studies that provide initial indications that acupuncture might reduce hot flashes in menopausal women (8, 19, 20, 21). Even though the studies were small, and no significant group differences were observed between the control and active treatments, all studies found reductions over time in 24-h hot flashes. One study observed reductions in nocturnal hot flashes (19), and another found reductions in sleep disturbance (20). We also found some

Received September 3, 2005; revised and accepted February 12, 2006.
Supported by RSCH Incentive Fund Award 1057644 100 WAYNA, Stanford Office of Technology Transfer, Stanford, California.
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0015-0282/06/$32.00

doi:10.1016/j.fertnstert.2006.02.100

evidence for acupuncture to address sleep difficulties in the general population (22, 23).

Although acupuncture seems to hold promise for decreasing hot flashes and sleep disturbance, the activating mechanism is still not well understood. There is evidence that acupuncture may increase secretion of endogenous nocturnal melatonin, a hormone involved in regulating sleep (22, 24). In laboratory rats with ovariectomies, acupuncture increased levels of estrogen receptor mRNA and proteins (25) as well as choline-acetyltransferase (ChAT, a protein linked to estrogen production) (26) compared with rats not receiving acupuncture. Even more relevant, in a sample of postmenopausal women experiencing hot flashes, acupuncture increased secretion of vasodilating neuropeptide calcitonin gene–related peptide, a candidate for affecting the mechanism of hot flashes (8). Acupuncture not only may affect hormones directly related to sleep and menopause but also has been shown to activate endorphin pathways, thus increasing cerebrospinal fluid levels of met-enkephalin, β-endorphins, and dynorphins (22, 27, 28).

In the present placebo-controlled pilot study, we examined the efficacy of acupuncture for the treatment of hot flashes in postmenopausal women. We hypothesized that active acupuncture would be more effective at reducing the severity and frequency of nocturnal hot flashes than placebo acupuncture in postmenopausal women. Further, we hypothesized that improvements in nocturnal hot flashes would be associated with improved sleep.

MATERIALS AND METHODS

The Internal Review Board at the Stanford University School of Medicine approved this study. There were no conflicts of interest from the investigators or the research staff. Participants were recruited from March 2003 to January 2004 throughout the San Francisco Bay area through community flyers, classified and informational ads on the Internet, newspaper articles, and referrals from community physicians.

Participants

We selected qualified participants through a three-step screening process: initial phone interview, prospective hot-flash assessment, and laboratory test. The initial phone interview assessed participants for inclusion or exclusion. Qualified participants were between the ages of 45 and 65 years, with no menstrual period during the past 6 months. Initial exclusion criteria included self-reported serious medical or psychiatric conditions or current treatment for hot flashes (including HT, SSRIs, black cohosh, and phytoestrogens).

After the initial phone interview, qualified participants attended a study visit during which written informed consent was obtained and instructions were given on how to keep track of daily hot flashes. Participants were given business-sized diary cards to record the occurrence and severity of each hot flash, categorizing it as mild, moderate, or severe. A mild hot flash was defined as a fleeting warm sensation without sweating and which does not disrupt activity. A moderate hot flash was defined as a warm sensation (with or without sweating) which has a transient and insignificant impact on the participant's activity. A severe hot flash was defined as a hot sensation with sweating that significantly disrupts the participant's activity (29, 30). Participants were asked to separate hot flashes that occurred during the day or wakeful period from those that occurred during the nocturnal sleep period.

To ensure the quality of daily hot flash reports, participants were instructed to call or e-mail their reports daily. Failing to do so would merit a reminder call from the study coordinator.

Participants experiencing a weekly average of ≥7 moderate to severe hot flashes per day were invited for further screening. Laboratory tests confirmed postmenopausal status (E_2 <18 pg/mL, FSH 30.0–110.0 IU/L) and absence of thyroid disorder (TSH 0.40–4.0 μIU/mL). Demographic information was collected, along with the Pittsburgh Sleep Quality Index (PSQI), a validated measure of sleep disturbance (31).

Randomization

Participants were assigned to one of five acupuncturists based on geographic proximity. To ensure that each acupuncturist treated the same number of participants in each arm of the study, separate randomization tables, consisting of random permutations of two elements, were prepared for each acupuncturist.

