Effects of stellate-ganglion block on hot flushes and night awakenings in survivors of breast cancer: a pilot study

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Summary

Background Debilitating hot flushes and sleep dysfunction often affect survivors of breast cancer, most notably in those taking anti-oestrogen medications. Conventional treatments have been only partially effective in diminishing these issues, and some have serious risks. We did a pilot study to investigate our hypothesis that stellate-ganglion block can be a safe and effective treatment for hot flushes and sleep dysfunction in this patient population.

Methods 13 survivors of breast cancer (in remission) with severe hot flushes and night awakenings were treated with stellate-ganglion block at the anterolateral aspect of the C6 vertebra on the right side under fluoroscopy. Patients recorded hot flushes in a daily diary by use of the Hot-Flash Score, devised by Sloan and colleagues, and night awakenings by use of the Pittsburgh Sleep Quality Index. Both instruments were used 1 week before the procedure [A40] and then weekly after the procedure for 12 weeks. We used the generalised-estimating-equations method to analyse the longitudinal measurements of the number of hot flushes and night awakenings over time. This method is a popular approach to analysing datasets that have repeated measures from the same person, and is robust because it does not need the complete distribution of the outcomes to be specified. This trial is registered on the International Standard Randomised Controlled Trial Number register (ISRCTN14318565).

Findings There were no adverse events resulting from the stellate-ganglion block, although patients had temporary Horner's syndrome indicating the effectiveness of the block. Five patients had only one stellate-ganglion block and eight had two stellate-ganglion blocks. The total number of hot flushes decreased from a mean of 79·4 (SD 37·4) per week before the procedure to a mean of 49·9 (SD 39·9) per week during the first 2 weeks after the procedure (p=0·0002). The total number of hot flushes continued to decrease over the remaining follow-up period (weeks 3–12), and stabilised at a mean of 8·1 (SD 5·6) per week (p<0·0001). The number of very severe hot flushes was decreased to near zero by the end of the follow-up period (week 12; p<0·0001). Night awakenings decreased from a mean of 19·5 (SD 14·8) per week before the procedure to a mean of 7·3 (SD 7·1) per week during the first 2 weeks after the procedure (p<0·0001). The total number of night awakenings continued to decrease over the remaining follow-up period (weeks 3–12) and stabilised at a mean of 1·4 (SD 1·2) per week (p<0·0001).

Interpretation The findings of this study suggest that stellate-ganglion block can provide survivors of breast cancer with relief from hot flushes and sleep dysfunction with few or no side-effects. Long-term relief of symptoms has the potential to improve overall quality of life and increase compliance with anti-oestrogen medications for breast cancer.

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Introduction

Hot flushes are one of the most common symptoms associated with menopause, reportedly occurring in 68–82% of women undergoing natural menopause.[1] Surgical menopause is associated with an increased incidence and severity of hot flushes compared with natural menopause.[2] Carpenter and colleagues[3] report that women who have survived breast cancer have hot flushes that are "significantly more frequent, severe, distressing, and of greater duration" than in other women. These researchers also note that several unique factors, such as ovarian disruption caused by chemotherapy and subsequent early and artificial menopause, might mean that generalisations about healthy women with hot flushes cannot be applied to survivors of breast cancer.

Hot flushes can have a substantial effect on daily living, by disrupting sleep and causing fatigue and irritability during the day.[4] Severe hot flushes, which can cause rapid heartbeat, diaphoresis, nausea, dizziness, anxiety, headache, and weakness, also substantially increase the risk of sleep deprivation, depression, sexual dysfunction, and other serious medical conditions.

Hot flushes are a frequent and serious side-effect of pharmacological treatments for breast cancer, including oestrogen-synthesis inhibitors, oestrogen antagonists, and aromatase inhibitors. In survivors of breast cancer taking anti-oestrogen medications, hot flushes can even contribute to cancer recurrence by discouraging compliance with treatment regimens. Data show that more than 50% of such patients might be non-compliant after 180 days from initiation of anti-oestrogen treatment.[5] Poor adherence to medication regimens in patients with breast cancer is a serious issue, because these treatments have a major role in decreasing the recurrence of disease.[5]

In the past, many physicians might have under-rated the severity of hot flushes that result from anti-oestrogen medications and the negative effects of severe hot flushes on patients' lives and health. Although the scale of this issue after breast-cancer treatment is probably still underestimated, hot flushes are beginning to receive attention from health-care professionals.[6]

Current treatment options for hot flushes have varying degrees of effectiveness. Available options include: hormone treatment; herbal remedies; and non-hormonal pharmaceuticals.

