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Vasomotor symptoms decrease in women with breast cancer randomized to treatment with applied relaxation or electroacupuncture: a preliminary study

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Abstract

Objective: To evaluate the effect of applied relaxation and electro-acupuncture on vasomotor symptoms in women treated for breast cancer.

Methods: Thirty-eight postmenopausal women with breast cancer and vasomotor symptoms were randomized to treatment with electro-acupuncture (n=19) or applied relaxation (n=19) during 12 weeks. The number of hot flushes was registered daily in a logbook before and during treatment and after 3 and 6 months of follow-up.

Results: Thirty-one women completed 12 weeks of treatment and 6 months of follow-up. After 12 weeks of applied relaxation, the number of flushes/24 h had decreased from 9.2 (95% confidence interval (CI) 6.6-11.9) at baseline to 4.5 (95% CI 3.2-5.8) and to 3.9 (95% CI 1.8-6.0) at 6 months follow-up (n=14). The flushes/24 h were reduced from 8.4 (95% CI 6.6-10.2) to 4.1 (95% CI 3.0-5.2) after 12 weeks of treatment with electro-acupuncture and to 3.5 (95% CI 1.7-5.3) after 6 months follow-up (n=17). In both groups, the mean Kupperman Index score was significantly reduced after treatment and remained unchanged 6 months after end of treatment.

Conclusion: We suggest that applied relaxation and electro-acupuncture should be further evaluated as possible treatments for vasomotor symptoms in postmenopausal women with breast cancer.

Introduction

Breast cancer is the most common cancer in women, with a lifetime incidence of almost 10% in Swedish women¹. Breast cancer incidence increases continuously with age, but the increase is slower after 50 years of age, probably because of a cessation of ovarian estrogen and progesterone production². The incidence has also increased over time, especially for women between 50 and 69 years, with annual increments of $3.3-4.3\%^3$. Current use of hormone therapy (HT) with combined estrogen and progestin treatment has been associated with a slight, albeit significant, increase in the incidence of breast cancer and the increase is dependent on the total duration of use⁴.

Many women with breast cancer develop menopausal symptoms spontaneously or due to the cancer treatment. Both cytotoxic and adjuvant endocrine therapy with tamoxifen may cause premature menopause and tamoxifen may also intensify hot flushes⁵. Vasomotor symptoms negatively influence quality of life, while sleep disturbances and depression increase with the severity of vasomotor symptoms in women with breast cancer⁶. Although women may have severe vasomotor symptoms after breast cancer treatment, HT is usually not recommended due to the theoretical risk of recurrence of the disease or a new primary breast cancer⁷. The HABITS (hormonal replacement therapy after breast cancer - is it safe?) study recently found an increased risk for recurrence of breast cancer after receiving HT⁸, mainly based on combined estradiol and norethisterone. Such results indicate that non-hormonal alternatives are needed.

Treatments like paced respiration⁹, relaxation¹⁰, and acupuncture¹¹ have previously been applied successfully on vasomotor symptoms in non-cancer patients. Anti-depressant drugs like venlaxafine have been suggested as alternative treatment of hot flushes¹², but have a number of side-effects that must be considered. We introduced applied relaxation, a behavioral therapeutic method, as a possible alternative treatment of vasomotor symptoms in women without breast cancer¹³. This method has not yet been tried in women with breast cancer.

The actual mechanisms of action of applied relaxation are unknown. The low concentrations of estrogen after menopause seem to lead to instability in the thermoregulatory center in the hypothalamus, possibly due to changed β -endorphin and noradrenergic activity. The central activities of noradrenaline and β -endorphins that have been suggested to be important in the mechanisms of flushes^{14,15} might be changed by applied relaxation.

We have previously found that vasomotor symptoms decreased in healthy postmenopausal women treated with acupuncture¹¹. Women in that study were not randomized to different treatments but to two different types of acupuncture. The use of acupuncture for climacteric complaints has not up to now been well acknowledged, whereas acupuncture as treatment for pain is well investigated and accepted¹⁶⁻¹⁹. Physical exercise and acupuncture increase the activity of hypothalamic β -endorphin²⁰⁻²² and exercise has been associated with a lower prevalence of vaso-motor symptoms^{23,24}. Since acupuncture is known to increase central β -endorphin activity, we want-ed to evaluate if this treatment could also ameli-orate flushes in women treated for breast cancer.