Interventions

Seven weeks of treatment were given with two treatments per week in the first 2 weeks, and one treatment per week thereafter. All sessions were 20 min long. In the placebo arm of the study, acupuncturists selected four to five points off any acupuncture channels (also known as "sham points"; Table 1). A plastic ring was placed over the targeted point, and medical tape was applied over the plastic ring. A Streitberger placebo needle was then applied through the medical tape into the middle of the plastic ring (32, 33). Upon touching the surface of the skin, the flat-tipped needle retracted into its own shaft, and did not penetrate the skin. The ring and tape held the placebo needle in place and hid the fact that the needle did not penetrate the skin. Even though the use of a medical sheet and plastic rings is not typical in acupuncture practice, the method has been validated for blinding participants to the treatment they are receiving (33).

In the active acupuncture arm of the study, real acupuncture needles that penetrated the skin were administered. To maintain consistency with the technique used in the placebo condition, the protocol required that the medical tape and plastic rings be similarly used. Each session involved administration of five to seven active treatment points. Three to six of the points addressed an individual's primary manifestation of hot flashes, and one to two points addressed secondary symptoms, includ-

TABLE 1

Standardized algorithm to determine point prescription.

1. Standardized active acupuncture.

Please circle the pattern(s) and mark the points chosen; indicate left (L), right (R), or bilateral (bi). Select a total of 5–7 points. Select *basic main points*. Add or replace 2–4 points from *primary pattern (I)*. Add 1–2 supplemental points from *secondary patterns* (II) or *additional symptoms* (III).

Basic main points			
Patient's position	Supine	Prone	
	☐ Kd 3 (bi) ☐ Sp 6 (bi) ☐ Ren 4	☐ Kd 3 (bi) ☐ Sp 6 (bi) ☐ UB 23	
I. Primary pattern			L/R
a. Kidney yin vacuity, vacuity heat	Replace Kd 3 w/ ☐ Kd 6 Add ☐ Lu 7	Replace Kd 3 w/ ☐ Kd 6 Add ☐ Lu 7	
b. Ascendant hyperactive Lv yang	Add ☐ GB 20 ☐ Lv 3	Add ☐ GB 20 (bi) ☐ Lv 3	
c. Phlegm fire	Add ☐ St 40 ☐ LI 11	Add ☐ St 40 ☐ LI 11	
c1. If phlegm predominates	Replace Ren 4 w/ ☐ Ren 12	Replace UB 23 w/ ☐ UB 20	
c2. If heat predominates	Add ☐ Lv 2	Add ☐ Lv 2	
d. Heart/kidney not interacting	Add ☐ Ren 15 ☐ Ht 6	Add ☐ UB 15 ☐ Ht 6	
e. Qi stagnation/blood stasis	Add ☐ Sp 4 ☐ P 6	Add ☐ Sp 4 ☐ P 6	
e1. If stagnation predominates	Add ☐ Lv 3 ☐ LI 4	Add ☐ Lv 3 ☐ LI 4	
e2. If stasis predominates	Add ☐ Sp 10	Add ☐ Sp 10	
f. Dual vacuity of Kd yin and yang	Replace Ren 4 w/ ☐ Ren 6 Add ☐ Lu 7	Add ☐ UB 52 ☐ Kd 7	
g. Dual vacuity of Sp qi—Ht blood	Add ☐ Ren 14 & ☐ Ht 7	Add ☐ UB 15 & ☐ Ht 7	
II. Secondary pattern	Consider		
h. Sp qi vacuity	☐ Ren 12 ☐ St 36 ☐ Sp 3	☐ UB 20 ☐ St 36 ☐ Sp 3	

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TABLE 1

Continued.

