



## Prostate Cancer

# Two Modes of Acupuncture as a Treatment for Hot Flashes in Men with Prostate Cancer—A Prospective Multicenter Study with Long-Term Follow-Up

Jessica Frisk<sup>a,b,\*</sup>, Anna-Clara Spetz<sup>a</sup>, Hans Hjertberg<sup>c</sup>, Bill Petersson<sup>c</sup>, Mats Hammar<sup>a</sup>

<sup>a</sup> Division of Obstetrics and Gynaecology, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University, Linköping, Sweden

<sup>b</sup> Department of Surgery, County Council of Östergötland, Norrköping, Sweden

<sup>c</sup> Department of Urology, County Council of Östergötland, Norrköping and Linköping, Sweden

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### Abstract

**Background:** Hot flashes are common and distressing among men with castrational treatment for prostate cancer. Of the few treatments, most have side effects.

**Objective:** Assess changes in hot flashes of electrostimulated (EA) and traditional acupuncture (TA).

**Design, Setting, and Participants:** Thirty-one men with hot flashes due to prostate cancer treatment were recruited from three urological departments in Sweden, from 2001 to 2004.

**Intervention:** Thirty-one men were randomized to EA (12 needle points, with 4 electrostimulated) or TA (12 needle points) weekly for 12 wk.

**Measurements:** Primary outcome: number of and distress from hot flashes in 24 h and change in “hot flush score.” Secondary outcome: change in 24-h urine excretion of CGRP (calcitonin gene-related peptide).

**Results and Limitations:** Twenty-nine men completed the treatment. Hot flashes per 24 h decreased significantly, from a median of 7.6 (interquartile range [IQR], 6.0–12.3) at baseline in the EA group to 4.1 (IQR, 2.0–6.5) ( $p = 0.012$ ) after 12 wk, and from 5.7 (IQR, 5.1–9.5) in the TA group to 3.4 (IQR, 1.8–6.3) ( $p = 0.001$ ). Distress by flushes decreased from 8.2 (IQR, 6.5–10.7) in the EA group to 3.3 (IQR, 0.3–8.1) ( $p = 0.003$ ), and from 7.6 (IQR, 4.7–8.3) to 3.4 (IQR, 2.0–5.6) ( $p = 0.001$ ) in the TA group after 12 wk, (78% and 73% reduction in “hot flush score,” respectively). The effect lasted up to 9 mo after treatment ended. CGRP did not change significantly. Few, minor side effects were reported.

**Limitations:** small number of patients; no placebo control, instead a small group controlled for 6 wk pretreatment.

**Conclusions:** EA and TA lowered number of and distress from hot flashes. The hot flush score decreased 78% and 73%, respectively, in line with or better than medical regimens for these symptoms. Acupuncture should be considered an alternative treatment for these symptoms, but further evaluation is needed, preferably with a non- or placebo-treated control group.

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\* Corresponding author. Department of Surgery, Östergötland, Vrinnevisjukhuset, 601 82 Norrköping, Sweden. Tel. +46 11 22 20 00; Fax: +46 13 14 81 56.  
E-mail address: [jessica.frisk@imk.liu.se](mailto:jessica.frisk@imk.liu.se) (J. Frisk).

## 1. Introduction

Prostatic carcinoma is the most common cancer in men. Surgical or medical castration therapy is the standard treatment in generalized disease but causes long-lasting hot flushes in 58–80% of the men [1,2], and up to 27% report flushes as the most troublesome adverse effect [3]. Many regimens have been tried for the flushes (eg, diethylstilbestrol, cyproterone acetate, selective serotonin reuptake inhibitors [SSRIs], gabapentin, megestrol acetate, and clonidine), but have shown weak effects or potentially serious side effects [4–6].

Thus, there is room for treatment alternatives for these symptoms. A pilot study showed that acupuncture decreased the number of hot flushes by 70% after 10 wk of treatment, and that 3 mo after treatment ended, the average number of flushes was 50% lower than before the acupuncture [7]. This finding is in accordance with studies on menopausal women, but not confirmed in larger studies in men.

