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A comparison of acupuncture and oral estradiol treatment of vasomotor symptoms in postmenopausal women

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Key words HOT FLUSHES, ACUPUNCTURE, ALTERNATIVE TREATMENTS, MENOPAUSE

ABSTRACT

Objective To compare the effects of electro-acupuncture with oral estradiol and superficial needle insertion on hot flushes in postmenopausal women.

Material and methods Forty-five postmenopausal women with vasomotor symptoms were randomized to electro-acupuncture, superficial needle insertion or oral estradiol treatment during 12 weeks, with 6 months' follow-up. The number and severity of flushes were registered daily and the Kupperman index and a general estimate of climacteric symptoms were completed before, during and after therapy.

Results In the electro-acupuncture group, the mean number of flushes/24 h decreased from 7.3 to 3.5 (ANOVA, $p < 0.001$). Eleven of the 15 women had at least a 50% decrease in number of flushes (with a mean decrease of 82%). Superficial needle insertion decreased the number of flushes/24 h from 8.1 to 3.8 ($p < 0.001$). In seven out of 13 women, the number of flushes decreased by at least 50% (mean decrease 83%). In the estrogen group, the number of flushes decreased from 8.4 to 0.8 ($p < 0.001$). The decrease in number of flushes persisted during the 24-week follow-up period in all treatment groups. The Kupperman index and the general climacteric symptom score decreased, and remained unchanged 24 weeks after treatment in all groups ($p < 0.001$). Electro-acupuncture decreased the number of flushes/24 h significantly over time, but not to the same extent as the estrogen treatment. No significant difference in effect was found between electro-acupuncture and the superficial needle insertion.

Conclusion We suggest that acupuncture is a viable alternative treatment of vasomotor symptoms in postmenopausal women and cannot recommend superficial needle insertion as an inactive control treatment.

INTRODUCTION

Hot flushes occur in the majority of women around menopause[1,2]. Estrogen is the treatment of choice, but, due to side-effects and relative contraindications in some women, there is a great need for alternative treatments.

The flushes are probably initiated from the thermoregulatory center in the hypothalamus[3]. Studies of luteinizing hormone (LH) pulsatility indicate that β-endorphin activity is low after menopause and is increased by estrogen ther-

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apy[4,5]. Nappi and colleagues found lower concentrations of β-endorphins in cerebrospinal fluid from postmenopausal women than in women of fertile age[6]. The low central β-endorphin activity after menopause may contribute to elevated levels of LH and lability in thermoregulation[7]. Opioids increased the thermoregulatory set point after intracerebral injection[8,9].

During estrogen treatment, increased central opioid activity may explain the decrease in vasomotor symptoms[7]. Physical exercise and acupuncture also increase the activity of hypothalamic β-endorphin[10–14] and exercise has been associated with a lower prevalence of vasomotor symptoms[15,16].

In a previous study, we found that vasomotor symptoms decreased in women treated with acupuncture[17]. We used two modalities of acupuncture, one where an electric current was applied to some of the needles (electro-acupuncture) and one with superficial needle insertion without further stimulation. The choice of acupuncture points was a modification of points used in previous studies on acupuncture treatment of dysmenorrhea[17]. The use of acupuncture for climacteric complaints is not well documented. Very few published studies are available in English, and their results are difficult to interpret due to poor design and diagnostic criteria as well as a lack of valid outcome measures. A few published studies have reported decreased vasomotor symptoms after acupuncture treatment, but these studies were uncontrolled, and usually not randomized[18–20]. There have, however, been a number of studies on the effect of acupuncture on pain relief[21–24]. The method of a very superficial insertion was used as a 'near-placebo' method, since it has been suggested to elicit a weaker peripheral stimulation than electro-acupuncture.

In our earlier study[17], no other treatment than acupuncture was offered and it could be argued that only women with a positive attitude towards alternative methods participated. The present study assesses the effects of acupuncture in women who would accept estrogens as well as alternative methods. The present study compares the effects of electro-acupuncture treatment with oral estradiol and superficial needle insertion on number and severity of hot flushes in postmenopausal women. Spontaneous fluctuations of flushes in a non-treated comparison group were also recorded. The primary outcome was the number and severity of flushes registered daily in logbooks.