i. Lv blood—Kd yin vacuity	☐ Lv 8 ☐ Kd 10 ☐ Kd 6 w/ ☐ Lu 7	☐ Lv 8 ☐ Kd 10 ☐ UB 18 ☐ Kd 6 w/ ☐ Lu 7	
j. Ht qi vacuity	☐ Ht 5 ☐ P 6 ☐ Ren 17 ☐ Ren 6	☐ Ht 5 ☐ P 6 ☐ UB 15 ☐ UB 20	
k. Kd yang vacuity	☐ Kd 7	☐ UB 52 ☐ Kd 7	
l. Lu qi/yin vacuity	☐ Lu 1 ☐ Lu 7 ☐ Lu 5	☐ UB 13 ☐ Lu 7 ☐ Lu 5	
m. Lv depression qi stagnation	☐ Lv 3 ☐ LV 14 ☐ Lv 13 ☐ GB 34	☐ Lv 3 ☐ UB 18 ☐ GB 34	
III. Additional symptoms		Consider	L/R/bi
n. Sweating/heat			
n1. Profuse sweating due to qi vac		☐ Kd 7 ☐ Lu 9	
n2. Severe hot flushes due to replete heat		☐ Du 14	
n3. Night sweats due to pronounced yin vacuity		☐ Kd 7 w/ ☐ Ht 6	
o. Emotional distress (shen disturbance)			
o1. Depression, anxiety or moodiness due to liver depression qi stagnation		☐ Lv 3 w/ LI 4 or w/ ☐ P6	
o2. Lack of concentration of interest due to vacuity of qi and yang		☐ Du 20	
o3. Agitation, restlessness due to hyperactive liver yang		☐ Du 24 w/ ☐ GB 13 ☐ P 7	
o4. Agitation, restlessness due to heart fire		☐ Ht 8 ☐ Ht 6 ☐ Ren 15	
o5. Rumination, obsessive thinking due to phlegm confounding		☐ GB 18 ☐ St 40	
p. Sleep disturbances		☐ Ren 15 ☐ UB 15 ☐ Anmian ☐ Shishen w/ ☐ Du 20	

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TABLE 1

2. Standardized placebo acupuncture (sham points with placebo needle).

Select a total of 4–5 points, distributed in balance throughout the body.

Point	Patient position	Anatomic landmark	Point location	Relationship to channels
Arm, A I	Supine	Between cubital crease and axillary fold	Anterior upper arm, 5 cun proximal to cubital crease, 4 cun below the axillary fold, on the bulge of the biceps brachii	2 cun below Pc 2, 5 cun above Pc 3, 0.5 cun lateral to the Pc channel
Arm, A II	Prone	Olecranon tip	On the lateral border of the humerus, 3 cun above the olecranon	Between the LI and TH channels, 1 cun proximal and 1.5 cun lateral to TH 11
Forearm, FI	Supine; Forearm Supine		On the forearm, about 6 cun proximal to the transverse wrist crease, medial to m. palmaris longus	1 cun medial and 1 cun proximal to Pc 4, about 1 cun lateral to the Heart channel
Forearm, F II	Supine	Lateral epicondyle of the humerus	On the extensor surface of the forearm	Midway between the LI and TH channels, 1 cun distal and 1 cun lateral to LI 11
Back, B I	Prone	T12	5 cun lateral to T 12	2 cun lateral to outer UB line
Abdomen, Ab I	Supine	Navel	2 cun above the navel and 5 cun lateral	1 cun lateral to Spleen channel
Leg, L I	Supine, knee partly flexed	Anterior crest of the tibia	On the anterior crest of the tibia, 7 cun below the base of the patella	1 cun distal and 1.5 cun medial to St 37
Leg, L II	Prone	Head of the fibula	5 cun distal to the head of the fibula, on the posterior-lateral aspect of the leg, about 2 cun posterior to the midline of the fibula	Midway between the GB and UB channels
Thigh, T I	Supine	Patella, rectus femoris	On the bulge of the rectus femoris, 5 cun above the middle of the superior border of the patella	2 cun lateral and 3 cun proximal to Sp 10; 3 cun proximal and 2 cun medial to St 32
Thigh T II	Prone	Popliteal fossa	3 cun above the center of the popliteal fossa	3 cun proximal to BL 40

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ing sleep (Table 1). Points were selected based on their ability to target hot flashes, according to principles of traditional Chinese medicine (TCM). Acupuncturists used a standardized algorithm to determine which points would be applied, as has been done in other studies (34, 35). It is important to note that although TCM approaches hot flashes holistically, the treatment algorithm primarily targeted hot flashes and allowed limited attention to sleep disturbances as a secondary symptom.

Acupuncturists conducted weekly assessments to reevaluate point prescriptions based on the participant's symptoms and side effects. Because the study acupuncturists knew the type of treatment they were administering, efforts were made to control for nonspecific therapeutic elements. Acupuncturists were instructed to limit verbal contact to the most pertinent clinical information and to refrain from counseling and offering advice. All sessions were audiorecorded and 5% of the tapes were reviewed by an independent rater to assure adherence to the protocol. In addition, we assessed the success of blinding efforts by asking participants what treatment they believed they received.

A week after the last study treatment (session 9), participants received an additional treatment (no. 10), and were subsequently told what type of treatment they had been receiving. Note that the week after the tenth treatment was not included in the analysis of the main outcome so as not to confound the results by the fact that participants were no longer blinded to the type of treatment received. Participants were then free to seek treatment in the community, and we asked them to continue reporting daily hot-flash diaries for an additional month.

