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***Effects of acupuncture, applied relaxation, estrogens and placebo on
hot flushes in postmenopausal women –
an analysis of two prospective, parallel, randomised studies.***

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Short title: Alternatives to HT and placebo

Key words: Vasomotor symptoms, hot flushes, acupuncture, applied relaxation, placebo

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Abstract:

Objective To assess if transdermal or oral estrogens, acupuncture and applied relaxation decrease the number of menopausal hot flushes/24 h and improve climacteric symptoms, as assessed by the Kupperman index, more than transdermal placebo treatment.

Setting An outpatient clinic at a Swedish university hospital.

Methods A total of 102 postmenopausal women were recruited to two studies performed in parallel. In Study I, the women were randomized between transdermal placebo or estrogen treatment and, in Study II, between oral estrogens, acupuncture or applied relaxation for 12 weeks. Climacteric symptoms were measured with daily logbooks on hot flushes. Women completed the assessment questionnaire for the Kupperman index at baseline and after 12 weeks.

Results The number of flushes/24 h decreased significantly after 4 and 12 weeks in all groups except the placebo group. Both at 4 and 12 weeks, acupuncture decreased the number of flushes more ($p < 0.05$; $p < 0.01$, respectively) than placebo. At 12 weeks, applied relaxation decreased the number of flushes more ($p < 0.05$) than placebo. The Kupperman index score decreased in all groups except the placebo group. The decrease in score was significantly greater in all treatment groups than in the placebo group ($p < 0.01$).

Conclusion Acupuncture and applied relaxation both reduced the number of hot flushes significantly better than placebo and should be further evaluated as alternatives to hormone therapy in women with menopausal vasomotor complaints.

INTRODUCTON

Vasomotor symptoms with hot flushes are very common in menopausal women, when estrogen production decreases (1). One theory for these symptoms is that, when sex steroid production decreases, hypothalamic β -endorphin and noradrenergic activities change, which in turn affects the thermoregulatory center in the hypothalamus, and makes it less stable (1-4). A sudden drop in the temperature set point will cause reactions in order to decrease central body temperature to the new set point (1,2). This is achieved by vasodilatation and sweating (3), reactions that have been suggested to be mediated by calcitonin gene-related peptide (4).

The most common form of cancer in women is breast cancer (5). Hot flushes have been reported to be even more common in breast cancer survivors than in menopausal women in general (6). Antiestrogens like tamoxifen increase the frequency and severity of hot flushes (7), which in turn affect sleep and mood (8).

Hormone therapy (HT) including estrogens combined with progestagens or estrogens alone is the most effective treatment of hot flushes and sweating (9). Although HT is an effective treatment, some women are not recommended to use this treatment, e.g. due to breast cancer or thromboembolic disease. HT seems to increase breast cell proliferation (10) and therefore promotes breast cancer growth. Women on HT have increased risk of breast cancer compared with non-treated women (5,11). A randomized study showed that 2 years of HT increased the risk of breast cancer recurrence in women with breast cancer compared with women with non-hormonal treatment (12). Retrospective and prospective studies have demonstrated that HT increases the relative risks of venous thromboembolism two- to three-fold (13). Some women do not want to use HT because of side-effects or fear of side-effects (14). A number of case-control studies indicated a protective effect of HT on cardiovascular disease, but prospective, placebo-controlled studies have been unable to confirm these cardiovascular advantages in primary and secondary preventive studies like the Women's Health Initiative (WHI) study (15) and the Heart and Estrogen/progestin Replacement study (HERS) (16). In these studies, there was even an increased risk of cardiovascular events during the first year after initiation of HT. These factors are all reasons why it is important to develop alternative treatments of menopausal vasomotor symptoms.

Acupuncture has been suggested to be an alternative to HT, based on the fact that acupuncture increases central β -endorphin activity and therefore may make the thermoregulation more stable and decrease hot flushes and sweating (4). Wyon and colleagues demonstrated that acupuncture significantly decreased the number of hot flushes after menopause and that the effect with electroacupuncture persisted at least 3 months after the end of treatment. Acupuncture has yet not been compared with placebo because a placebo method has been difficult to develop. A placebo needle has been constructed (17) but even this needle is probably not completely non-effective.