MATERIALS AND METHODS

Design

The study was a prospective trial including 75 women randomized to treatment with electro-acupuncture, superficial needle insertion, physical exercise, oral estrogen treatment or applied relaxation; there were 15 patients in each group. The study comprised a 2-week baseline period, 12 weeks of treatment and a 6-month follow-up period. Only data on the 45 women randomized to treatment with acupuncture or oral estradiol are presented in this report. Data from the other treatment groups will be presented separately.

Randomization was performed by the use of identical, opaque, sealed envelopes, containing a label to determine the treatment. The gynecologists and nurses evaluating the patients were blind to treatments, i.e. at evaluation, the physician and research nurse did not know which acupuncture treatment each woman had and not until after analysis of the results did we unveil the treatment modalities. Furthermore, the patients were only informed that two different modalities were used but not that we expected one to be more efficient. To assess effects during the treatment period and whether the effect persisted 6 months after treatment, the data are evaluated after the 12 weeks of treatment, and after a 6-month follow-up period.

In order to compare the treatment effect with spontaneous fluctuations of flushes, data were collected from 12 women during the 8 weeks preceding the start of treatment. This non-treated 'waiting list' group comprised eight women from the present study, and another four women from a similar and parallel study on hot flushes in women with breast cancer.

Patients

The present study included 45 women, aged between 48 and 63 years, with vasomotor symptoms and a spontaneous menopause at least 6 months previously. The women were recruited by advertisement in the local papers and at the gynecological outpatient clinic at the Linköping University Hospital, Sweden. Four of the 45 women had undergone hysterectomy, but none with bilateral oophorectomy. The exclusion criteria were severe metabolic, thrombo-embolic or endocrine disease, uncontrolled hypertension (> 95 mmHg diastolic) or use of sedatives, anxiolytic or antidepressant medication, or use

of narcotics. Women who exercised regularly more than 1 hour/week were also excluded.

Before inclusion, the women underwent a general medical examination by a gynecologist. Postmenopausal status was verified by analyses of follicle stimulating hormone (FSH) and estradiol concentrations in all women before treatment. After the 12 weeks of treatment, these analyses were repeated, both as a control of compliance in the estrogen group and to verify that the possible treatment effect in the acupuncture groups was not due to a spontaneous recurrence of ovarian function.

All women randomized to electro-acupuncture and estradiol therapy completed the 12 weeks of treatment. In the superficial needle insertion group, one woman did not start therapy due to severe migraine, and another was excluded due to repeated non-attendance. In all, 43 women completed the treatment period of 12 weeks. After completed treatment, one woman in the superficial needle insertion group and two in the electro-acupuncture group chose to discontinue and, 3 months after the end of treatment, another two women in the latter group discontinued, all but one due to insufficient effect on their flushes.

In the estrogen group, six patients were dropped after the 12 weeks of initial treatment. Five of these six women continued estrogens, but did not come to the follow-up visits, and one interrupted her estrogens due to unwanted bleedings. In all, 11 women in the electro-acupuncture group, 12 in the superficial needle insertion group and nine in the estrogen treatment group completed the 6-month follow-up period.

Treatment

Acupuncture was administered by a physiotherapist experienced and skilled in acupuncture treatment. In the two acupuncture groups, 30-min treatments were given twice a week for the first 2 weeks and once a week for 10 weeks, in all 14 treatments over 12 weeks.

In the electro-acupuncture group, 12 sterile stainless-steel acupuncture needles (Hwato, 0.25 mm diameter, 15 mm long, and 0.30 mm diameter, 30 mm long) were inserted to a depth of 5–20 mm and twirled to evoke needle sensation (De Qi), described as tension, numbness and often as a radiating sensation from the point of insertion, reflecting activation of muscle nerve afferents (mainly A-delta fibers). The four needles in the lower back were attached to an electrical stimulator (IC-1107, Ito Co., Ltd, Japan) giving a low burst frequency of 2 Hz alternating current stimulation (internal pulses within the burst frequency were square wave pulses with alternating polarities, with a pulse duration of 0.1 ms, 80 pulses/s). The stimulation elicited non-painful local muscle contractions. The acupuncture points used were BL 15, 23 and 32 bilaterally (paraspinally at thoracic and lumbar levels), HT 7 (wrist), SP 6 and 9 (lower leg), LR 3 (foot), PC 6 (wrist), and GV 20 (head) unilaterally, previously used in our earlier study[17]. As there was very sparse experience of acupuncture therapy for climacteric symptoms, the choice of acupuncture points used was a modification of points used in previous studies on acupuncture treatment of dysmenorrhea[17].

