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Pilot evaluation of a stellate ganglion block for the treatment of hot flashes

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Abstract

Purpose—Hot flashes are a significant problem in breast cancer patients, especially because the most effective therapy, estrogen, is often contraindicated. Based on recent pilot data from a single group supporting the use of a stellate ganglion block for the treatment of hot flashes, the present pilot trial was done to further evaluate the hypothesis that a stellate ganglion block may be a safe and effective therapy for hot flashes.

Methods—In women with breast cancer who had hot flashes, a stellate ganglion block was performed after 1 week of baseline hot flash data collection. The main efficacy measures were the changes from baseline in hot flash frequency and hot flash score during the 6th week.

Results—Ten patients were enrolled between 4/23/2009 and 7/10/2009; eight patients were evaluable. After the stellate ganglion block, the mean hot flash frequency and score decreased from baseline values by over 60% during some of the post-treatment weeks. The mean hot flash frequency and score at week 6 decreased from baseline values by 44% and 45%, respectively. There were no significant adverse events clearly attributed to the stellate ganglion blocks.

Conclusions—The results of this pilot trial support that stellate ganglion blocks may be a helpful therapy for hot flashes. A prospective placebo-controlled clinical trial should be done to more definitively determine this contention.

Keywords

Hot flashes; Stellate ganglion block; Vasomotor symptoms; Nonhormonal therapy

Introduction

Hot flashes occur in up to 90% of perimenopausal women [4,5,8]. Though not life-threatening, hot flashes can significantly impact a woman's quality of life and functional ability [3,5,8]. Hot flashes are especially problematic in breast cancer patients because menopause can occur prematurely as a result of chemotherapy or tamoxifen therapy and because the primary effective treatment option for control of menopausal symptoms, estrogen, is contra-indicated [4,23,33]. Furthermore, it has been reported that menopausal symptoms may be more severe in breast cancer survivors compared with healthy women experiencing natural menopause and may even affect their willingness to continue anticancer therapies [3,4].

Estrogens and progesterone analogs are the most effective agents known to date for reducing hot flashes, with reductions of about 80% [22,26,30]. Nonetheless, the current sentiment of many is that estrogen therapy should not be prescribed for breast cancer survivors until there is evidence from prospective, randomized trials that prove it safe [33]. Likewise, there is hypothetical concern that progestational agents may stimulate tumor growth [22,26,33] and, thus, this therapy is not readily utilized in many women with a history of breast cancer.

Clearly, alternatives to the problem of menopausal symptoms, hot flashes in particular, are needed. Investigators have been studying such alternatives over the past decade. Prior to the present decade, the best established alternative was clonidine which reduces hot flashes by about 35% to 40% [12,32], slightly better than the 20–25% reduction that is commonly seen with a placebo [35]. Newer antidepressants have been illustrated to be helpful, with the first publication of a randomized trial occurring in 2000 [1,25,28,29,38–40]. This initial trial was a double-blinded, placebo-controlled study of venlafaxine in women with hot flashes, whereby venlafaxine, 75 mg per day, reduced hot flashes by about 60% [25]. Other antidepressants, demonstrated to be effective in randomized, placebo-controlled trials, include fluoxetine, citalopram, paroxetine, and desvenlafaxine. These agents decrease hot flashes by about 25–30% more than does a placebo [28]. In addition, randomized controlled trials of gabapentin demonstrate that this agent, at a target dose of 900 mg/day, and pregabalin, at a target dose of 75 mg twice a day, also decreases hot flashes to a similar degree [13,27,31].

Although these results are encouraging, the efficacy of these agents is still significantly below the 80% reduction seen with hormonal agents. In addition, each of these therapies has toxicities that limit its use [22]. Therefore, further research needs to be done to define more effective and safer alternatives to hormonal therapies.

The stellate ganglion block is a selective sympathetic blockade that has been used for at least 60 years for the treatment of multiple pain syndromes including migraines and upper extremity pain [18,21,41]. In 2005, Lipov et al. published a case series report involving six women, none of whom had breast cancer, but all of whom had trouble with hot flashes [16]. In a 2008 issue of *Lancet Oncology*, they reported on a prospective pilot trial ($n=13$) looking at stellate ganglion blockade as a means for alleviating hot flashes in patients with a prior history of breast cancer [19]. In both of these manuscripts, these authors reported a marked diminution of hot flashes in the treated patients. In addition, an update to the 2008 pilot trial was published and reported a sustained decrease in hot flashes lasting the duration of the follow-up, 10 months. Of note, most of the patients required a repeat stellate ganglion block at a median time of 11 weeks [20]. Neven et al. have also reported similar results from a recent pilot trial involving 24 women [14].

The exact mechanism of action of the stellate ganglion block and why it might work in a multitude of clinical situations is not completely understood. However, Lipov et al. have

proposed a mechanism based on Westerhaus and Loewy's work, which used pseudorabies virus to identify connections of the stellate ganglion to several brain structures. Westerhaus and Loewy concluded that the stellate ganglion interacts with several key structures known to modulate core body temperature [43]. Lipov et al. proposed that modulation of these connections is the reason that stellate ganglion blocks may be effective in reducing hot flashes [18].