Applied relaxation is another alternative to HT, and it has been suggested that behavioral relaxation methods reduce sympathetic activity (18,19). Applied relaxation significantly decreased menopausal hot flushes after 12 weeks of treatment (20), but has not been compared with placebo. Since it is difficult to find a placebo treatment for both acupuncture and applied relaxation, estrogen therapy and placebo could be used for comparison in a controlled, randomized, prospective study.

Our group has previously presented studies concerning the effects of applied relaxation and acupuncture on vasomotor symptoms in postmenopausal women (4,20,21). These studies, however, must be interpreted with caution due to the fact that, for different reasons, no placebo groups were included. The present study is a re-analysis of the results from the previous studies, but now in relation to a placebo group from another, not yet published, study with very similar design performed at the same center.

The aim of this study was to assess if transdermal or oral estrogens, acupuncture and applied relaxation decrease the number of menopausal hot flushes/24 h and improve the Kupperman index score significantly more than transdermal placebo treatment.

METHODS

Patients: In total, 102 women were recruited to two studies performed in parallel at the same outpatient clinic of the University Hospital of Linköping, Sweden (Figure 1). They were all postmenopausal and the effects of therapy were monitored in identical ways with the use of logbooks and assessment by the Kupperman index. The same staff of nurses and gynecologists met the women. Women were recruited by advertisement in the local papers and at the gynecological outpatient clinic of the University Hospital of Linköping, Sweden. The length of time from their last menstrual bleeding had to be at least 6 months and the women had to suffer from hot flushes severe enough to cause them to ask for therapy.

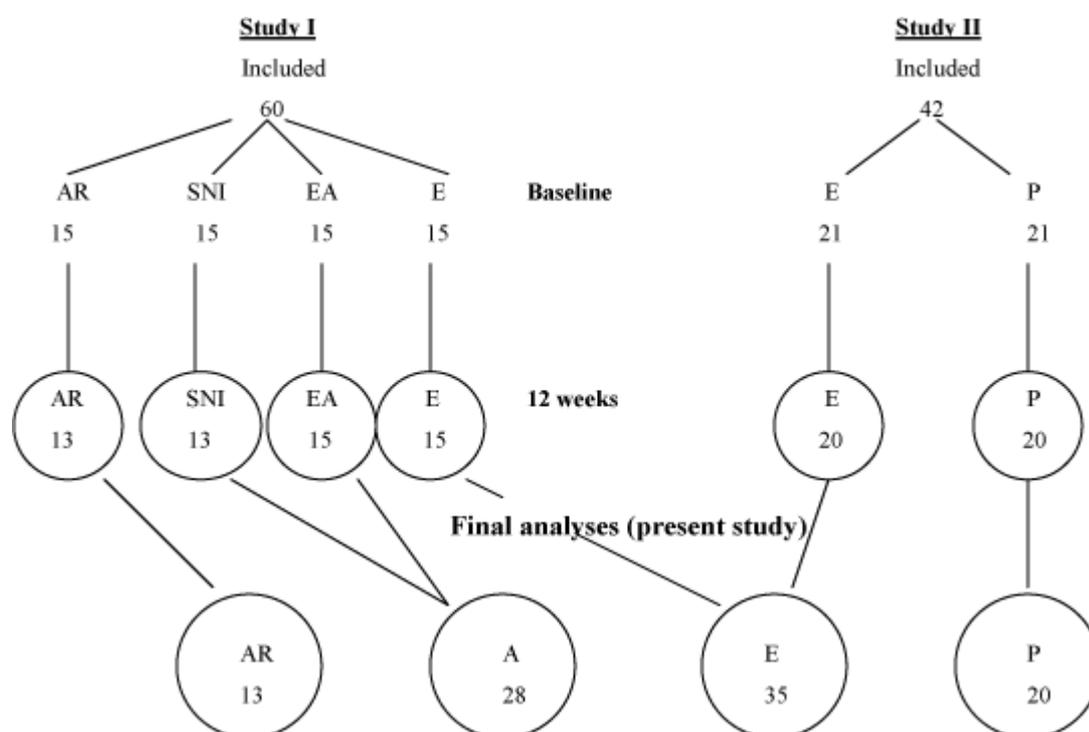


Figure 1. The distribution of the patients included in the different studies and patients available for analyse in the present study. AR= applied relaxation, SNI = superficial needle insertion, EA = electroacupuncture, E = estrogen, P = placebo, A= acupuncture.