In the superficial needle insertion group, small dimension needles (Hwato, 0.25 mm diameter, 15 mm long) were superficially inserted (0.5–1 mm) parallel to the skin, approximately 1–5 cm away from the points used in the electro-acupuncture group in all but three of the needles. Three needles (the upper needle of BL 15, BL 23 and BL 32) were moved laterally on the back about 10–15 cm. After insertion, no additional stimulation was given. 'De Qi' was not obtained. This method was used as a 'near-placebo' method,since it has been suggested to elicit a weaker peripheral stimulation than electro-acupuncture.

The women randomized to estrogen treatment were given unopposed 2 mg 17β-estradiol orally for 12 weeks (approximately equivalent to 0.625 mg of conjugated estrogens). Thereafter, it was suggested that they continue their estrogen treatment with additional sequential progestogens given monthly.

At inclusion, all women were informed that they could choose to discontinue their treatment whenever they wanted, and at every visit to the clinic they were asked specifically if they wanted to change therapy.

Monitoring

At least 2 weeks before and during the 12 weeks of treatment, and 1 week every month during the 6-month follow up period, the women daily registered the number and severity of flushes in a logbook. Logbooks were completed by the patients every night before bed-time and were collected at the visits to the outpatient clinic, before treatment, after 4, 8 and 12 weeks of treatment and 12 and 24 weeks after the end of therapy. The baseline value for flushes/24 h, in the treatment groups as well as the comparison group,

was calculated from the mean per day and night of the 2 weeks prior to start of therapy. For each of the 12 treatment weeks, a mean of the number of flushes per 24 h was calculated for each week from the mean of flushes per night and day during that week. Severity was reported in the logbook as a figure from 0 to 10, where 10 indicated, regardless of the number of flushes, that the flushes were experienced as 'extremely severe' and 0 'not troublesome at all'. A mean severity score per 24 h was calculated from the 7 days of values of severity for each week evaluated. At the visits to the outpatient clinic, the women also completed a slightly modified version of the Kupperman index[25] and a general summary of the climacteric symptom intensity on a visual analog scale. In the Kupperman index, symptoms were assessed and subjectively graded into a four-point scale, between 0 and 3. The severity scores for sweating, sleep disturbances and irritability were multiplied by 2, and the score for hot flushes was multiplied by 4[25]. The highest total score possible was 51. On the visual analog scale, the women gave an estimate between 1 and 10 as a general summary of the total climacteric symptom intensity and distress that they experienced from their symptoms, where 1 denoted 'no distress' and 10 'very severe distress'[17]. Control of compliance was performed by the therapist's record of attendance for treatment, and by the woman herself, who daily registered 'treatment' or 'no treatment' in the logbook, and, in the estrogen treatment group, also by means of analysis of FSH and estradiol in serum after 12 weeks of treatment.

The local Ethical Review Board at the Linköping University approved the study. Oral and written informed consent was obtained from each patient.

Statistical evaluations were performed using StatView 5.1 (Abacus SAS Institute Inc. NC, USA). Baseline demographic data for the groups were analyzed by non-parametric comparisons using the Kruskal–Wallis test and the χ^2 test. Analysis of variance for the effects of treatments and time was performed on the dependent variables: the number and severity of flushes, the score on the Kupperman index and the general summary of the climacteric symptom intensity scale (ANOVA for repeated measurements). For analysis of changes within each treatment group, we used one-sample ANOVA.

RESULTS

We confirmed that none of the dependent variables showed any deviations from a Normal distribution at the stated p level (StatView normality test, Kolmogorov–Smirnov's test). No significant differences in the demographic data between the groups were found at baseline except that women in the estrogen group were slightly younger (Table 1). The treatment groups did not

Table 1 Baseline data. Social and medical characteristics at baseline of postmenopausal women treated with two different regimens of acupuncture: electro-acupuncture, superficial needle insertion and oral estrogen. Statistical evaluation was carried out by the Kruskal–Wallis and the χ^2 test. Data are given as mean (range) or percentages or number, as appropriate