Outcomes

The main outcomes were measures of nocturnal hot flashes (daily diaries completed from screening to the end of a 1-month follow-up phase) and sleep (PSQI global score, completed at baseline, midtreatment, end of treatment, and 1-month follow-up).

Statistical Methods

Statistical analyses were performed using the SPSS statistical package program (SPSS, Inc., Chicago, IL). All data was entered twice and cleaned to ensure accuracy. Analyses of the differential impact of treatment on nocturnal hot flashes were performed on the intent-to-treat sample (all randomized women; n = 29). Analyses of the impact of treatment on sleep applied listwise deletion when data was missing at any time point. *P* values for within-subject effects in repeated-measures analyses were based on Huyndt-Feldt corrections for sphericity.

Severity and frequency of nocturnal hot flashes were independently analyzed. The frequency of nocturnal hot flashes was calculated as the sum of the number of mild, moderate, and severe nocturnal hot flashes. The severity of nocturnal hot flashes was calculated by dividing the weighted sum (1 × the number of mild hot flashes plus 2 × the number of moderate hot flashes plus three × the number of severe hot flashes) by the frequency of nocturnal hot flashes.

Baseline nocturnal hot-flash severity and frequency were computed as the daily average of diary values from the 10 days preceding the first treatment. For participants completing the treatment, the endpoint hot-flash values were computed as the mean from the night following the ninth study session until the night that preceded the tenth session. For those participants who had not completed all study treatments, the endpoint hot-flash values were based on the last available diary data, up to a week after the last treatment. Means of weekly hot flashes were computed from the date of the first treatment for the week until the date before the next week's treatment.

Testing of group differences in baseline demographic characteristics used χ^2 statistic for dichotomous variables (history of HT) and *t* tests for ordinal variables and continuous variables (mean baseline severity and frequency of nocturnal hot flashes, body mass index [BMI], age, PSQI, and time-related variables).

Pearson correlation analyses were performed to evaluate the relationships between baseline values of sleep disturbance and the two hot flash measures.

We used two types of statistical analyses to assess the differential effect of active and placebo treatments on measures of nocturnal hot flashes. The first was a Mann-Whitney test with the percentage change in nocturnal hot flashes as the test variable and treatment as the grouping variable. Percentage change was computed as the difference between endpoint and baseline values divided by the latter. Effect sizes were computed with an area under the curve (AUC) strategy. In addition, to take advantage of all available nocturnal hot-flash data, we performed a random regression analysis. Given the small sample size, we used a simulated random regression model by fitting individual regression lines to every subject's data, yielding a slope to represent individual change (36). We performed an analysis of variance (ANOVA) to compare the slopes of individual regression lines, with the treatment group as the fixed factor.

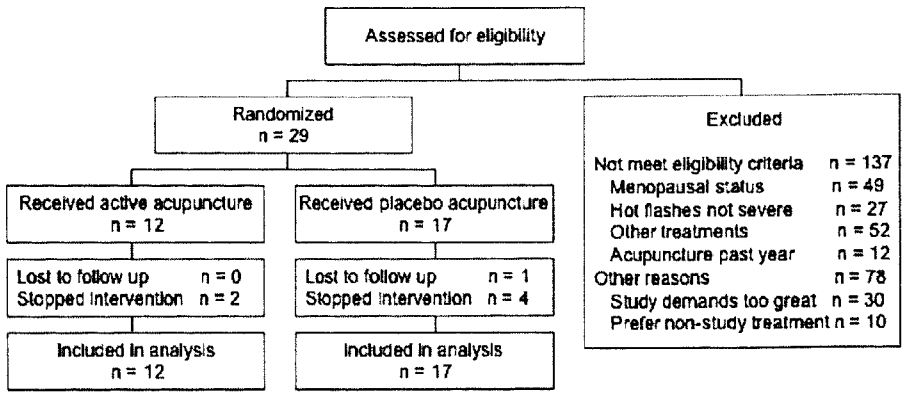
We also assessed within-group change in hot flashes by splitting the file, and running separate repeated measures of variance with weekly means as repeated measures (eight levels).

For the 1-month follow-up, we performed an analysis of covariance (ANCOVA) using nocturnal hot flashes at 1-month follow-up as the dependent variable, baseline nocturnal hot flashes as the covariate, and treatment group as the fixed factor.