The exclusion criteria were severe metabolic, thromboembolic or endocrine disease, uncontrolled hypertension (>95 mmHg diastolic pressure) or daily use of sedatives, tranquilizers or antidepressant medication.

Before inclusion, the women met a gynecologist and underwent a general medical and gynecological examination. Serum follicle stimulating hormone and estradiol concentrations were analyzed to verify postmenopausal status before the start of treatment and after 12 weeks of treatment, both as a control of compliance in the women receiving estrogen and to verify that the possible treatment effects in the non-estrogen groups were not due to a spontaneous recurrence of ovarian function. The distribution of patients in the different groups is shown in Figure 1.

Study I: Parts of this study have been previously published (20,21). Sixty women were recruited and randomized to therapy with applied relaxation ($n = 15$), electroacupuncture ($n = 15$), superficial needle insertion ($n = 15$) or oral estradiol therapy ($n = 15$). Thirteen of the 15 women randomized to applied relaxation completed the 12 weeks of treatment. Two did not fulfil the treatment because they considered the training program to be too time-consuming. All women randomized to electroacupuncture and oral estradiol completed the 12 weeks of treatment, while one woman randomized to superficial needle insertion did not start treatment due to severe migraine and another woman was excluded because of repeated absence from the therapy.

Study II: Another 42 women were recruited to a study that primarily aimed at studying effects of transdermal estrogen therapy or placebo on postural balance. The effects on balance will be reported separately. Two women chose to discontinue the treatment, one due to a dermal reaction induced by the patch and another due to balance problems that made her non-eligible for the study of postural balance.

Monitoring: Women daily registered the number and severity of flushes in a logbook during a baseline period and the 12 weeks of treatment. In Study I, women also registered flushes daily during 1 week every month during a 6-month follow-up time. The baseline registration of flushes in Study I was 2 weeks before start of therapy, while in Study II it was 7-14 days (mean 13.5 days, median 14 days) before the start of therapy. The patients filled in the logbook every night before bedtime and the logbooks were then collected at the visits to the clinic. These visits were before treatment, after 4, 8 and 12 weeks of treatment and, for the women randomized to applied relaxation or acupuncture, 3 and 6 months after end of treatment, whereas the women randomized to estrogen or placebo were not followed after the

end of the 12-week treatment period (i.e. not at 3 and 6 months). All women were informed that, whenever they wanted, they could choose to discontinue their treatment.

A slightly modified version of the questionnaire for the Kupperman index (22) was completed at baseline and after 12 weeks of treatment. For the Kupperman index, women assess 11 different symptoms subjectively graded into a four-point scale between 0 and 3. The highest total score possible is 51, as the scores for hot flushes are multiplied by 4 and sweating, sleep disturbances and irritability by 2.

Treatment: Study I: The training for applied relaxation consisted of different components (20). The instructor was trained in applied relaxation and met the patients in a group ($n = 4-6$) during a 12-week period, with weekly sessions lasting 60 min each. The training of applied relaxation consisted of the following components: progressive relaxation, release-only relaxation, cue-controlled relaxation, differential relaxation, rapid relaxation, application training and maintenance program. The women were told to train on each component at home at least once a day; after the 12-week period, no more organized applied relaxation sessions took place during the follow-up period.

Acupuncture was administered by a physiotherapist experienced and skilled in acupuncture treatment and was given 30 min twice a week for the first 2 weeks and once a week for another 10 weeks (21). Twelve sterile stainless-steel acupuncture needles were inserted to a depth of 5-20 mm in defined points and twirled to evoke needle sensation (De Qui), described as tension and numbness radiating from the point of insertion, reflecting activation of afferent muscle nerves - mainly A- δ fibers. In women randomized to electroacupuncture, the four needles in the lower back, BL 23 and 32 bilaterally, were attached to an electrical stimulator, giving a low-burst frequency of 2 Hz alternating current stimulation, which elicited a non-painful local muscle contraction. Superficial needle insertion was performed as previously described (21).