	Electro-acupuncture ($n = 15$)	*Superficial needle insertion* ($n = 13$)	*Estrogen* ($n = 15$)	*p Value*
Age (years)	54.5 (46–59)	53.4 (49–58)	50.9 (43–55)	0.02
Years since menopause	3.2 (0.5–9)	5.2 (0.5–14)	1.8 (0.5–5)	NS
Body mass index (kg/m^2)	26.4 (19.5–31.2)	25.9 (21.0–36.6)	25.6 (21.3–29.5)	NS
Smoking				
yes	20%	31%	31%	NS
no	80%	69%	69%	
Education				
compulsory school	2	0	1	NS
High school	0	1	1	
professional education	8	10	8	
university degree	5	2	4	
Employment				
yes	13	13	13	NS
no	2	0	2	

differ at baseline regarding the demographic or the dependent variables nor did the groups evaluated after 12 weeks of treatment differ compared to the subgroups that remained for evaluation 6 months after the end of treatment.

12-week treatment

After 12 weeks of treatment, the women in the acupuncture groups still had estradiol and FSH levels within the normal ranges for postmenopausal women, whereas serum estradiol concentrations increased in the estrogen group. The number of flushes/24 h decreased significantly over time by both methods of acupuncture as well as by estrogen treatment (ANOVA, $p < 0.001$).

In the 'waiting list' group, the mean number of flushes/24 h was 7.3 at baseline and varied between 92 and 107% of baseline during 8 weeks.

In the electro-acupuncture group (15 women), the mean number of flushes/24 h decreased from 7.3 to 3.5 (ANOVA, $p < 0.001$; Tables 2 and 3) after 12 weeks of treatment. Eleven of the 15 women had at least a 50% decrease in number of flushes/24 h, with a mean decrease of 82%. In the superficial needle insertion group, 13 women fulfilled 12 weeks of treatment and the number of flushes/24 h decreased from 8.1 to 3.8 (ANOVA, $p < 0.001$). In seven out of the 13 women with at least a 50% decrease in the number of flushes/24 h, the mean decrease was 83%. In the estrogen group, the mean number of flushes decreased from 8.4 to 0.8 ($p < 0.001$). In the group of six women in the estrogen group who chose to discontinue from the study after 12 weeks, all but one had at least a 90% decrease. The number and severity of flushes per day and night decreased significantly over time by both methods of acupuncture as well as by estrogen treatment already after 4 weeks ($F(2,40) = 69.6$, $p < 0.001$).

There was no group difference over time between the electro-acupuncture treatment group compared to the estrogen treatment group in number and severity of flushes after the 12 weeks of treatment, but there was a significant interaction between the variables group and time, due to the more pronounced effect in all women in the estrogen group. The two different acupuncture groups did not differ over time (Table 2). The visual analog scale estimate of the general climacteric symptom intensity and the Kupperman index score decreased significantly over time in both the electro-acupuncture group and the estrogen group after 12 weeks of treatment (Tables 2 and 4). There was no group difference, but a significant interaction between the variables group and time, showing a difference in effect over time, due to the more pronounced effect in the estrogen group (Table 2).

24-week follow-up period

During the follow-up period, the decrease in number of flushes/24 h remained unchanged in all the treatment groups (Tables 2 and 3). In the subgroup of women in the electro-acupuncture group, who completed the follow-up period, the number of flushes/24 h was 2.4 after 12 weeks of treatment and 3.3 at the end of follow-up. In the superficial needle insertion group, the corresponding figures were 3.6 and 3.6, respectively.

During the follow-up period, no interaction between the variables group and time was found concerning the visual analog scale estimate or in Kupperman index score between the women in the electro-acupuncture and the estrogen groups that completed the whole study, due to a more similar effect over time (Tables 2 and 4). After the 24-week follow-up, still no difference was found between the superficial and the electro-acupuncture groups concerning these variables. The mean score of these two variables remained unchanged after the follow-up period within each treatment group (Table 4).