The present study aimed to explore the effects of applied relaxation and electro-acupuncture on the frequency of vasomotor symptoms in postmenopausal women with breast cancer, randomized between these two treatments. We expected that vasomotor symptoms would decrease after both treatments, even in women using tamoxifen.

Patients and methods

Thirty-eight women aged 30-64 years with treatment-induced or spontaneous menopause and treated for breast cancer were invited. Previous treatment for breast cancer is summarized in Table 1. At the time of the study, all cancer therapy was completed, except for tamoxifen, which was still ongoing in eight women. The mean age in both groups was 53 years. The median time since menopause was 1.5 years (0.5-7 years) in the applied relaxation group and 2 years (1-10 years) in the electro-acupuncture group. They all had moderate to severe vasomotor symptoms, and at least two flushes/24 h. The women were consecutively recruited from the outpatient clinics at the Department of Oncology and the Department of Breast Surgery, Linköping University Hospital.

Treatment	Applied relaxation*	Electro-acupuncture*	Total	
Surgery	5	7	12	
Surgery and tamoxifen	0	1	1	
Surgery and radiotherapy	3	5	8	
Surgery, tamoxifen and radiotherapy	5	3	8	
Surgery and chemotherapy	1	1	2	
Total	14	17	31	

Table 1: Previous treatment of breast cancer in women treated with applied relaxation or electro-acupuncture

*Ongoing tamoxifen: applied relaxation, five women; electro-acupuncture, three women

Before inclusion, all women underwent a physical examination by a gynecologist. Postmenopausal status was verified by means of analyses of follicle stimulating hormone and estradiol concentrations in serum. Information about the medical history including the breast cancer andts treatment was collected at the first visit. Thereafter, the women were randomly allocated to either applied relaxation (n=19) or electro-acupuncture (n=19) using labels in sealed, opaque envelopes.

During the 2 weeks before inclusion, the patients were asked to report the number of night and daytime flushes in a logbook, in order to register the baseline frequency of the symptoms. Thus, the logbook was kept daily from baseline, 2 weeks before starting treatment, and during the 12-week training period. During a period of 6 months after treatment, the logbook was filled in daily every 4th week. Climacteric symptoms were estimated according to the slightly modified Kupperman's Index²⁵ at baseline and 4, 8 and 12 weeks as well as 3 and 6 months after the end of treatment. The women assessed hot flushes, sweating, sleep disturbance, nervousness, depression, vertigo, fatigue, arthralgia, headache, tachycardia, and vaginal dryness and the severity was graded from 0 to 3. The severity score for sleep disturbance, sweating, nervousness was multiplied by 2 and that for hot flushes by 4, so that the highest possible score was 51.

Treatments

Treatment with applied relaxation

The training for applied relaxation took 12 sessions and consisted of the following components: progressive relaxation, release-only relaxation, cue-controlled relaxation, differential relaxation, rapid relaxation, application training and maintenance program²⁶. The trainer (E.N.) met the patients in a group (n=4-6) during a period of 12 weeks, with weekly sessions of 60 min each. The women were told to practice each component at home at least once a day. During the first session, the women were given information about menopause and about theories of hot flushes. The aim of applying applied relaxation in view of coping with vasomotor symptoms was discussed. The group was given a rationale of applying applied relaxation as a coping technique for handling sudden unanticipated symptoms by quick calming down, and thus gaining control over the situation. Then the first part of the progressive relaxation program was taught (contraction and relaxation of muscles in arms, face, neck and shoulder). In session 2, a program for progressive relaxation of the whole body was practiced. In session 3, a condensed version (relaxation without muscle straining) of progressive relaxation was trained. In session 4, cue-controlled relaxation was introduced (self-instructed relaxation) and trained. Sessions 5 and 6 focused on differential relaxation (relaxation of non-used muscle groups). Sessions 7 and 8 regarded rapid relaxation. Then the patients were asked to practice the present program about 15-20 times per day. By then, the patients should be able to relax within 20-30 s. In sessions 9 and 10, application training was started. The patients were asked to use the rapid relaxation as soon as the vasomotor symptoms appeared. Session 11 and 12 were used for rehearsal and, finally, a summary of a maintenance program was handed out.