The women randomized to estrogen treatment were given oral tablets containing 17 β -estradiol 2 mg for 12 weeks. After this treatment, they were given additional oral progestagens (10 mg medroxyprogesterone acetate daily) for another 2 weeks in order to shed the endometrium.

Study II: The women randomized to estrogen treatment were given transdermal estradiol by means of a patch delivering 50 µg/24 h. The patch was changed twice weekly for 12 weeks. The women randomized to placebo were given identical patches but containing no estrogen. After 12 weeks of treatment, all women were given the same patch with additional oral progestagens (10 mg medroxyprogesterone acetate daily) for another 2 weeks in order to shed the endometrium in women who had been randomized to estrogens.

Statistics: We calculated the mean number of flushes per 24 h during the 14-day baseline period as well as during the first, 4th and 12th weeks of therapy. Changes in number of flushes/24 h from baseline to the first, 4th and 12th weeks of therapy were compared with ANOVA and thereafter a post-hoc test was performed between the different treatments, with both parametric and non-parametric (Mann-Whitney test) methods.

Ethics: Each patient gave her oral and written consent and the local Ethical Committee at the Faculty of Health Sciences, Linköping University approved the studies. The studies were performed according to the principles of the Declaration of Helsinki.

RESULTS

Number of flushes/24 hours: The number of flushes/24 h decreased significantly from baseline after 4 and 12 weeks in all groups except the placebo group. The decrease in number of flushes in the electroacupuncture and superficial needle insertion groups did not differ significantly from each other, as has been previously described (21) and therefore they were analyzed together as one acupuncture group. The same was true for the oral and transdermal estrogen groups, which were therefore also analyzed as one estrogen group.

According to the ANOVA, there was a significant difference in change between groups at both 4 and 12 weeks but not at the 1st week. At both 4 and 12 weeks, according to the Mann-Whitney test, the number of flushes/24 h had decreased significantly more ($p < 0.01$) in the estrogen group than in the applied relaxation and placebo groups (Table 1) but not significantly more than in the acupuncture group.

Table 1. Changes in number of flushes/24 hours including 95% confidence interval after 1, 4 and 12 weeks of therapy after treatment with acupuncture (A), applied relaxation (AR), estrogen (E) and placebo (P). The mean absolute number of flushes/24 hours +/- SD is given for the baseline period.

Therapy	Baseline	1 week	4 weeks	12 weeks
A (n=28)	7.9+/-4.4	-0.7 (-1.4/0.8)	-2.9 (-4.0/-1.9)	-4.3 (-5.7/-2.8)
AR (n=13)	6.1+/-2.4	0.23 (-0.6/1.0)	-1.0 (-1.8/-0.1)	-2.8 (-4.1/-1.5)
E (n=35)	6.9+/-2.8	-0.9 (-1.6/-0.1)	-4.7 (-5.8/-3.6)	-6.1 (-7.0/-5.1)
P (n= 20)	6.7+/-2.3	-0.3 (-1.0/0.4)	-1.5 (-2.5/-0.5)	-1.3 (-2.2/-0.5)

Both at 4 and 12 weeks, acupuncture had decreased the number of flushes significantly more ($p < 0.05$; $p < 0.01$, respectively) than placebo. At 12 weeks, applied relaxation had decreased the number of flushes significantly more ($p < 0.05$) than placebo.

Kupperman's Index: The Kupperman index score at baseline decreased in all groups except the placebo group. According to the ANOVA, there was a significant difference in change between groups at 12 weeks, and a post-hoc test showed that the decrease in score was

significantly greater in all treatment groups than in the placebo group ($p < 0.01$), whereas there was no significant difference between the changes in the other groups (Table 2).

Table 2. Changes in scores of the Kupperman's Index including 95% confidence interval after 12 weeks of treatment with acupuncture (A), applied relaxation (AR), estrogen (E) and placebo (P). The mean scores of the Kupperman's Index +/- SD is given for the baseline measurement.