Hot flushes are the most common reason for women to seek hormone treatment,[7] and this treatment option can be effective. However, hormone treatment has substantial complications, including headache, nausea, water retention, premenstrual irritability, and vaginal bleeding, which have a deleterious effect on quality of life.[8] Withdrawal bleeding is the most common reason for why women discontinue hormone treatment.[9] Moreover, for survivors of breast cancer, hormone treatment is generally considered contraindicated. A study published in 2004[10] showed a substantial increase in new breast-cancer events in survivors of breast cancer on hormone treatment, leading to early termination of the study because of "unacceptable risk". Consequently, survivors of breast cancer use hormone treatment much less frequently (fewer than 5% of survivors of breast cancer are on hormone treatment) than women who have not had breast cancer.[10] Use of this treatment option in patients with breast cancer has also decreased noticeably since the Women's Health Initiative reported conflicting and disturbing findings regarding its efficacy and side-effects in survivors of breast cancer.[11]

For herbal remedies, data suggest that these and lifestyle interventions are, at best, only slightly more effective than placebo.[4,8,12,13] Specifically, reviews of non-hormonal treatments for hot flushes concluded that phyto-oestrogens[14] and black cohosh,[15,16] are both ineffective in providing symptomatic relief.

The most promising non-hormonal pharmaceutical treatments include selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and gabapentin. These drugs have been reported to decrease hot-flush scores. However, SSRIs seem to be much less effective than hormone treatment.[13] Venlafaxine, an SNRI, can lead to rapid development of anasarca[17] and possible Q–T extension with a possible increase in sudden death.[18] Gabapentin has been reported to decrease hot flushes, but has been associated with a higher risk of suicide[19] and with weight gain,[20] compared with placebo.

Another possible treatment for debilitating hot flushes is stellate-ganglion block, used as a means of interrupting parts of the sympathetic nervous system involved in temperature regulation. This procedure might also help treat sleep dysfunction, which is often reported by menopausal women, including survivors of breast cancer on anti-oestrogen medications.

Stellate-ganglion blocks have been done safely for more than 60 years.[21] We suggest that a properly done stellate-ganglion block might be a safer and more effective treatment for hot flushes and sleep dysfunction in survivors of breast cancer than current pharmacological alternatives. To investigate this hypothesis, we did a pilot study to assess the safety and efficacy of this procedure in a group of survivors of breast cancer. To our knowledge, there have been no previous reports investigating the potential benefits of stellate-ganglion block for hot flushes and night awakening in this patient population. Our previously published anecdotal research on this procedure in 2005 reports a significant decrease of hot flushes in six patients without breast cancer.[22] The current study includes survivors of breast cancer.

Methods
Patients and procedure
Female survivors of breast cancer were referred, by their oncologists or gynaecologists, for assessment for stellate-ganglion block as a treatment for their hot flushes and sleep dysfunction. Participation in the study group was elective. Women who had acute infections or cardiac compromise at the time of assessment, who were on hormone treatment, or who had a blood-clotting disorder or an American Society of Anesthesiologists (ASA) physical status score[23] of 3 or higher were excluded from the study. These patients were excluded because of the possible increased risk of complications from any perispinal blockade in the above settings. Furthermore, we do not believe there would be a difference in response in the control of hot flushes in patients with ASA 3 or higher, because the mechanism of action will not change for patients with different ASA classifications.

Patients underwent a stellate-ganglion block at the anterolateral aspect of the C6 vertebra on the right side under fluoroscopy. Briefly, after local analgesia (lidocaine 2%), a 22-gauge Quincke needle was placed in the anterolateral aspect of the C6 vertebral body. When the needle contacted the bone, it was drawn back 1 mm, after which 3 mL of iohexol contrast dye (180 mg/mL) was injected to visualise the ganglion and confirm needle placement and to rule out intravascular or subarachnoid spread via radiography. 7 mL of 0·5% bupivacaine was subsequently injected next to the stellate ganglion to produce a sympathetic block. The length of time for the procedure was around 10 min. Ten patients had the procedure done with local anaesthetic and three patients had it done with local anaesthetic plus mild sedation (fentanyl and midazolam). The choice between local anaesthetic versus local anaesthetic plus mild sedation was made by each patient. After completion of the procedure, each patient was assessed for signs of the sympathetic block and for any signs of complications after the block. Patients were followed-up after 1 week for reassessment, specifically of hot flushes, in terms of quantity and quality, night

awakenings, and any possible complications, including, but not restricted to bleeding, infection, hypertension, hypotension, and CNS changes.

The effect of the stellate-ganglion block on the sympathetic nervous system was confirmed by the presence of Horner's syndrome (ie, facial anhydrosis, enophthalmos, ptosis, swelling of the lower eyelid, miosis, and blood-shot conjunctiva), and an increase in the temperature of the right hand of at least 2°F from baseline.

If the effect of the stellate-ganglion block on hot flushes and night awakenings did not last throughout the study's 12-week follow-up period, the block was repeated. The decision to repeat the block was made by the patients if they subjectively believed that the hot flushes or night awakenings were returning. Stellate-ganglion block has been used for decades, and many blocks have been done in the same patient without any increase in morbidity or mortality.[24]

Patient confidentiality was maintained throughout the study. Authorisation for the use of protected health information, in accordance with the Health Insurance Portability and Accountability Act, was obtained from each study participant as part of the informed consent process, and only information needed to accomplish the goals of the study was collected. Written informed consent was obtained from all patients before their enrolment in the study. Approval of the study protocol was obtained from the Alexian Brothers Hospital Network Institutional Review Board (IL, USA).

Data were obtained independently by a research assistant (KW); the primary study authors (EGL and JRJ) did not participate in patient interviews.