Acupuncture has been suggested as treatment of hot flushes because it probably affects  $\beta$ -endorphin and serotonin activity in the central nervous system [8,9], which regulates these symptoms. When sex steroid production decreases, brain opioidergic, noradrenergic, and serotonergic activities change [10,11], making the thermoregulatory center in the hypothalamus unstable. This phenomenon, in turn, may cause a sudden drop in the temperature set point, leading to vasodilatation and sweating, thus decreasing central body temperature to the new set point [12]. These reactions seen in men with prostate cancer during hot flushes [13] have been suggested to be mediated by calcitonin gene-related peptide (CGRP), which is a potent vasodilator and stimulator of cholinergic sweating [14,15]. CGRP increased in plasma in men with prostate cancer during flushes [13] and decreased in 24-h urine after acupuncture therapy in women with hot flushes [16].

The aim was to assess the effect of two modes of acupuncture on frequency of hot flushes and distress caused by hot flushes in men with prostatic carcinoma and castration treatment.

## 2. Methods

### 2.1. Patients

Three urological clinics in Sweden were involved: Jönköping, Linköping, and Norrköping. Patients at the outpatient clinic with complaints of hot flushes were recruited. Inclusion criteria were castration (surgery or gonadotrophin-releasing hormone [GnRH] analogue) at least 3 mo previously and more

**Table 1 – Demographic data at baseline (means or numbers) for 31 men\***

	EA (n = 15)	TA (n = 16)
Age (yr), mean (SD)	67.2 (9.4)	71.1 (9.1)
BMI (kg/cm <sup>2</sup> ), mean (SD)	27.3 (2.8)	26.8 (2.2)
Smokers (yes/no)	2/13	3/13
Living alone/living together	9/6	11/5
Exercising > 5 h/wk (yes/no)	6/9	9/7
Castration therapy (surgical/GnRH-a)	0/15	2/14
Change of castration therapy during the time included (yes/no)	1/14	1/15

EA, electrostimulated acupuncture; TA, traditional acupuncture; SD, standard deviation; BMI, body mass index; GnRH-a, gonadotrophin-releasing hormone analogue.  
\* There were no significant differences in demographic data between groups.

than 20 hot flushes per week. Exclusion criteria were hormonal treatment other than GnRH analogue, daily treatment with psychotropic drugs, newly started or changed alternative medications with possible effects on flushes, uncontrolled hypertension or metabolic disease, inability to move/lie on the side, and treatment with anticoagulants or a pacemaker. Demographic data at baseline are shown in Table 1. Time since diagnosis of cancer was 0.25–8 yr (median, 2 yr) in the electrostimulated acupuncture (EA) group, and 0.25–5 yr (median, 2 year) in the traditional acupuncture (TA) group.