<u>Therapy</u>	<u>Baseline</u>	<u>12 weeks</u>
A (n=28)	22.1 +/-6.2	-10.1 (-13.2/-6.8)
AR (n=13)	22.0 +/-5.8	-11.2 (-16.0/-6.4)
E (n=35)	20.6 +/-5.4	-13.9 (-16.1/-11.8)
P (n=20)	19.3 +/-5.4	-0.1 (-4.2/4.0)

DISCUSSION

Both applied relaxation and acupuncture decreased the number of flushes/24 h after 12 weeks of treatment, which has previously been reported (20,21). In the present analysis, we were able to show that there was a significantly greater decrease in number of flushes with these treatments than with placebo and that estrogens decreased the number of flushes significantly better than applied relaxation and placebo. The women treated with acupuncture and applied relaxation were followed for another 6 months after the end of therapy and the decrease in number of flushes was even more pronounced after another 6 months (20,21).

It is a weakness that we have analyzed two separate studies together. Ideally, we should have designed a study where women were randomized between acupuncture, applied relaxation, estrogens and placebo from the very beginning. At that point, however, due to a restricted number of patients, we estimated that too long a time would have been needed for recruitment to such a study and a separate, parallel study on effects from estrogens or placebo on postural balance. Our rationale for permitting us to analyze the studies together is that the inclusion criteria were almost identical, that the women in both studies were monitored in identical ways with the use of logbooks and the Kupperman index by the same staff of nurses and gynecologists and during the same time period.

It could also be argued that we could have used the placebo acupuncture needle, which has been introduced (17). At the time when our studies were designed, that needle had not been introduced and, furthermore, it induces some tactile stimulation, thus inducing more than just placebo effects.

Placebo treatment as such has been suggested to induce β -endorphin release, based on the fact that placebo-induced pain relief can be blocked by naloxone (23,24). Since β -endorphin is involved in the mechanisms of thermoregulation, it is not surprising that placebo reduces the number of hot flushes. A systematic review of 21 trials published by the Cochrane Collaboration (9) showed that placebo causes a 50% reduction in number of flushes but most of these studies did not have an observation time of more than 3 months. However, other studies show no or very little placebo effect on vasomotor symptoms during 12 weeks of treatment or longer (25). In the present study, the effects of placebo on vasomotor symptoms were noticed after 4 weeks of treatment but then remained stable compared with 12 weeks, whereas the effects from estrogen, acupuncture and applied relaxation showed further

improvement at 12 weeks. Furthermore, the placebo effect was similar to that of applied relaxation after 4 weeks but a significant difference was noted after 12 weeks, suggesting a delay in the effects of applied relaxation, probably explained by the time needed to learn the method.

In clinical trials, double blinding is desirable to minimize bias in interpreting results. This was impracticable in our studies with applied relaxation and acupuncture and the women who had oral estrogens had an open therapy. Actually, only the 40 women with transdermal estrogens or placebo had a double-blind therapy.

In the studies by Nedstrand and colleagues (20) and Wyon and colleagues (21), the lack of a placebo group raised questions in the interpretation of the results. In the present study, we have tried to compensate for that and the interpretation remains, i.e. applied relaxation and acupuncture have significant effects on vasomotor symptoms that we suggest are not only explained by a placebo effect. Still, estrogen therapy seems to have the most pronounced and rapid effect on these symptoms.

We could only speculate on the mechanisms elicited by applied relaxation and acupuncture, which may explain why they decrease vasomotor symptoms. As mentioned, acupuncture increases central β -endorphin activity and therefore this therapy may make the thermoregulation more stable and decrease the occurrence of hot flushes and sweating (4). Furthermore, we have found that the urinary excretion of calcitonin gene-related peptide, which seems to be involved in eliciting hot flushes, decreased during acupuncture therapy given to postmenopausal women with flushes (4). Behavioral relaxation methods, like applied relaxation, have been shown to reduce sympathetic activity (18,26). As increased central noradrenergic activity is related to hot flushes (27,28), effects of applied relaxation on sympathetic activity and coping may be mechanisms behind the beneficial effects on hot flushes.

Since many women do not want to use or cannot use HT, it is important to find treatment options with few or no side-effects. Recent studies from different countries (29,30) show that many women have discontinued HT use following the WHI and HERS. It could be assumed that many of these women still suffer from vasomotor symptoms and are willing to try alternative, safe methods with documented effects. We suggest that acupuncture and applied

relaxation should be further evaluated, and the mechanisms behind their effects further explored, in order to develop alternative methods for women with menopausal complaints.

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