For 1 week before and every week after the procedure, patients kept a daily log detailing the frequency and severity of hot flushes and sleep disturbances, and the length and overall quality of sleep. Baseline data were collected from week –1 to week 0 (timepoint of the first block). Patients completed survey forms and the Pittsburgh Sleep Quality Index[25] 1 week before the procedure and then weekly after the procedure for 12 weeks. Patients were also contacted weekly by telephone for 12 weeks after the procedure to assess long-term effects of the treatment and had a follow-up visit after any procedure.

The Hot-Flash Score, devised by Sloan and colleagues[26] was used to quantify recorded hot flushes for analytical assessment after all data were collected. A system, described by Finck and co-workers[27] for defining four levels of severity of hot flushes (ie, mild, moderate, severe, and very severe) was used to categorise recorded hot flushes for analysis. The Hot-Flash Score has been verified as reliable by both Sloan and colleagues and Finck and co-workers.[26,27] The Hot-Flash Score was not selective to hot flushes at night or during the day; instead, it looked at the total number of hot flushes and their intensity during the 24-h period.

There are many advantages of using the Hot-Flash Score; for example, this instrument takes into account the described severity of a hot flush. If a patient has 15 very severe hot flushes per day before intervention, which then change to 15 mild hot flushes per day after intervention, the intervention would be classed as a theoretical therapeutic advantage that would be measured specifically by the Hot-Flash Score metric, but not by a hot-flush frequency metric. Another advantage of this instrument is

	1	2	3	4	5	6	7	8	9	10	11	12	13
Age, years	58	47	38	51	54	54	52	58	42	58	71	45	59
Weight, kg	75·4	66·1	90·7*	99·8*	73·5	63·9	98·9	86·2*	79·9	45·5*	51·3	80·5	78·9
Height, m	1·65	1·68	1·60	1·68	1·60	1·58	1·58	1·55	1·68	1·52	1·63	1·70	1·52
BMI	27·6	23·4	35·4	35·5	28·7	25·6	39·9	35·9	28·4	19·5	19·4	27·8	34·0
Smoker	Y	Y	N	N	N	N	N	N	N	N	N	N	N
Cancer type	IDC	IDC	IDC	IDC	IDC	ILC	IDC	IDC	AC	IDC	IDC	IDC	IDC
Hormone treatment†	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Disease stage	DCIS	DCIS	III	DCIS	II	II	II	DCIS	I	I	I	II	I
ER/PR	N/A	+	+	–	N/A	+	N/A	N/A	+	N/A	+	N/A	+
Menopause, years‡	7	2	5	1	5	5	1	4	2	2	7	2	8
Hysterectomy	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N
Mastectomy	N	N	Y	N	N	N	Y	N	N	N	Y	N	Y
Lumpectomy	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y	N
Chemotherapy	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	N	N
Radiotherapy	Y	N	N	Y	Y	N	Y	Y	Y	N	N	N	N
Oestrogen blocker	T	T	T	None§	T	None§	T	A	T	T	None¶	A	A

Numbers in first row are individual patient numbers. *Approximate value provided by patient. †Before breast cancer. ‡Before stellate-ganglion blockade. §Patient not prescribed oestrogen blockers. ¶Patient refused oestrogen blockers because of severe hot flushes before start of any oestrogen treatment. BMI=body-mass index. Y=yes. N=no. IDC=infiltrating ductal carcinoma. ILC=invasive lobular carcinoma. AC=adenocarcinoma. DCIS=ductal carcinoma in situ. ER=oestrogen receptor. PR=progesterone receptor. N/A=not available. +=positive. –=negative. T=tamoxifen. A=anastrozole.