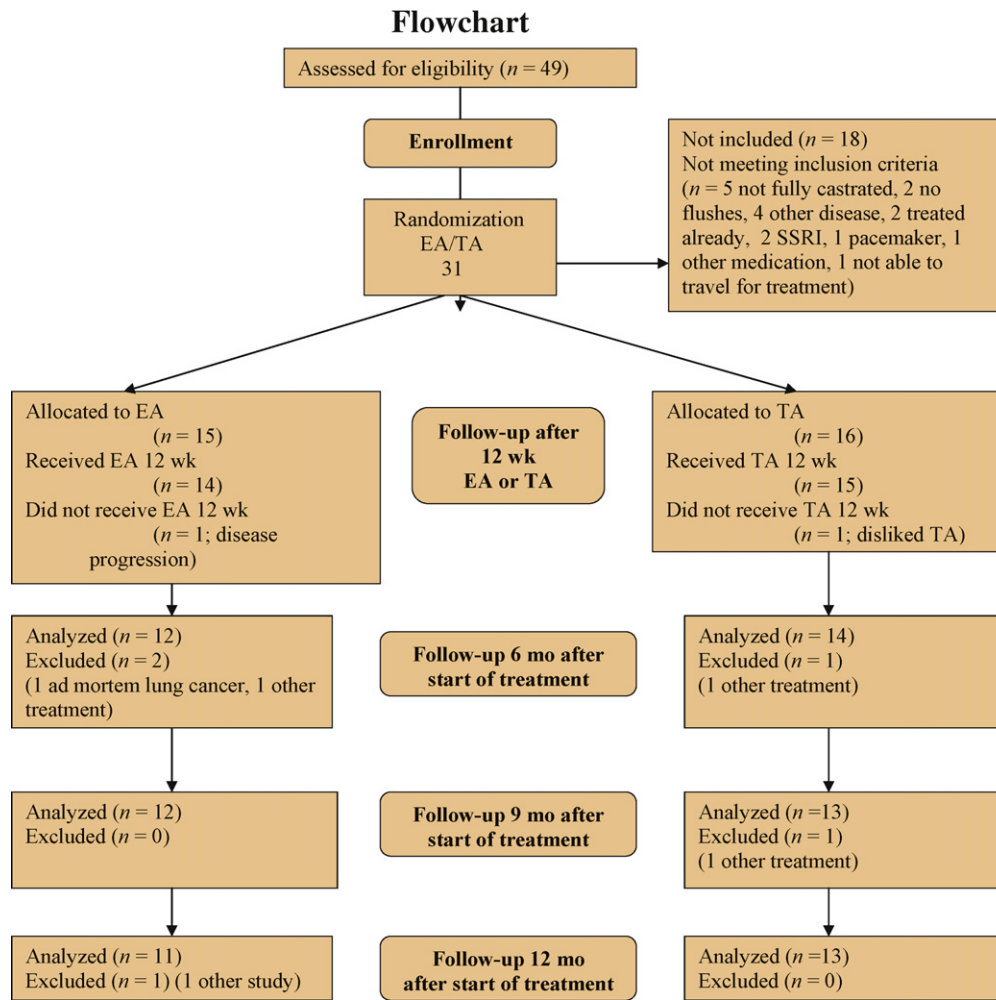
### 2.2. Procedure

Inclusion was performed between March 2001 and December 2004 with randomization to EA or TA in blocks of four (two EA, two TA). Treatment was blinded to patients and monitoring personnel. The acupuncturists received envelopes with a note in each indicating the treatment chosen. We assessed 49 men at a screening visit; 13 were not eligible, and 36 men were randomized. Five of them turned out not to be fully castrated (revealed after s-testosterone analysis) and were thereafter excluded. Thirty-one men (3 from Jönköping, 13 from Linköping, and 15 from Norrköping) were planned for 12 wk of EA or TA, but 2 were excluded before 4 wk of treatment because of disease progression (1) or distress from the acupuncture therapy (1). They were, however, included in the intention-to-treat analysis (Fig. 1).

### 2.3. Treatment

Treatment was given by a physiotherapist for 30 min twice a week during the first 2 wk, and then once a week during 10 wk, with the patients lying on the side. Five physiotherapists administered EA and TA at hospitals and private practices. They were instructed not to discuss treatment effects with the patients.

Twelve sterile stainless-steel acupuncture needles either 0.25 mm in diameter and 15 mm long, or 0.30 mm in diameter and 30 mm long (Hwato, Suzhou Medical Instruments, China) were inserted 5–20 mm in defined points and twirled to evoke needle sensation (de Qi, a feeling of tension and numbness),



**Fig. 1 – Chart diagram showing the inclusion of patients with prostatic carcinoma and vasomotor symptoms in the study of electrostimulated acupuncture (EA) and traditional acupuncture (TA) of vasomotor symptoms. SSRI; selective serotonin reuptake inhibitor.**

which reflects activation of muscle nerve afferents. In the EA group, acupuncture was given with 2 Hz in four points on the lower back, and in TA in eight points as previously described [16] (Table 2).