Electro-acupuncture treatment

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 10 weeks. 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 fibers²⁷. The four needles in the lower back were attached to an electrical stimulator, giving low-burst frequency of 2 Hz alternating current stimulation, which elicited a non-painful local muscle contraction. 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 study¹¹. 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 aiming at increasing β -endorphin activity¹¹.

Statistics

Normal distribution of data was tested and verified by means of the Kolmogorov-Smirnov test. After having completed a few missing values with the mean of the measurement before and after in each case, changes in the number of flushes/24 h and the sum-scores of the Kupperman Index were statistically tested with analysis of variance (ANOVA) for repeated measurements. Possible relationships between changes in hot flush frequency and

demographic variables were tested with Spearman Rank Correlation (age and years since menopause).

Ethics

The local Ethical Committee at the Faculty of Health Sciences, Linköping University approved the study. Written and oral informed consent was obtained from each patient before participation in the study.

Power

The power of the study was 95% with p < 0.05 to show a significant reduction in hot flushes after 12 weeks.

Results

A significant change of flushes over time appeared already after 4 weeks in both treatment groups and no further significant change was seen thereafter up to 6 months after the end of treatment. Thus, the decrease in number of flushes persisted even at 3 and 6 months follow-up. No relationship was found between changes in the number of flushes and the demographic variables age and years since menopause.

Table 2: Effects of therapy for vasomotor symptoms in breast cancer-treated women by
means of applied relaxation or electro-acupuncture, as measured by means of flushes/24 h
and Kupperman Index

		Flushes/2	4 h			Kupperman Index				
Time	Mean	Standard deviation	95% CI	p Value	Mean	Standard deviation	CI	p Value		
Applied relaxation $(n = 14)$										
Baseline	9.2	4.6	6.6-11.9		25.0	5.2	21.9-28.0			
Treatment										
4 weeks	5.3	4.0	3.0-7.6	< 0.001	14.6	6.0	11.1-18.1	< 0.001		
8 weeks	4.8	2.6	3.3-6.3		12.8	6.8	8.9-16.7			
12 weeks	4.5	2.2	3.2-5.8	< 0.0001	13.5	6.7	9.5-17.4	< 0.001		
Follow-up										
3 months	4.3	3.5	2.2-6.3		12.7	4.8	9.9-15.5			
6 months	3.9	2.7	1.8-6.0	< 0.0001	13.1	4.6	10.4-15.8	< 0.001		
Electro-acupuncture (n = 17)										
Baseline	8.4	3.4	6.6-10.2		24.6	6.8	21.1-28.0			
Treatment										
4 weeks	5.5	3.3	3.8-7.2	< 0.001	20.3	8.9	15.7-24.9	< 0.001		
8 weeks	4.6	2.3	3.4-5.8		15.5	6.6	12.1-18.9			
12 weeks	4.1	3.3	3.0-5.2	< 0.0001	14.9	7.3	11.2-18.7	< 0.001		
Follow-up										
3 months	4.1	2.2	2.4-5.8		15.5	6.3	12.2-18.7			
6 months	3.5	3.5	1.7-5.3	< 0.0001	14.6	6.8	11.1-18.2	< 0.001		

Mean sum-score, standard deviation and 95% confidence interval (CI) for flushes/24 h and Kupperman Index at baseline, after 4, 8 and 12 weeks of treatment and at 3 and 6 months follow-up after the end of treatment with electro-acupuncture or applied relaxation. p Values denote tested change in relation to baseline (ANOVA)

Applied relaxation

In the applied relaxation group, five of the 19 women dropped out during or before the 12 weeks of treatment, one between inclusion and start of therapy, due to practical problems of attending the training program. Another woman stopped treatment due to social reasons, two women did not want to wait for the start of applied relaxation treatment, and the fifth woman reported too mild symptoms after inclusion, and did not want to continue the training. All the 14 women who completed the 12 weeks of training with applied relaxation also completed the 6 months follow-up.

According to the logbooks, the mean number of flushes/24 h decreased significantly already after 4 weeks of applied relaxation from 9.2 (95% confidence interval (CI) 6.6-11.9) to 4.5 (95% CI 3.2-5.8) at 12 weeks of therapy and to 3.9 (95% CI 1.8-6.0) at 6 months follow-up (Table 2), F = 5.48, p < 0.001.