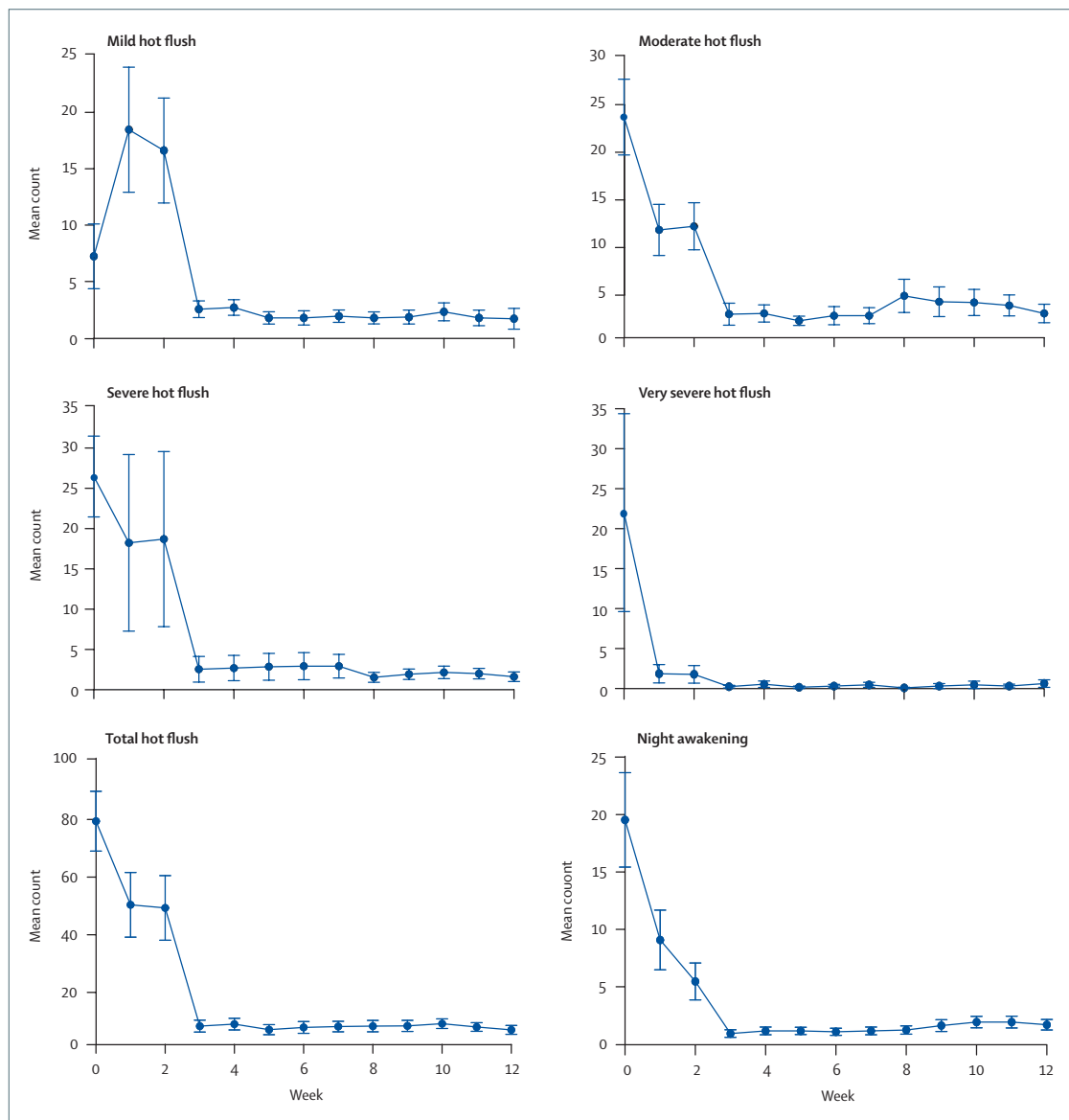*Table:* **Summary of patient profiles**

Figure 1: Effect of stellate-ganglion block on total number of recorded hot flushes and night awakenings and on severity of hot flushes over the 12-week follow-up period

Error bars represent mean and standard error. Standard error equals the standard deviation divided by the square-root of N, and N=13 is our sample size.

confirmation of the validity of the reporting. A well-validated psychometric approach is to ask patients to record their perceptions of the frequency and intensity of observable and understandable clinical events in a diary,[28–32] including examples of symptoms, such as pain and fatigue. The use of self-report diaries for data collection has long been established as a valid approach to obtaining data on subjective factors, such as patient-reported symptoms and perceptions.[33–36] Diaries have been used successfully to produce data with greater detail and accuracy than objective measures in many situations.[37–39] Women who participated

in a hot-flush trial[40] described what they considered to be mild, moderate, severe, and very severe hot flushes. These severity definitions were descriptively analysed, and the categorisation of these definitions into clear and congruent representations of severity was apparent.[41] This work showed that patients could indeed describe a hot flush and delineate the various component symptoms that a hot flush consists of.

This trial is registered on the International Standard Randomised Controlled Trial Number register (ISRCTN14318565).

Statistical analysis

The data were analysed for total number of hot flushes and night awakenings and for number of hot flushes of different intensities. Daily records were aggregated to weekly data. The generalised-estimating-equations method[42] was used to assess the effect of treatment on the number and intensity of hot flushes and night awakenings. In the analysis, the outcome is the longitudinal measurement of the number of hot flushes and night awakenings. Independent variables include a so-called dummy variable for weeks 1–2 and a dummy variable for weeks 3–12. We used this model to assess separately the treatment effect during the first 2 weeks after the procedure and the treatment effect during the remaining follow-up period (weeks 3–12). When doing such tests for treatment effects, the generalised-estimating-equations method also properly accounts for a correlation between repeated findings within the same patient. Wald tests at the 0·05 level of significance are then used to test the null hypothesis of no treatment effects. The Proc GENMOD in the SAS statistical software version 9·1 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Role of the funding source

This study was self funded by the primary authors (EGL and JRJ). There were no additional sponsors for this study. EGL had full access to all of the data and the final responsibility for the decision to submit for publication.

Results

13 female survivors of breast cancer (age range 38–71 years) with severe hot flushes were included in this pilot study (table). All patients remained in the study throughout the 12-week follow-up period.

Of the 13 patients, five had only one stellate-ganglion block and eight had two stellate-ganglion blocks. There were no adverse events resulting from this procedure. Patients reported minimum pain or no pain on injection because all blocks were done under local anesthaetic or local anaesthetic plus sedation. Figure 1 shows the change in number of hot flushes and night awakenings immediately after the procedure and throughout the follow-up period.