DISCUSSION

In this study, the mean number of hot flushes decreased significantly during treatment with electro-stimulated as well as with superficial needle insertion and oral estrogen treatment. The decrease persisted over the 24-week follow-up period in all groups. It appeared that about 75% of the women responded well to electro-acupuncture (with a decrease in number of flushes/24 h of more than 50% of baseline), whereas the rest responded poorly (no response or a decrease of less than 50% of baseline). According to many surveys on acupuncture treatment, 20–30% of the population are likely to be non-responders, or low responders[26]. Low responders are also found in animal studies[27], and here the definition was set to animals that had a response of less than 50% (tail flick latency). On average, in both groups, the number of flushes decreased to below 50% of baseline including the patients who did not respond. In the responders (about 75% of the women), the number of flushes per 24 h decreased to 20–25% of baseline. Flushes were totally

Table 2 Effects of two modes of acupuncture and estrogen on vasomotor symptoms over 36 weeks. Analysis of variance concerning the variables: flushes/24 h, severity of flushes, general climacteric symptoms on a visual analog scale (VAS), and Kupperman index (KI), for the groups: electro-acupuncture (EA, $n = 15$), superficial needle insertion (SNI, $n = 13$) and estrogen (E, $n = 15$). The number of patients in the different groups changed at 24 weeks after treatment (T) due to drop out

			Flushes/24 h		*Severity day*		*Severity night*		*VAS*		*KI*	
Group/moment	*n*	*df*	*F value*	*p value*	*F value*	*p value*	*F value*	*p value*	*F value*	*p value*	*F value*	*p value*
EA/E												
Baseline–12 w T	30	1,28										
Main effect group			3.16	NS	1.79	NS	0.49	NS	2.5	NS	3.01	NS
Main effect time			61.0	< 0.001	36.0	< 0.001	23.0	< 0.001	75.0	< 0.001	64.0	< 0.001
Interaction			5.52	0.002	10.0	< 0.001	4.02	0.01	3.84	0.01	3.36	0.02
EA/SNI												
Baseline–12 w T	28	1,26										
Main effect group			0.10	NS	0.43	NS	0.001	NS	0.017	NS	1.4	NS
Main effect time			25.2	< 0.001	2.0	< 0.001	9.67	< 0.001	29.9	< 0.001	24.5	< 0.001
Interaction			0.06	NS	1.12	NS	0.07	NS	1.78	NS	2.22	NS
EA/SNI												
Baseline–24 w after T	23	1,21										
Main effect group			0.38	NS	0.24	NS	0.07	NS	0.04	NS	1.1	NS
Main effect time			1.8	< 0.0001	9.99	< 0.0001	8.22	< 0.0001	1.8	< 0.0001	17.5	< 0.0001
Interaction			0.27	NS	0.58	NS	0.90	NS	1.28	NS	1.0	NS
EA/E												
Baseline–24 w after T	20	1,18										
Main effect group			1.22	NS	1.11	NS	0.52	NS	2.7	NS	4.36	NS
Main effect time			39.0	< 0.001	17.0	< 0.001	15.0	< 0.001	41	< 0.001	29.3	< 0.001
Interaction			4.41	< 0.001	2.98	0.015	1.59	NS	1.96	NS	1.72	NS

NS, not significant

Table 3 Flushes per 24 hours before, during and after end of treatment with electro-acupuncture, superficial needle insertion and estrogen. Mean, standard deviation (SD) and 95% confidence interval (CI) given for baseline, at 4, 8, and 12 weeks of treatment and at 12 and 24 weeks after end of treatment. Weeks 1–8 include the untreated 'waiting list' group

	'Waiting list' group ($n = 12$)			*Electro-acupuncture* ($n = 15$)			*Superficial needle insertion* ($n = 13$)			*Estrogen* ($n = 15$)		
	Mean	*CI*	*SD*	*Mean*	*CI*	*SD*	*Mean*	*CI*	*SD*	*Mean*	*CI*	*SD*
Baseline				7.6	5.5–9.8	3.8	8.1	5.0–11.2	5.2	8.4	6.6–10.1	3.1
Week 1	7.3	4.3–10.3	4.7	7.6		4.2	6.7		4.9	6.4		3.2
Week 4	7.0	3.7–10.3	5.5	4.6	2.6–6.7	3.7	5.4	2.4–8.3	4.9	2.3	1.0–3.5	2.2
Week 6	7.0		5.2	4.4		4.0	4.9		4.4	1.8		2.4
Week 8	7.8	4.8–10.7	4.6	3.8	1.6–6.1	4.0	4.2	1.7–6.8	4.2	1.2	0.1–2.2	1.9
Week 12				3.5	1.2–5.7	4.0	3.8	0.9–6.7	4.8	0.8	0.1–1.5	1.2
Follow-up				($n = 11$)			($n = 12$)			($n = 9$)		
Week 12				2.9	0.9–4.9	3.0	4.5	1.1–8.0	5.4	0.5	0–1.4	1.1
Week 24				3.3	0.9–5.6	3.5	3.6	0.3–6.9	5.2	0.8	0–1.9	1.4