**2.4. Monitoring**

At inclusion and after 12 wk of treatment, s-testosterone and s-luteinizing hormone (s-LH), were analyzed to confirm castrational levels of sex steroids, and that the subjects' castrational status had not changed during treatment, which could have affected the results. To measure CGRP urinary excretion (u-CGRP), we performed a 24-h urine collection pretreatment, after 12 wk of treatment, and at 6, 9, and 12 mo after start of treatment.

The week before treatment started, the men used a scale of zero to 10 to register daily in logbooks the numbers of hot flushes per day and night, and the distress the flushes caused during the day and night. Distress in 24 h was then calculated from the sum of daytime and nighttime recordings. Eight patients filled in logbooks during 6 wk or more until treatment

**Table 2 – Acupuncture points and the anatomical position used for needle insertion**

Acupuncture points	Anatomical position
Bilaterally at	
BL 15 (urinary bladder)	Thoracic part of the back
BL 23 (urinary bladder)	Lumbar part of the back
BL 32 (urinary bladder)	Lumbar part of the back
Unilaterally at	
GV 20 (Governor vessel)	Top of the head
HE 7 (heart)	Ulnar side of the wrist
PC 6 (pericardium)	Volar side of the distal forearm
LR 3 (Liver)	Dorsal side of the foot
SP 6 (spleen)	Lower leg, medial side
SP 9 (spleen)	Lower leg, medial side, below the knee
* Stimulated with 2 Hz.	

started; their recordings were used to control that the decrease of flushes at 4 wk was not a spontaneous decrease, but by intervention.

All patients were treated for 12 wk; during that period they filled in logbooks daily. They also filled in which days they received acupuncture as a control for compliance.

The patients were then followed up at 6, 9, and 12 mo after start of treatment; they recorded the number of flushes and distress experienced by hot flushes in logbooks for 7 d before the follow-up visit. Any side effects and changes in medical treatment were recorded in the case record forms.

Logbooks have been widely used as a valid method of measuring hot flushes, and they correlate well with the number of flushes objectively recorded [17,18]. The “Hot Flush Score” (distress  $\times$  number of flushes [17,19]) was then counted.

### 2.5. CGRP analysis

Samples were extracted and concentrated five times with the use of a reverse-phase C18 cartridge (Sep Pak; Waters Corp, Millford, MA, USA), and analyzed for calcitonin gene-related peptide-like immunoreactivity (CGRP-LI) with the use of competitive radio immunoassays (BD). CGRP-LI was analyzed with the use of antiserum CGRPR8 raised against conjugated rat CGRP. HPLC-purified (125) I-histadyl rat CGRP was used as radioligand and human CGRP as calibrator. The cross-reactivity of the assay to substance P, neurokinin A, neurokinin B, neuropeptide K, gastrin, neurotensin, bombesin, islet amyloid polypeptide, adrenomedullin, neuropeptide Y, and calcitonin was less than 0.01%. Cross-reactivity toward human CGRP $\alpha$  and  $\beta$  was 93% and 24%, respectively, and toward rat CGRP $\alpha$  and  $\beta$  100% and 120%, respectively. Intra- and interassay coefficients of variation were 8% and 14%, respectively. The lower limit of detection in the original samples was 0.4 pmol/l for CGRP.

### 2.6. Statistics

Analyses were made with SPSS, version 12.0.1 (SPSS Inc, Chicago, IL, USA). The changes in numbers of flushes per 24 h, distress caused by flushes per 24 h, and u-CGRP were analyzed within and between both treatment groups with the use of the analysis of variance (ANOVA) for repeated measures, and the Wilcoxon signed rank sum test was used for paired comparisons within each group. For demographic data, t test was used. *p* values  $<$  0.05 were considered statistically significant, and decreases in numbers and distress by flushes  $>$  50% were considered clinically significant [20].

Handling of missing data: Four logbooks were missing because of loss of follow-up (EA, *n* = 1 [3%]; TA, *n* = 3 [2%]). The mean value for each group was used to replace these missing data, because there were no following measuring points in these cases.

u-CGRP data were missing at three times in the EA group (5%) and three times in the TA group (4%). Missing data were replaced as above, except in one case, for which we had data from the measuring point before and after the missing data, and thus used the average of those two points.