In general, both hot flushes and night awakenings were substantially decreased immediately after the procedure and the decreases were significant when compared with baseline reports. The occurrence of hot flushes and night awakenings continued to decline over the 12-week follow-up period, eventually stabilising at much lower frequencies than at baseline (figure 1).

The total number of hot flushes declined from a mean of 79·4 (SD 37·4) per week before the procedure to a mean of 49·9 (SD 39·9) per week during the first 2 weeks after the procedure. The mean decrease in this period from the baseline was 29·5 (SD 31·4) (p=0·0002). After 2 weeks, the total number of hot flushes continued to

decline over the remaining follow-up period (weeks 3–12) and stabilised at a mean of 8·1 (SD 5·6) per week. The mean decrease in this follow-up period from baseline is 71·3 (SD 32·6) (p<0·0001).

The number of mild hot flushes increased during the first 2 weeks after the procedure (from a mean of 7·2 [SD 10·4] to a mean of 17·5 [18·2]) per week, taking the mean of the first 2 weeks; p=0·06), but then decreased to 2·0 (SD 1·6) per week throughout the remaining follow-up period. The mean decrease during weeks 3–12 from baseline was 5·2 (SD 10·8) (p=0·03). Moderate and severe hot flushes both decreased during the first 2 weeks after the procedure, from a mean of 23·7 (SD 14·3) to a mean of 12·0 (SD 9·1) per week (for both weeks combined) for moderate hot flushes (p<0·0012) and from a mean of 26·5 (SD 18·1) to a mean of 18·5 (SD 39·1) per week for severe hot flushes (p=0·44). Both outcomes continued to decrease during the remaining follow-up period to below a mean of 5 per week (p<0·0001 for comparison with the baseline for both outcomes). Very severe hot flushes showed a more substantial decrease within 1 week after the procedure, from a mean of 22 (SD 44·6) per week at baseline to a mean of 1·8 (SD 3·8) during the first 2 weeks combined after the procedure (p<0·0001); the means remained near zero for the remainder of the follow-up period (p<0·0001).

The number of night awakenings decreased by about two thirds during the first 2 weeks after the procedure, from a mean of 19·5 (SD 14·8) per week at baseline to a mean of 7·3 (SD 7·1) per week (p<0·0001) for weeks 1 and 2 combined. This number continued to decline throughout the remainder of the follow-up period and stabilised at a mean of 1·4 (SD 1·2) per week (p<0·0001).

The duration of the block in this study ranged from 2 weeks to the end of the study (one patient had a second block 1 week after the first block at their request, before the severity of their symptoms increased). Only the measured findings are reported (figure 2). Anecdotally, all patients reported good relief from hot flushes and night awakenings beyond the 12-week period. After repeated blocks, when necessary, patients reported more lasting relief of symptoms than after the first procedure. All patients, including those taking tamoxifen or anastrozole, reported relief of both hot flushes and sleep dysfunction throughout the follow-up period after one or two blocks.

Discussion

This study shows that stellate-ganglion block can significantly decrease the number and intensity of hot flushes and night awakenings in survivors of breast cancer. The total number of hot flushes was significantly decreased, and the number of very severe hot flushes was decreased to near zero.