To determine if the five acupuncturists administering treatment affected the percentage change in nocturnal hot flashes, we performed an ANOVA, with the percentage change in nocturnal hot flashes as the dependent variable and the randomization group and acupuncturist as the fixed factors.

FIGURE 1

Participant flow.



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To examine the differential effect of acupuncture on sleep disturbances, we performed a repeated-measures ANOVA with the PSQI at baseline, midtreatment, and end of treatment as within-subject variables, and treatment group as the between-subjects factor. Group comparison of sleep disturbance at the 1-month follow-up consisted of an ANCOVA, with the PSQI at the 1-month follow-up as the dependent variable, baseline PSQI as the covariate, and treatment group as the fixed factor.

We investigated the relationship between changes in sleep disturbances (percentage change in PSQI from baseline to endpoint) and changes in nocturnal hot flashes (percentage change and, separately, the slope of individual regression lines) using Pearson correlations.

We assessed the success of blinding efforts by performing a χ^2 test using the number of participants who correctly guessed their treatment group as the dependent variable and the treatment group as the grouping variable.

RESULTS

Participant Flow

Two hundred forty-four women were assessed for eligibility, of which 215 were excluded (Fig. 1). Twenty-nine women were randomized, 12 into the active acupuncture group and 17 into the placebo acupuncture group.

Description of Sample

Baseline characteristics of the randomized sample are shown in Table 2. No significant baseline differences existed between the two groups in the main outcome measures (the frequency and severity of nocturnal hot flashes and PSQI). No significant baseline group differences emerged for ethnicity, BMI, age at menopause, years since menopause, and history of and time since HT. Participants in the active acupuncture group were, however, on average 3.21 years older than participants in the placebo group (P=.020).

Relationship Between Hot Flashes and Sleep at Baseline

Twenty-six of the 29 participants had PSQI scores >5, an established criterion indicating significant sleep disturbance (31). There was no group difference in the proportion of participants in the active and placebo groups whose PSQI exceeded the clinical threshold (83% vs. 94%, respectively). Baseline PSQI was correlated significantly with the frequency of nocturnal hot flashes (r = 0.414; P=.026), but not with the severity of nocturnal hot flashes (r = −0.118; P=.541).

Acupuncture's Effects on Nocturnal Hot-Flash Severity

At the end of treatment, there was a significantly greater percentage reduction in nocturnal hot-flash severity in women receiving active acupuncture (27.84 ± 30.67%) compared with placebo treatment (6.26 ± 18.49%; Mann-Whitney U = 48.00; P=.017; effect size = 0.76). This differential reduction was also evident in the random regression analysis (P=.012). Although both groups improved throughout treatment, improvement in the active acupuncture group reached levels of statistical significance (repeated-measures ANOVA P=.002), whereas improvement in the placebo group did not (P=.107). At the 1-month follow-up, ANCOVA revealed that the change from baseline severity of nocturnal hot flashes was significantly lower in the active acupuncture group (36.56 ± 40.0%) compared with the placebo group (8.28 ± 16.7%; P=.012). Weekly mean nocturnal hot-flash severity is shown in Figures 2A and 3A.

Acupuncture's Effects on Nocturnal Hot-Flash Frequency

At the end of treatment, there was no significant group difference in the reduction of nocturnal hot-flash frequency (active = 47.43 ± 35.68% vs. placebo = 23.72 ± 45.68%; U = 71.00;

TABLE 2

Baseline characteristics of randomized sample.

Characteristics	Active acupuncture	Placebo acupuncture	Complete sample
Hot flashes			
Baseline nocturnal hot-flash severity	2.50 ± 0.39	2.46 ± 0.51	2.48 ± 0.46
Baseline nocturnal hot-flash frequency	3.29 ± 1.13	3.74 ± 1.49	3.55 ± 1.35
PSQI	10.50 ± 3.45	10.47 ± 2.90	10.48 ± 3.08
Ethnicity			
White	12/12	16/17	28/29
Black	0/12	1/17	1/29
BMI	24.62 ± 3.70	23.27 ± 3.16	23.87 ± 3.42
Menopause			
Age (y)[a]	56.92 ± 1.73	53.71 ± 4.24	55.03 ± 3.75
Age at menopause (y)	50.18 ± 2.96	48.57 ± 6.77	49.24 ± 5.50
Time since menopause (y)	7.02 ± 4.06	5.85 ± 6.84	6.33 ± 5.79
HT			
History of HT	10/12 (83%)	13/17 (76%)	22/29 (79%)
Time with HT (y)	6.85 ± 3.62	5.11 ± 3.69	5.87 ± 3.69
Time since HT (mo)	8.30 ± 4.16	15.23 ± 11.57	12.22 ± 9.61

HT = hormone therapy.
[a] P=.020.