### 2.7. Ethics

This study was approved by the ethics committee at the University of Linköping and was performed according to the Declaration of Helsinki and Good Clinical Practice guidelines. The patients were informed in writing and orally before they gave their informed consent.

## 3. Results

Thirty-one patients started, and 29 fulfilled 12 wk of treatment (14 EA, 15 TA). Twenty-four (11 EA, 13 TA) men were followed for 12 mo. Reasons for dropouts are shown in a flowchart (Fig. 1). Three of the 29 patients asked for other treatment for the flushes during the follow-up. No serious side effects were reported, but one patient felt that treatment caused distress, another reported fatigue on the treatment day, and a third reported a centimeter-sized hematoma at the insertion site.

### 3.1. Six-week pretreatment control group

Eight patients filled in logbooks 6 wk or more pretreatment; their recordings were used to (1) validate the 1-wk pretreatment recording as a description of the pretreatment situation and (2) determine whether changes over 6 wk during therapy seemed due to natural changes or treatment.

Patients had a median number of flushes of 8.0 (interquartile range [IQR], 5.5–9.8) at 6 wk pretreatment and 8.9 (IQR, 5.7–9.6) flushes per 24 h (*p* = 0.833) at 1 wk pretreatment. The median distress per 24 h was 7.8 (IQR, 5.8–10.3) at 6 wk pretreatment and 7.5 (IQR, 4.3–9.7) at 1 wk pretreatment (*p* = 0.483). After 4 wk of treatment, the median number of flushes (3 EA, 5 TA) was 4.6 (IQR, 3.1–7.0) (*p* = 0.012, compared with 6 wk pretreatment), and 3.1 (IQR, 1.5–7.2) (*p* = 0.012) at 8 wk of treatment. The median distress caused by flushes had changed to 3.9 (IQR, 1.6–7.12) (*p* = 0.012, compared with 6 wk pretreatment) at 4 wk of treatment, and to 2.6 (IQR, 0.5–6.4) (*p* = 0.012) at 8 wk of treatment.

In summary, the number of flushes per 24 h and distress caused by the flushes did not change spontaneously during 6 wk of observation in these eight patients, but changed significantly after 4 and 8 wk of treatment.

### 3.2. Number of flushes

The numbers of flushes per 24 h decreased significantly in both groups from baseline to 4 wk of



**Table 3 – Median numbers of hot flushes and distress caused by hot flushes per 24 h in the EA group**

N	Time from baseline	Median no of flushes (IQR, 25–75%)	<i>p</i> *	Median distress (IQR, 25–75%)	<i>p</i> *
15	Baseline	7.4 (5.5–12.0)	—	8.2 (6.5–10.7)	—
14	4 wk	7.6 (4.9–8.7)	0.028	6.4 (3.2–9.5)	0.064
14	8 wk	6.3 (3.6–7.5)	0.003	5.7 (1.6–8.4)	0.006
14	12 wk	4.1 (2.0–6.5)	0.002	3.3 (0.3–8.1)	0.003
12	6 mo	5.5 (2.6–7.4)	0.012	5.6 (1.3–6.7)	0.004
12	9 mo	4.7 (1.6–6.8)	0.015	3.9 (1.2–7.5)	0.005
11	12 mo	6.2 (4.2–6.5)	0.271	5.5 (3.8–6.9)	0.016

EA, electrostimulated acupuncture; IQR, interquartile range.

\* The *p* value denotes decrease from baseline.

treatment and remained at this decreased level at all measuring points, except at 12 mo after start of treatment in the EA group, when flushes tended to increase (Tables 3 and 4). There was no significant difference between the groups over time ( $p = 0.25$ ; ANOVA).

Of men receiving 12 wk of treatment, 57% (8 of 14) in the EA group and 47% (7 of 15) in the TA group showed a decrease larger than 50%; they had a mean decrease of 74% (median, 74%) and 69% (median, 65%) of number of flushes after 12 wk of therapy, respectively. Six months after start of treatment, 33% (4 of 12) of the EA-treated and 43% (6 of 14) of the TA-treated men still experienced a decrease larger than 50%, despite the fact that 2 of the patients with more than a 50% decrease in the EA group were excluded at this point. Twelve months after start of treatment, 18% (2 of 11; EA) and 46% (6 of 13; TA) still experienced a decrease in number of flushes of 50% or more.