The symptoms of hot flushes that occur in menopausal women—eg, sudden sensations of intense heat with sweating, flushing, and peripheral vasodilation—are
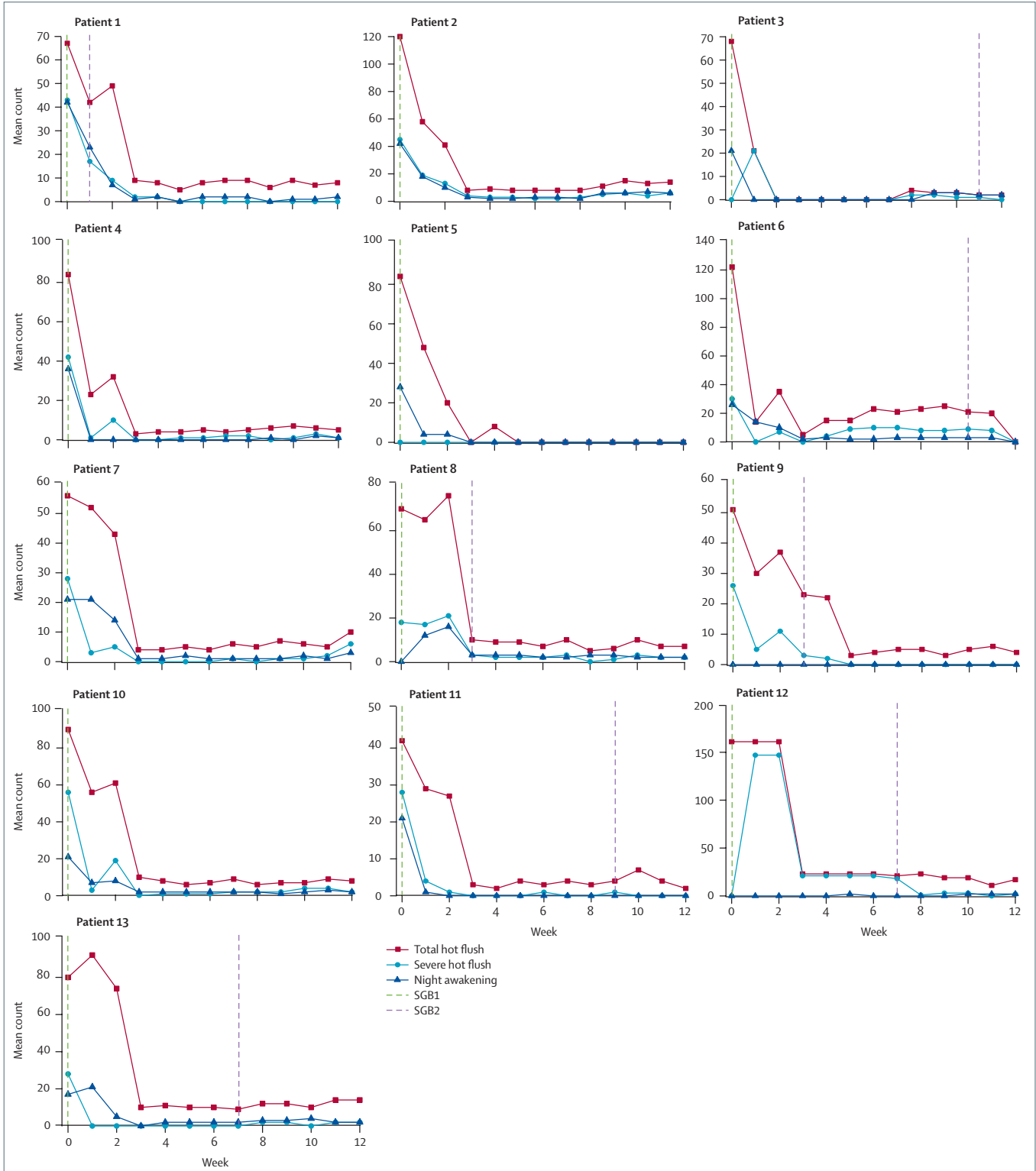
Figure 2: Effect of stellate-ganglion block on total number of recorded hot flushes and night awakenings, and number of hot flushes per patient over a 12-week period
SGB=stellate-ganglion block.

characteristic of a heat-dissipation response. Core temperature is regulated between an upper threshold for sweating and vasodilation and a lower threshold for shivering and vasoconstriction; between these thresholds is the thermoneutral zone, where thermoregulatory adjustments do not occur. Freedman and Krell hypothesise that hot flushes result from the narrowing of this thermoneutral zone.[1,43]

Women who have hot flushes show increases in central sympathetic activation. The increases in core body temperature that precede hot flushes are accompanied by a significant increase in the plasma concentrations of a metabolite of brain norepinephrine, but not of a peripheral metabolite.[44,45] Peripheral vasoconstriction does not occur during hot flushes and the metabolic rate increases only after the rise in core temperature.[43]

Studies in both animals and humans have shown that thermoregulation is controlled mainly by the hypothalamus.[46,47] However, temperature control is complex and needs integration of information from the peripheral nerves. Many studies suggest that the regions of the human brain involved in regulating homoeostatic responses to changes in environmental temperature include the somatosensory cortex, insular cortex, anterior cingulate, and thalamus, in addition to the hypothalamus.[48–50]

In a controlled study of postmenopausal women with hot flushes, Freedman and colleagues[51] used functional MRI to identify regions of brain activation associated with hot flushes and with sweating in women without hot flushes. Surprisingly, the hypothalamus was not the primary region of activation associated with hot flushes. Instead, the insula and anterior cingulate cortex showed substantial activation during these flushes. Women without hot flushes also showed activation of the anterior cingulated cortex and the superior frontal gyrus during sweating, but not the insular cortex. Other studies have shown that the insular cortex can be viewed as the gateway of the sympathetic system to the brain.[52,53] The fact that activation of the anterior cingulate cortex occurs in women with and without hot flushes suggests that this activation might be related to an affective component of thermosensation. Oestrogen treatment has also been shown to increase neural activity in the insular cortex.[54,55]

One of the most direct means of showing connections between two brain nuclei is use of anatomical labelling techniques. In the course of mapping regions of the cerebral cortex related to the sympathetic nervous system, Westerhaus and Loewy[56] used pseudorabies-virus injections to identify connections of the stellate ganglion. Pseudorabies virus allows identification of neural pathway connections through two to three synapses from the point of injection of the virus. By use of this method, the researchers noted that in the early stage of infection (ie, within 5 days of injection) labelling was seen in the hypothalamus and central nucleus of the amygdala, followed soon after by the lateral, basolateral, and medial amygdala. After 6–8 days, extensive transneuronal labelling in the infralimbic, insular, and ventromedial temporal cortical regions was seen. These data suggest that the stellate ganglion interacts with several key structures known to modulate core body temperature (figure 3). These data also correspond with the findings of functional MRI reported by Freedman and colleagues,[57] which showed that the insular cortex is activated during hot flushes and that the stellate ganglion provides neural input into this area.