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P=.170; effect size = 0.65; random regression P=.658). However, reductions in weekly values of nocturnal hot-flash frequency were statistically significant in both the active acupuncture group (F = 9.656; P=.001) and the placebo group (F = 5.417; P=.001). Further, at the 1-month follow-up, ANCOVA revealed that the frequency of nocturnal hot flashes was significantly lower in the active acupuncture group (59.56 ± 30.57%) compared with the placebo group (23.63 ± 32.95%), P=.027. Weekly mean nocturnal hot-flash frequency is shown in Figures 2B and 3B.

Acupuncturist's Effects on Reductions in Nocturnal Hot Flashes

No significant differences appeared in the percentage change in nocturnal hot-flash severity (F = 1.974, P=.150) or frequency (F = 2.434; P=.095) among the five acupuncturists administering treatment in this study.

Acupuncture's Effects on Sleep Disturbance

At the end of treatment, there were improvements in PSQI, albeit not statistically significant within each group ($P \geq .059$; Cohen d effect size for the difference between before and after values was 0.65 for the active group and 0.53 for the placebo group), with no significant difference between the two groups in the pattern of change (F = 0.226; P=.799; Cohen d effect size for the group difference in before and after change was 0.245). Moreover, the proportions of participants whose PSQI at the end of treatment exceeded the clinical threshold of 5 were high in both groups (67% for active and 82% for placebo) and not significantly different between the groups (χ^2 = 0.882; P=.348). At the 1-month follow-up, there was no significant group difference in PSQI after controlling for baseline values (F = 1.447; P=.245). Figure 4 depicts PSQI at baseline, midtreatment, end of treatment, and 1-month follow-up.

Relationship Between Improvements in Nocturnal Hot Flashes and Improvements in Sleep

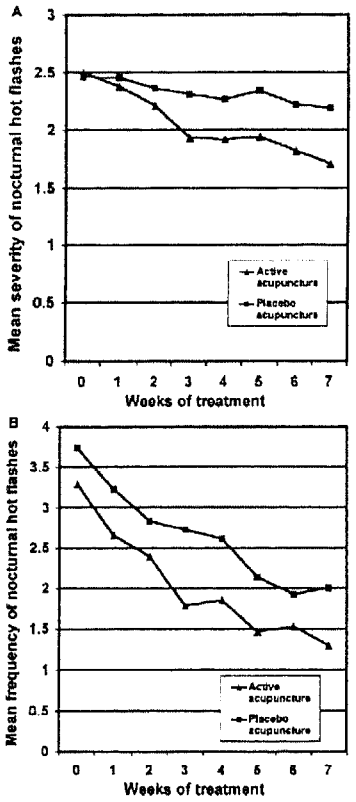
Change in PSQI from baseline to end of treatment correlated significantly with measures of improvement in nocturnal hot-flash severity (r = 0.62 for percentage change; r = 0.59 for slopes of individual regression lines; $P<.05$) and with measures of improvement in nocturnal hot-flash frequency (r = 0.74 for percentage change; r = 0.41 for slopes of individual regression lines; $P<.001$).

Success of Blinding

At the end of treatment, 9 of the 16 participants (56.2%) receiving placebo treatment thought they were receiving the active treatment and 3 of the 12 participants (25%) receiving active acupuncture thought they were receiving placebo treatment (χ^2 = 2.73; P=.098). The observed distribution of correct and incorrect ratings in the two groups yields a Youden index of 0.19 (with sensitivity 0.75 and specificity 0.44). This is an index that locates the association between random (0) and perfect (1.0). Generally, indices on this scale

FIGURE 2

Reduction in nocturnal hot flashes by treatment: All available data are included. The number of participants with available data for each week in the active group was 12 for baseline and week 1, 11 for week 2, and 10 thereafter. The number of participants with available data for each week in the placebo group was 17 for baseline and week 1, 16 for week 2, 15 for week 3, 14 for weeks 4 and 5, and 13 thereafter. (A) Severity of nocturnal hot flashes, random regression analysis, $P=.012$. (B) Frequency of nocturnal hot flashes, random regression analysis, $P=.658$.