Table 4 Summary of general climacteric symptoms on a visual analog scale and the Kupperman index score, before, during and 24 weeks after treatment, with electro-acupuncture, superficial needle insertion and estrogen therapy. Mean, standard deviation (SD) and 95% confidence interval (CI) given for baseline, 4 and 12 weeks of treatment and 24 weeks after treatment

	Electro-acupuncture			*Superficial needle insertion*			*Estrogen*		
	Mean	*CI*	*SD*	*Mean*	*CI*	*SD*	*Mean*	*CI*	*SD*
Summary of general climacteric symptoms									
Baseline	6.1	5.3–6.9	1.5	5.2	4.0–6.5	1.5	6.6	5.7–7.5	1.6
Treatment		($n = 15$)			($n = 13$)			($n = 15$)	
Week 4	3.7	2.7–4.7	1.8	3.7	2.8–4.6	1.2	3.3	2.2–4.4	2.1
Week 12	2.7	2.0–3.4	1.2	2.8	1.8–3.9	1.0	1.8	1.2–2.3	0.9
After treatment		($n = 11$)			($n = 12$)			($n = 9$)	
Week 24	2.9	1.6–4.2	2.0	3.1	1.7–4.5	2.2	1.6	0.6–2.6	1.3
Kuppermann index									
Baseline	22.7	18.9–26.6	7.0	23.9	19.3–28.5	7.6	23.8	20.9–26.8	5.3
Treatment		($n = 15$)			($n = 13$)			($n = 15$)	
Week 4	17.0	12.6–21.4	8.0	17.2	13.2–21.2	6.6	11.7	7.8–15.6	7.1
Week 12	10.5	7.7–13.4	5.2	16.5	11.5–21.4	8.1	6.6	4.0–9.3	4.8
After treatment		($n = 11$)			($n = 12$)			($n = 9$)	
Week 24	11.4	6.6–16.2	7.2	14.4	9.9–18.9	7.1	5.6	0–11.7	7.9

abolished in some of the responders, but all responders, including those with some remaining flushes, were content with the acupuncture treatment and did not want any other therapy during or after the 6-month follow-up period. In the estrogen group, flushes were not totally abolished in seven out of 15 women, although all women in this group had a decrease in number of flushes (58–100% decrease of flushes/24 h). In some patients in this group, the effect developed very slowly, and the number of flushes continued to decrease after the 12 initial weeks of treatment.

After 12 weeks of treatment, there was a difference in the effect over time in score of the Kupperman index and the general summary of the climacteric symptom intensity scale between the estrogen and the electro-acupuncture group, and this difference was no longer significant after the follow-up period. This was probably due to the fact that three of the four women who discontinued in the electro-acupuncture group were 'non-responders'. Even if a few non-responders were still included in this group, the effects in estrogen and the electro-acupuncture groups were more similar during the follow-up period.

We noticed no serious side-effects from the acupuncture or estrogen treatment. In the present study, the women randomized to acupuncture did not actively ask for acupuncture, but were prepared to receive any of the treatments offered. Baseline data show that smoking and level of education were around average for Swedish women. We therefore believe that acupuncture could be offered to women with vasomotor symptoms in general.

It could be argued that hot flushes may cease spontaneously in some women during the 9-month study period and that we have only observed this phenomenon. Since we had no non-treated control group over 9 months, we cannot fully contradict this statement. However, we were unable to find any spontaneous decrease in number of hot flushes in 12 untreated women who daily recorded the flushes over 8 weeks (Table 3). Furthermore, in a study of 876 women[28], neither placebo nor raloxifene decreased hot flushes over 30 months in the women who reported flushes.

Another explanation for our findings may be a placebo effect causing a decrease in number of hot flushes. Placebo treatment as such has been suggested to induce β-endorphin release[29–31], based on the fact that placebo-induced pain relief could be blocked by naloxone[31,32]. If β-endorphins are involved in the vasomotor symptoms, a

placebo effect may explain why the vasomotor symptoms decrease during acupuncture treatment. The long-standing effects for at least 6 months without any further therapy, however, suggest more than only placebo effects.