Freedman and colleagues[57] also recorded bilateral finger temperature and bloodflow after the digital nerves on one hand of a patient had been blocked with a local injection of lidocaine to assess whether a peripheral, digital block would have an effect on hot flushes. The effectiveness of the nerve blocks was verified by a reflex vasoconstriction test. Significant increases in finger temperature and bloodflow occurred during the hot flushes, both in nerve-blocked and non-nerve-blocked fingers. These findings suggest that digital vasodilation during hot flushes is due to a circulating vasodilating substance.

We believe that the effect of stellate-ganglion block is more central than peripheral in view of the findings of the retroviral-labelling study.[56] Furthermore, Freedman's later work in 1998[44] showed that changes in the concentration of the main metabolite of brain norepinephrine, 3-methoxy-4-hydroxy-phenylglycol (MHPG), are consistent with events that are central rather than peripheral in origin. The concentration of this central metabolite is increased before and during menopausal hot flushes. Because catecholamine measurements during hot flushes have yielded inconsistent findings,[57] we did not try to measure catecholamine concentrations before or after hot flushes. Additionally, plasma MHPG and vanillyl mandelic acid half-life levels are short (about 45 min),[58] and these short half-lives would result in inaccurate morning urine measurements for the assessment of the sympathetic effect of stellate-ganglion block.

Thus, the findings of these studies point to the possibility of relieving hot flushes by interrupting the stellate ganglion's input into the sympathetic system that governs thermoregulation, especially the insular cortex.

Data from our pilot study strongly support our earlier hypothesis regarding the mechanism of action of stellate-ganglion block on hot flushes.[52] Patients had decreases in the number and severity of hot flushes and in the number of night awakenings.

Although we chose to follow our patients in this study for 12 weeks because of the need for close follow-up, we have monitored patients outside the study who have had relief of hot flushes for more than 2 years after a single block. This finding highlights the value of a larger study with longer-term follow-up to more thoroughly assess the potential of this treatment option.

In 1992, Wulf and Maier[59] described complications after stellate-ganglion block in 45000 patients. Severe
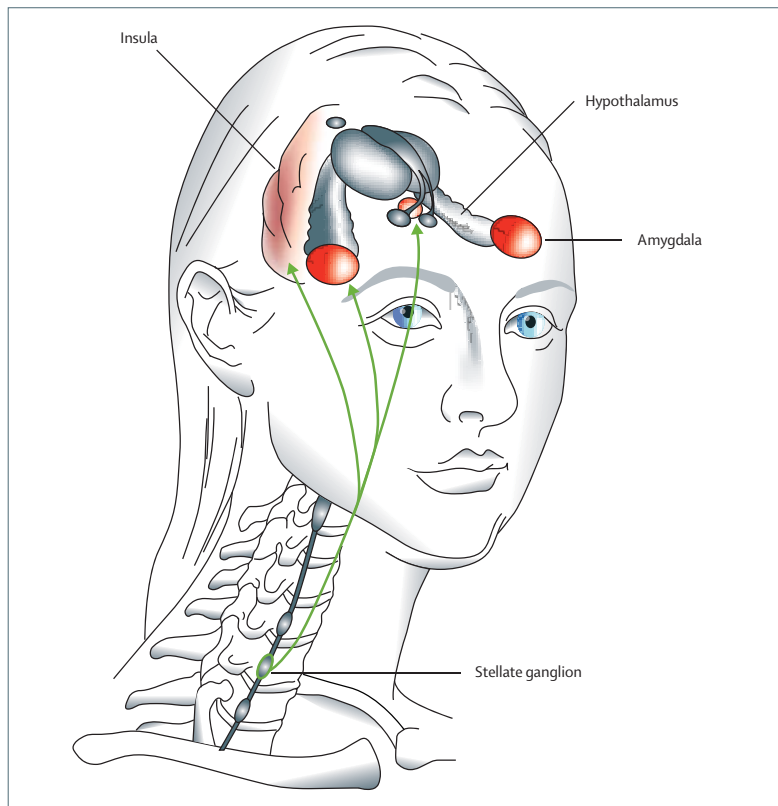
Figure 3: **Neural connections between the stellate ganglion and the hypothalamus, amygdala, and regions of the prefrontal cortex, in particular the insular cortex, might explain the effect of stellate-ganglion block on hot flushes**
Interruption of the sympathetic nervous system might allow temperature-regulating mechanisms to reset.

complications occurred in only 1·7 of 1000 procedures. Most were CNS complications (eg, convulsions). Other serious complications included high subarachnoid block (six patients), high epidural block (three patients), pneumothorax (nine patients), and allergic reactions (two patients). All stellate-ganglion blocks in the study were done without fluoroscopic guidance. As of April, 2008, this was the only large study assessing complications of stellate-ganglion block that was available in a PubMed search. Other large-scale studies of complications, in which fluoroscopy is used, have most probably not been done as a result of a substantial decrease in complications by use of this technique.

We believe that our technique is safer than reported in the study by Wulf and Maier[59] in 1992, because we approach the stellate ganglion at the C6 level rather than the more common approach at C7, thereby decreasing the risk of pneumothorax. All procedures in our study were done under fluoroscopic guidance, thereby decreasing the risk of subarachnoid and epidural block and convulsions. These two details should decrease the already low number of complications for this procedure even further. The only side-effect or complication that we noted was signs of Horner's syndrome, which is an

expected effect of a successful stellate-ganglion block and which resolves as the anaesthetic is absorbed, generally in less than 8 hours. Both effects resolve within 8 hours after the block, as predicted in view of the half-life of the local anaesthetic.