Five women used adjuvant endocrine therapy with tamoxifen throughout the study-period. There was no difference in the mean number of hot flushes at baseline between the women with (n=5) and without tamoxifen treatment (n=9). There was, however, a main effect for time, F(1,12)=6.5, p < 0.001), but no interaction effect for groups and time, F(1,12)=1.4, p=0.24. This is explained by the fact that women with tamoxifen did not have a significant reduction of flushes until after 12 weeks of treatment, F(4,1)=9.4, p < 0.05, whereas, for women without tamoxifen, this appeared already after 4 weeks of treatment (Table 3).

	Treatment group, all $(n = 14)$			Tamoxifen (n = 5)			No tamoxifen (n = 9)		
Time	Mean	SD	95% CI	Mean	SD	95% CI	Mean	SD	95% CI
Baseline	9.2	4.6	6.6-11.9	9.7	4.6	3.9-15.5	9.0	4.7	5.3-12.7
Treatment week									
1	8.6	4.9		9.7	6.1		7.9	4.4	
2	11.0	6.9		12.2	10.9		10.2	4.1	
3	6.3	3.6		8.3	4.3		5.1		
4	5.3	4.0	3.0-7.6	8.4	3.7	3.8-13.0	3.6	3.0	1.3-6.0
5	5.3	4.2		8.2	4.8		3.7	2.9	
6	5.8	3.5		8.8	2.9		4.0	2.5	
7	5.8	3.5		8.1	2.2		4.4	3.5	
8	4.8	2.6	3.3-6.3	6.1	1.5	4.3-8.0	4.1	2.8	1.9-6.3
9	4.2	2.6		5.2	1.9		3.7	2.8	
10	4.7	2.6		6.2	1.7		3.9	2.7	
11	4.5	2.1		5.3	0.8		4.2	2.5	
12	4.5	2.2	3.2-5.8	4.7	1.3	3.9-6.4	4.4	2.7	2.3-6.4
Follow-up									
3 months	4.3	3.5	2.2-6.3	4.8	1.3	2.0-7.4	3.9	4.1	0.7-7.1
6 months	3.9	2.7	1.8-6.0	3.6	2.2	0.8-6.4	4.0	4.2	0.8-7.3

 Table 3: Effects of applied relaxation on number of flushes/24 h over 36 weeks in breast cancer-treated women with or without adjuvant endocrine therapy

Mean flushes/24 h, mean, standard deviation (SD) and 95% confidence interval (CI), given for baseline, weeks of treatment, 3 and 6 months after treatment with applied relaxation

The mean sum-score for climacteric symptoms according to the Kupperman Index was significantly reduced (Table 2).

Electro-acupuncture

In the electro-acupuncture group, two of the 19 women dropped out during or before the 12 weeks of treatment, one because she moved away from the region, and one who did not start treatment for unknown reasons. All the 17 women who completed the 12 weeks of treatment with electro-acupuncture also completed the 6 months follow-up. Three of these women had treatment with tamoxifen throughout the study period. According to the logbooks, all three had decreased flushes after the treatment period of 12 weeks and also at 6 months follow-up, but we did not analyze these women separately, as they were so few.

According to the logbooks, the mean number of flushes/24 h decreased significantly in the whole group, from 8.4 at baseline (95% CI 6.6-10.2) to 4.1 (95% CI 3.0-5.2) at 12 weeks of therapy and to 3.5 (95% CI 1.7-5.3) at 6 months follow-up (Table 2), F = 11.78, p < 0.0001.

The sum-score for climacteric symptoms according to the Kupperman Index was significantly reduced after therapy and during follow-up (Table 2).

Discussion

This study showed that hot flushes decreased during 12 weeks of treatment with applied relaxation and electro-acupuncture in women treated for breast cancer. The effect appeared already after 4 weeks of treatment and still persisted at 6 months after the end of treatment in both groups. Although the treatment groups were quite small, the power of the primary outcomes was strong (95% and more).

There are some problems when designing studies on alternative therapies, e.g. the problem with blinding or use of placebo. A non-treated control group would have been advantageous but we decided not to use such a group without therapy for the 9-month study period, with women having breast cancer and bothered by significant symptoms. A patient-therapist relation may have affected the results. The effects of both electro-acupuncture and applied relaxation in this study might, to some extent, depend on the care of the therapists and by calmness, sedation and relaxation induced by both treatments. In order to reduce the bias caused by the patient-therapist relation, the therapists were excluded from all follow-up visits and evaluations.