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(like a correlation coefficient) are considered small, medium, and large at about 0.1, 0.3, and 0.5, respectively (37).

Side Effects

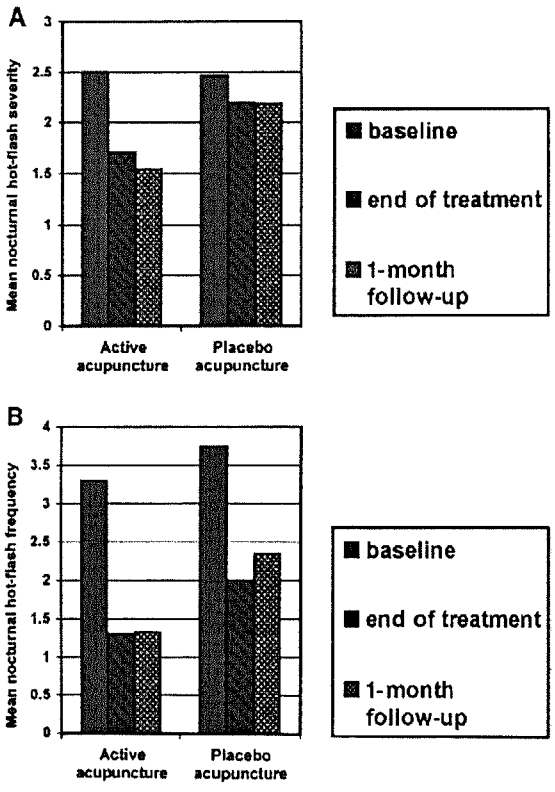
During treatment, more participants receiving active acupuncture experienced bleeding and discomfort at the injection site compared with those receiving placebo acupuncture (bleeding 66.7% vs. 5.9%, discomfort 58.3% vs. 35.3%, respectively), Between treatment, side effects reported for the active versus the placebo groups, respectively, included insomnia (16.6% vs. 11.8%), pain (8.3% vs. 5.9%), itchiness (8.3% vs. 0%), twitching (8.3% vs. 0%), irritability or restlessness (0% vs. 17.6%), low energy (0% vs. 5.9%), resentment (0% vs. 5.9%), and gas (0% vs. 5.9%).

DISCUSSION

Our findings suggest that acupuncture holds promise for the treatment of nocturnal hot flashes in postmenopausal women. Active acupuncture was associated with a significant reduction in the severity and frequency of nocturnal hot flashes, with the former being significantly greater than the reduction observed in the placebo treatment. In contrast, sleep disturbances did not decrease differentially between the groups, though there was a strong trend for improved sleep in the active group. Nevertheless, within each group, decreases in sleep disturbance were significantly correlated with decreases in both the severity and the frequency of nocturnal hot flashes.

FIGURE 3

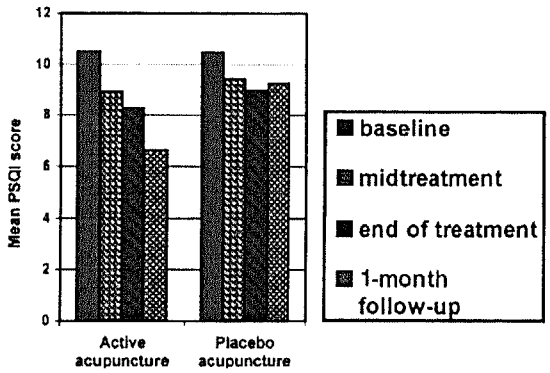
(A) Mean nocturnal hot flash severity: Mann-Whitney analysis of percentage change for baseline and end of treatment, U = 48.00; $P=.017$. Analysis of covariance with 1-month follow-up values as the dependent variable and baseline value as a covariate, F = 7.497; $P=.012$. (B) Mean nocturnal hot-flash frequency: Mann-Whitney analysis of percentage change for baseline and end of treatment, U = 71.00; $P=.170$. Analysis of covariance with 1-month follow-up values as the dependent variable and baseline value as a covariate, F = 4.494; $P=.046$.



Huang. Nocturnal hot flashes and sleep. Fertil Steril 2006.

FIGURE 4

Mean PSQI scores: Repeated-measures ANOVA for baseline, midtreatment, and end of treatment, F = 0.226; P=.799. Analysis of covariance with 1-month follow-up value as the dependent variable and baseline value as the covariate, F = 1.447; P=.245.



Huang. Nocturnal hot flashes and sleep. Fertil Steril 2006.