The safety and efficacy of this procedure are based on the assumption that practitioners who do the block use a technique similar to ours, such as fluoroscopy and entry at the C6 level. Furthemore, practitioners should have extensive formal training in stellate-ganglion block, such as anaesthesiologists, and should have interventional-pain fellowship training and board certification.

The findings in this pilot study were self-reported, and no objective measurements were made, such as sternal skin conductance. However, in a study[60] where patients self-reported hot flushes and wore sternal skin conductance monitors for objective information, substantial under-reporting of hot flushes was noted. This study, involving 55 women, showed that hot flushes were substantially under-reported by women when compared with direct skin conductance. Additionally, more under-reporting occurred at night compared with during the day.[60] The estimated probability that a woman would record a true monitor-verified hot flush subjectively by diary or event marker was between 36% and 50% of the time if she was awake and between 22% and 42% of the time if she was asleep.[60] Although this study did not use any objective devices, such as direct skin conductance, evidence suggests objective and reported data do not directly correlate.[60] As previously stated, self reporting is considered valid data.[26,27]

Furthermore, no placebo control group was included in our study. A placebo group could have been obtained by randomly assigning patients to the procedure versus no procedure; however, the patient would clearly know the difference. We explained to every patient the signs of successful sympathetic blockade before the procedure. This explanation included a description of Horner's syndrome. Patients who would have been randomly assigned to a saline or placebo group would not have had a sympathetic blockade or Horner's syndrome, and this absence would be immediately perceived differently by the patient and the physician and this would have been a clear indication of a failed blockade and might have changed the findings of a placebo group. Thus, a double-blind placebo design would be problematic, because an ideal placebo control group for this study does not exist.

However, we do not believe that the findings of this study are invalid on the basis of an absence of a placebo control. We previously reported an internal control in our 2005 publication of the effect of stellate-ganglion block on hot flushes.[22] A patient underwent her first stellate-ganglion block with good Horner's syndrome and associated signs. She had a good response to the procedure and a significant decrease in her hot flushes. When her hot flushes returned, a second stellate-ganglion block was done. The patient showed a delayed Horner's syndrome and and absence of

anhydrosis after the block, suggesting that stellate-ganglion blockade had been unsuccessful. Because we had not specifically discussed the delayed Horner's syndrome with this patient, on completion of the block, she was under the impression that the procedure had been successful. Despite this belief, she reported no effect on the quantity or intensity of her hot flushes. She then requested a third stellate-ganglion block, which produced positive Horner's syndrome and anhydrosis, suggesting a successful block. Once again, a significant decrease in her hot flushes was reported.[22]

Although our study only assessed patient reporting of hot flushes up to 12 weeks after the first stellate-ganglion block, one patient, who was contacted during routine follow-up 37 weeks after she had a stellate-ganglion block, reported no hot flushes or night awakenings. Although not all patients had the same outcome as this patient, the findings for this patient highlight the possible long-term use of this blockade, which should be addressed in future studies.

In this study, local anaesthetic was used for stellate-ganglion blockade. However, anaesthetic drugs have a risk of seizure and allergic response. An alternative method that could be used in future studies is pulsed radiofrequency, which has been used to extend relief for various pain conditions.[61–67] We did an anecdotal study of this method, in which we applied pulsed radiofrequency to the stellate ganglion in four women with severe hot flushes, who had previously undergone stellate-ganglion block. These patients noted beneficial effects equal to or better than stellate-ganglion block by use of local anaesthetic injection, suggesting that this technique might be an effective instrument for extending the duration of relief from hot flushes and night awakenings and decreasing the chance of seizures and allergic response associated with anaesthetics (unpublished). We have also reported successful use of pulsed radiofrequency of the stellate ganglion for resistant complex regional pain syndrome type I,[63] where pulsed radiofrequency was substantially more effective than previous stellate-ganglion block with local anaesthetic. Furthermore, pulsed radiofrequency also does not lead to Horner's syndrome allowing this technique to be used in double-blind placebo-controlled study.

Stellate-ganglion block by use of local anaesthetic has been used for years; its mechanism of action, however, might be more complex than just the local effect on the nerves. Spinal anaesthesia has been shown to lead to c-Fos expression in the spinal cord, which suggests increased neural activity.[64] Spinal anaesthesia is also correlated with expression of the immediate early oncogene protein-kinase C. This oncogene and c-Fos both have a role in the mechanism of spinal anaesthesia.[62] Peripheral electroacupuncture has been shown to trigger c-Fos activity in β-endorphin-related opioid receptors in the rostral ventrolateral medulla.[65] This finding is consistent with our theory. Pulsed radiofrequency can also lead to changes in c-Fos and early gene activation.[66,67]

In summary, the findings of this pilot study suggest that a properly done stellate-ganglion block might be a highly effective treatment for both hot flushes and night awakenings in survivors of breast cancer, but more studies are needed.

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