Seven men (3 EA, 4 TA) showed less than a 30% reduction in number of flushes and could be considered nonresponding to this mode of acupuncture (24% of the men).

### 3.3. Distress from flushes

The distress from flushes per 24 h was significantly reduced in both groups at almost all measuring points (Tables 3 and 4). There was no significant

difference between the groups over time ( $p = 0.65$ ; ANOVA). In those who received 12 wk of treatment, 50% (7 of 14) in the EA group and 60% (9 of 15) in the TA group showed a decrease above 50%. At that point, they had a mean decrease of 92% (median, 93%) and 71% (median, 65%) of distress by hot flushes, respectively. Six months after start of treatment, 50% (6 of 12) of the EA-treated and 50% (7 of 14) of the TA-treated men still experienced a decrease larger than 50%. Twelve months after start of treatment, these numbers were 36% (4 of 11; EA) and 46% (6 of 13; TA), respectively.

Six men (4 EA, 2 TA) showed a less than 30% reduction in distress of flushes (21% of the men).

### 3.4. The hot flush score

The hot flush score decreased by 78% and 73%, respectively, from baseline to 12 wk treatment in the EA and TA groups.

### 3.5. CGRP excretion

The 24-h u-CGRP changed from 10.9 (IQR, 6.4–12.8) pmol before treatment to 8.4 (IQR, 6.8–11.0) pmol after 12 wk of treatment in the EA group ( $p = 0.64$ ) and from 12.0 (IQR, 9.0–16.3) pmol to 11.4 (IQR, 7.6–14.9) in the TA group ( $p = 0.57$ ). No significant changes were recorded during follow-up. There

**Table 4 – Median numbers of hot flushes and distress caused by hot flushes per 24 h in the TA group**

N	Time from baseline	Median no of flushes (IQR, 25–75%)	<i>p</i> *	Median distress (IQR, 25–75%)	<i>p</i> *
16	Baseline	6.4 (5.2–9.4)	—	7.6 (4.7–8.3)	—
15	4 wk	4.8 (3.0–6.6)	0.003	5.1 (2.1–8.3)	0.010
15	8 wk	3.7 (2.0–6.9)	0.005	3.8 (1.7–7.0)	0.005
15	12 wk	3.4 (1.8–6.3)	0.001	3.4 (2.0–5.6)	0.001
14	6 mo	4.0 (1.7–7.2)	0.014	3.7 (1.7–8.6)	0.011
13	9 mo	4.5 (2.4–6.8)	0.036	4.5 (2.5–10.4)	0.126
13	12 mo	4.1 (2.7–5.2)	0.009	4.3 (1.3–7.7)	0.036

TA, traditional acupuncture; IQR, interquartile range.

\* The *p* value denotes decrease from baseline.

was no significant difference between groups over treatment period ( $p = 0.37$ ). In the 15 men from both groups with at least 50% reduced number of flushes at 12 wk of treatment, CGRP decreased nonsignificantly from 12.1 (IQR, 9.4–16.3) to 8.9 (IQR, 7.4–14.5) ( $p = 0.37$ ).

### 3.6. Change in s-testosterone

In the EA group, s-testosterone was 0.33 nmol/l (SD, 1.77) pretreatment and 0.62 nmol/l (SD, 0.55) after 12 wk of treatment ( $p = 0.08$ ). In the TA group, s-testosterone was 0.49 nmol/l (SD, 0.24) pretreatment and 0.61 nmol/l (SD, 0.40) after 12 wk of treatment ( $p = 0.16$ ).

## 4. Discussion

Both EA and TA significantly decreased the number of and distress caused by hot flushes per 24 h in men with prostate cancer and castrational treatment.