The rationale for the design to randomize between two treatment alternatives was not to compare treatment effects but to be able to measure effects within each group of women who were not allowed to decide the treatment they preferred. To compare the treatments would need a high number of women in each group. This study had not enough power to answer such a question.

The fact that the treatment effects persisted at least 6 months after the end of therapy may be explained by the maintenance program in the applied relaxation-treated group. When the woman obtained the skill to cope with her vasomotor symptoms through applied relaxation,

she probably felt calmer and more self-confident and motivated to continue the applied relaxation training by herself. We assume that the persistent reduction of flushes is an effect of continued training and that the women applied the relaxation technique as soon as they felt their symptoms coming back. When acupuncture is given as treatment of pain, there is a prolonged effect up to several months, which was also seen in the group receiving electro-acupuncture for flushes.

Although relaxation therapy has previously been used for vasomotor symptoms, the therapeutic mechanisms are not fully understood. It has, however, been reported that other kinds of behavioral therapies may induce both physiological and biological changes, e.g. affect blood pressure and norepinephrine concentrations in hypertensive women²⁸.

Plasma β -endorphin concentrations are low at the onset of hot flushes but rise during the flush^{29,30} which may be caused by stress triggered by the perception of soon having a flush.

A possible explanation as to why electro-acupuncture decreased flushes is based on the findings that hypothalamic β -endorphin seems to affect thermoregulation^{31,32}. If low β -endorphin activity makes the thermoregulation less stable, then electro-acupuncture that stimulates hypothalamic β -endorphin activity may counteract this instability.

It is known that non-noxious sensory stimulation may induce a psychophysiological response including decreased sympathoadrenal activity and increased vagal nerve tone, by release of endogenous oxytocin^{33,34}. Such phenomena were not studied in our report but must be included among non-specific mechanisms of both treatments used in the present study.

Placebo effects may contribute to our results. 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^{35,36}. A number of studies show that placebo effects cause nearby 50% reduction of flushes³⁷ but most of these studies did not have an observation time of more than 3 months. However, other studies show no or very little effect on vasomotor symptoms of placebo during 12 weeks of treatment or longer³⁸. Sloan and colleagues³⁹ reported from seven different clinical trials that one out of every four patients who receive placebo treatment reports that their hot flushes are reduced by 50%. However, the observation time was short, only 4 weeks. In the present study, women were observed for 6 months without organized therapy, during which time they only visited the clinic twice for a follow-up, i.e. after 3 and 6 months. The reduction in flushes that was reached after 12 weeks of therapy persisted after another 6 months, possibly as an effect of the women's self-training, at least in the applied relaxation group. This again suggests something more than a placebo effect is contributing to the decrease in flushes.

It could be argued that we treated a very select group of women, who were interested in trying either relaxation therapy or acupuncture. However, the women were randomized between the two treatment alternatives and were not allowed to decide themselves. It could also be argued that we have not measured hot flushes objectively, but only used women's subjective reports. Objectively measured hot flushes, however, correlate highly with patients' self-reported hot flushes⁴⁰.

Most women sooner or later have a spontaneous transition of their vasomotor symptoms. It may be that we only observed this phenomenon in our study group. In a prospective study, the prevalence of hot flushes was about 50% around the last menstruation, with a slow

decline to 40% 2 years later and to 20% after 4 years⁴¹. There is thus a definite, albeit slow, decline in number of flushes over time. In our study, the median time after menopause was 1.5-2 years and therefore it is unlikely that there would be a rapid spontaneous decrease (60%) of flushes in this short period. Actually, the most dramatic decrease in number of flushes/24 h was seen already during the first 4 weeks of therapy.

In conclusion, women with breast cancer who started therapy with applied relaxation and electro-acupuncture had significantly decreased vasomotor symptoms. The effects persisted at least 6 months after the end of therapy and were more pronounced than reported regarding a number of other suggested non-hormonal alternative treatments. Our results should be interpreted with caution due to the small study groups and drop-out rates, but we suggest that applied relaxation and electro-acupuncture should be further evaluated as useful tools in the management of hot flushes in those women who for medical reasons cannot use hormonal replacement therapy.

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Conflict of interest Nil.

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