To date, this is the first randomized controlled trial to find a statistically significant group difference for reductions in the severity of nocturnal hot flashes in postmenopausal women. Only one of the previous studies on acupuncture for postmenopausal hot flashes reported changes in nocturnal hot flashes (19). Although the investigators found significant reductions in nocturnal hot-flash severity with electroacupuncture, significant differences from the control group were not observed. Other studies that examined the efficacy of acupuncture for menopausal hot flashes separately evaluated its effects on sleep, with inconsistent results (8, 20).

However, it is difficult to compare those results with the findings from the present study. Inconsistencies in findings from these acupuncture studies are best explained by the small samples and the presence of pronounced methodologic differences. Methodologic differences are present in length of treatment (8 to 12 weeks), inclusion criteria (menopausal vs. postmenopausal, intensity of baseline hot flashes), outcome measures (standardized vs. nonstandardized measures), type of control (nonspecific or superficial acupuncture at valid points vs. placebo needles at nonvalid points), and type of active treatment (electroacupuncture vs. manual stimulation, and a fixed set of points vs. individually tailored treatments).

One of the strengths of this study is the implementation of a standardized algorithm (Table 1) that has been used in previous studies (34, 35). The advantage of this method allows for replication in future biomedical studies, without compromising the treatment principles of TCM used in clinical practice. In this study, five acupuncturists were able to perform treatment using this algorithm without yielding significantly different results. The flexibility of altering points models the process that occurs in clinical practice. In clinical practice, two women experiencing hot flashes may be diagnosed with different disharmonies, and receive different point prescriptions. Further, needles are inserted directly into the skin, to a depth that achieves the proper *deqi* sensation.

In our study, acupuncturists complained that the use of plastic rings and tape handicapped them from achieving the proper *deqi* sensation, potentially compromising the efficacy of the active treatment. Although the standardized algorithm allowed the acupuncturist freedom to prescribe specialized points, it focused primarily on hot flashes and only secondarily on sleep. It is possible that a different treatment protocol in which acupuncture is designed to more optimally address sleep in postmenopausal women with nocturnal hot flashes could be more effective in improving sleep. However, this assertion needs to be tested.

Even though we did not find a significant differential effect of active acupuncture on sleep disturbance, we found significant correlations between reductions in sleep disturbance and reductions in nocturnal hot flashes. Because we used a self-reported measure of both sleep and hot flashes, it is difficult to conclude that acupuncture is not effective for improving sleep. Although it would be more cumbersome, future studies can improve upon the present one by implementing objective measures of both hot flashes and sleep.

Several methodologic limitations merit discussion. First, the small and relatively selective sample limits the ability to apply the results to the general population. Second, the small sample size could result in type II error. Third, despite random assignment, the active acupuncture sample was an average of 3.2 years older than the placebo group—a baseline difference that reached statistical significance. It is not clear to what extent this affected the results, because this difference is small and likely reached significance because of smaller variability in the age range of the active acupuncture group compared with the placebo group.

The length of treatment provided in this study was determined somewhat arbitrarily. Significant group differences in both the frequency and severity of nocturnal hot flashes at the 1-month follow-up were present even after covarying baseline values, suggesting that a longer treatment phase might have yielded better outcome. Although this time point is confounded by the fact that participants knew what treatment group they had received, and were allowed to seek other treatment, participants in the active group had remarkable reductions from baseline compared with the placebo group (37% vs. 8% for severity, and 60% vs. 24% for frequency, respectively).

Considering that high placebo effects are common in both acupuncture and hot-flash studies (38–40), the emergence of differential statistically significant results in our study is noteworthy.

In conclusion, the severity of nocturnal hot flashes was significantly reduced in the active acupuncture group, but not in the placebo group, with a significant group difference. The frequency of nocturnal hot flashes was significantly reduced in

both the active and placebo groups, but no significance emerged at the end of treatment. Further, the strong connection between reductions in hot flashes and improvement in sleep emphasizes the need for treatments that effectively address both conditions. Though this pilot study was placebo controlled, its results have to be considered preliminary. Future studies are needed with a larger sample size, a longer treatment phase, use of objective measures, and an active acupuncture treatment that builds upon the standardization techniques from this study.

Acknowledgements: The authors thank licensed acupuncturists Ms. Catherine Burns, Ms. Khim Choong, Mr. Andrew Fitzcharles, Ms. Esther Gokhale, and Ms. Kathryn Ryan.

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