In a number of studies on various hormone replacement therapy regimes, effects on flushes have been compared to placebo. In a systematic review, the Cochrane Collaboration found that estrogens decreased the number of flushes by almost 90%, whereas placebo decreased the number of flushes by 50%[33]. Placebo effects were, however, usually observed in short trials of 3 months' duration. We had a follow-up period of 6 months, making the total observation time 9 months. It is unlikely that placebo effects persist for such a long period of time.

Acupuncture might well be expected to have a powerful non-specific placebo effect considering that it is a form of therapy with an aura of mysticism and that it has been used successfully in the Far East[34]. Therefore, it may be difficult to assess whether it has specific effects beyond this. In a previous study, however, we found significant changes in the 24-h urine excretion of calcitonin gene-related peptide[35] in parallel with decreased flushes, showing that both superficial insertion and electro-acupuncture actually induced biochemical changes in postmenopausal women[17]. We also found altered calcitonin gene-related peptide concentrations in cerebrospinal fluid after electro-acupuncture and physical activity in rat[36]. Acupuncture has been shown to induce other biochemical effects in a number of studies[10,11,14,37–39]. Using functional magnetic resonance imaging, electro-acupuncture, but not superficial needle insertion, has been shown to affect the hypothalamus and deactivate multiple limbic areas[40]. This suggests that acupuncture induces more than just unspecific effects. Electro-acupuncture seems to affect hypothalamic opioid activity and oxytocinergic mechanisms[41] as well as to induce spinal segmental effects[38]. Several modulating mechanisms may thus be involved in the effects observed in this study.

In general, it is very difficult to use a placebo method when studying acupuncture. It does not seem to be possible to insert needles without any sensorial stimulation[23,24]. In fact, even a very gentle form referred to as minimal or micro-acupuncture, where the needle is superficially inserted (1–3 mm) and left for a very short time (1–5 s) with no further stimulation, seems to exert an effect[26]. An ongoing discussion in the acupuncture field today is also that the acupuncture points should rather be referred to as acupuncture areas or zones, as needling in the areas around the traditional acupuncture points may also be efficient[26,34]. Recently, a placebo method of using patches has been suggested[42,43]. However, this method has not been validated and was not available when our studies were conducted, and even this method induces a kind of sensorial stimulation. In this study, we used the method of very superficial needle insertion as a control method that could be considered as 'near-placebo', even though it may have physiological effects[44]. Electro-acupuncture was believed to have a significantly stronger specific effect that would possibly decrease the number of flushes more. The acupuncture points used in the present study are thought to have general effects on patients with pain[45]. It is reasonable, however, that other points and different treatment duration and intervals could be even more efficient when treating postmenopausal women with vasomotor symptoms.

It appeared that the effect induced from the superficial insertion was strong enough to induce significant reduction of flushes in the responders and thereby no difference was found between the two methods. Also, other studies, mainly on treatment of pain, have shown good effects of superficial acupuncture[46–48]. In a larger group of women with higher statistical power, a difference might have been found between the different modes of acupuncture in the treatment of hot flushes, but a different form of placebo method is recommended in future studies.

During the 6-month follow-up period, the women only visited the clinic once in 3 months after the end of therapy. The care and contact from the acupuncture therapist that might also influence the result of treatment did not exist during this long period, yet the effect persisted.

In a study by Freedman and colleagues[3], control groups receiving muscle relaxation and alpha-wave feedback did not decrease their number of flushes per day, whereas the 'active' treatment with paced respiration decreased the number of flushes to about 50% of the pretreatment level. In relation to those results, the decrease in number of flushes induced by acupuncture does not seem to be a placebo effect.

In conclusion, all three treatments significantly decreased the intensity and frequency of hot flushes/24 h (electro-acupuncture, superficial needle insertion and estrogen treatment). The effects on hot flushes persisted for at least 6 months after the end of therapy. Even though the effect

was more pronounced in the estrogen treatment group, we suggest that acupuncture is a viable alternative treatment of vasomotor symptoms in postmenopausal women. Contrary to expectation, we found no significant difference between superficial needle insertion and electro-acupuncture at points where electro-acupuncture has previously been found to have a general effect on patients experiencing pain. We conclude that electro-acupuncture is an effective form of acupuncture for treating vasomotor symptoms, but cannot recommend the use of superficial needle insertion as an inactive 'near-placebo' treatment, as it has shown effects and includes penetration of the skin with neural and dermal effects.

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