This is to our knowledge the first published study on acupuncture in men with hot flushes due to prostatic cancer and castration therapy except for two small case series [7,21]. The decrease in the hot flush score was in line with or greater than that reported for most other regimens [22] and lasted up to 9 mo after treatment ended. We treated the patients with either EA or TA, because we expected the EA group to show more pronounced results as a result of the actual electrical stimulation at four points. This treatment has been shown earlier in studies of pain treatment [23,24] but was confirmed in neither our study nor previous studies on acupuncture therapy of hot flushes [25,26]. This finding may indicate that it is not the type of acupuncture that is important for the results, but rather the acupuncture as such; our results do not indicate that one type is superior to the other. Had there been a difference between the groups, this study could have served as the basis before performing a correctly powered, comparative study between the treatments.

A limitation of this study is the lack of a placebo or nontreated control group. There is so far no good placebo method for acupuncture. Several devices [27,28] have been tried, but these methods do not seem to be totally without effect, probably because they cause neuronal stimulation attributable to local pressure on acupuncture points [29].

Treating men with hot flushes due to prostatic cancer and castration therapy with placebo pills has not been shown to reduce the number of flushes more than 20–30% [5]. The effect of a placebo has not been reported to last longer than 3 mo after start of

treatment [30], whereas we found a more pronounced effect, which lasted up to 9 mo after actual treatment had ceased. Therefore, we do not consider the placebo effect in our study to have contributed to a major extent.

As a kind of control group, eight patients recorded the number of flushes and distress caused by flushes during a 6-wk pretreatment period. In this group, we saw no change during the observational time, but significant changes after 4 and 8 wk of treatment were observed. This finding supports our theory that acupuncture treatment in itself decreases both the number of flushes and distress caused by flushes. Ideally, a larger, independent group should have been studied for at least 12 wk without therapy, but we considered it unethical to recruit patients with a severe, malignant disease and bothersome symptoms to serve as control group for an even longer untreated period than the 6 wk used for eight patients. It could be argued that we have observed spontaneous regression of the symptoms, but the counter argument is that we observed no change at all during 6 wk without therapy. Furthermore, Karling [2] showed that, of the patients who experienced hot flushes after castration, 70% still had these symptoms after 5 yr, and a prospective evaluation of hot flushes during castrational therapy found that 70% of the men had no decrease in flushes after a median follow-up of 18 mo [1].

Another limitation is the small size of the study; however, both treatment groups did show significant changes, which are important for the patients and probably for their quality of life. In view of these findings, we suggest that further controlled studies should be made, with a larger number of patients.

The fact that u-CGRP decreased in healthy women treated with acupuncture for hot flushes supports the conclusion that a physiological effect is involved [16]. In our study, however, we could not confirm any significant changes of CGRP excretion. The reason for this is not necessarily that CGRP is unrelated to hot flushes in men, but rather a methodological problem. Multiple practical difficulties occurred for many of the men to collect 24-h urine (eg, urge to void, generally impaired physical condition, and social embarrassment).

## 5. Conclusion

Acupuncture, both electrostimulated and traditional, lowers the number of hot flushes per 24 h and the distress caused by hot flushes in men with prostate cancer and castrational treatment. Because

no serious side effects were recorded, acupuncture deserves further attention as a viable alternative for these symptoms. This is, however, a small study, and the results need to be confirmed in a larger study, preferably with a control group receiving a valid placebo method, proven not to cause any neuronal stimulation, or possibly a larger group of patients with a reasonably long pretreatment control period that involves no treatment.

**Author contributions:** Jessica Frisk had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Frisk, Hammar, Spetz.

**Acquisition of data:** Frisk, Spetz, Hjertberg, Petersson.

**Analysis and interpretation of data:** Frisk, Hammar.

**Drafting of the manuscript:** Frisk, Hammar.

**Critical revision of the manuscript for important intellectual content:** Frisk, Hammar, Spetz, Hjertberg, Petersson.

**Statistical analysis:** Frisk, Hammar.

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**Administrative, technical, or material support:** Hjertberg, Petersson.

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