Lipov et al. also suggest that a stellate ganglion block might be a safer treatment for hot flashes than currently utilized pharmaceutical agents. These investigators reported that there were no adverse events resulting from the procedure in the patients that they treated. They also noted that there is a relatively safe toxicity profile in the general literature, assuming that the procedures are done with the appropriate method and by formally trained personnel [19]. While this approach for treatment of hot flashes is novel and the published results are certainly encouraging, the results are preliminary and further work is necessary to clearly define the true efficacy of stellate ganglion blockade for treating hot flashes, including the conduct of confirmatory trials by independent investigators [24].

The current project represents a pilot trial to provide further information to support, or refute, the results published by Lipov et al.

Materials and methods

This trial involved women who reported bothersome hot flashes, defined by their occurrence ≥ 28 times per week and of sufficient severity to make the patient desire therapeutic intervention. The hot flashes must have been present for at least 1 month prior to study entry. An eligible woman had to be at least 18 years old and had to have a life expectancy of at least 6 months. Additionally, patients needed to have had an excellent performance status (i.e., an Eastern Cooperative Oncology Group performance status of 0 or 1).

Patients were not eligible for the study if they were receiving antineoplastic chemotherapy, androgens, estrogens, or progesterone analogs. They were permitted to be receiving tamoxifen, raloxifene, or aromatase inhibitors, as long as they had been on a constant dose for at least 4 weeks and were not expected to stop such medications during the primary 7-week study period. The use of other agents for treating hot flashes including vitamin E, antidepressants, or gabapentin was permitted as long as they were started more than 30 days prior to study initiation and were to be continued through the study period. Patients were not eligible if they were pregnant, nursing, or were of childbearing potential and unwilling to employ adequate contraception. In addition, patients were not eligible if they were currently using anticoagulants including aspirin, clopidogrel (Plavix), ticlopidine (Ticlid), and coumadin, or if they had a diagnosis of, or problems with, von Willebrand's disease or other bleeding disorders. This protocol was reviewed by the Mayo Foundation Institutional Review Board, and all patients signed an informed consent per federal guidelines.

The stellate ganglion blockade was performed after a 1-week baseline hot flash documentation period. After local anesthetic, a 25-gauge Quincke spinal needle was placed in the anterolateral aspect of the C6 vertebral body on the right side. Contrast dye (Omnipaque-300) was injected to visualize the ganglion and confirm needle placement. Seven milliliters of 0.5% bupivacaine was injected next to the stellate ganglion to produce a sympathetic block. The procedure took about 15 min after the patient was prepped and draped. After completion of the procedure, each patient was assessed for signs of sympathetic block, which included presence of Horner's syndrome (facial anhidrosis, enophthalmos, ptosis, swelling of the lower eyelid, miosis, and blood-shot conjunctiva).

Some patients were assessed for an increase in temperature of the right hand. All individual patients were observed for a minimum of 40 min to assess for any signs of complications.

Self-completed daily hot flash diaries and weekly symptom questionnaires were obtained at baseline (for 1 week prior to the stellate ganglion block) and for the duration of the study (post-treatment weeks 1 through 6). The hot flash diary has been shown to effectively discriminate the efficacy of various hot flash treatments [35]. A profile of mood status was completed at the end of the baseline week and at the completion of week 6. Each patient was contacted by a study nurse or other research personnel by telephone weekly during weeks 1–6 to assess for any toxicity, to encourage completion of the booklet, and to address any problems.

The main efficacy measures utilized in this study were the change from baseline in the mean average daily hot flash frequency and hot flash score during the 6th post-treatment week. The hot flash score was calculated as the daily hot flash frequency multiplied by the mean daily hot flash severity [22].

This protocol was developed as a pilot exploration involving 10 participants to gather initial estimates of hot flash reduction with stellate ganglion block. Data were analyzed using the methods developed for studies of hot flashes from previous experience [35]. Descriptive summary statistics including means, standard deviations, and percentages formed the basis of analysis for the current study. Supplemental graphical representations of the changes from baseline in hot flash frequency and score over the study period were also included. Toxicities and self-reported side effects were analyzed in a descriptive manner.

Results

A total of 10 patients were enrolled in this study between April 23, 2009 and July 10, 2009. One patient canceled participation prior to starting the study. One patient completed the study treatment and reportedly returned her hot flash booklet information, but, unfortunately, it was lost in the mail. The remaining eight patients completed all hot flash diary information for the entire protocol and returned protocol information for all study weeks. None of the patients were known to go off the study due to adverse events. All 10 patients who enrolled were women with a history of breast cancer. Women involved in this trial had failed the use of more conventional hot flash treatments to control hot flashes. Additional patient characteristics at the study entry are provided in Table 1.

Hot flash frequency and hot flash score data for the protocol participants are illustrated in Fig. 1. After the stellate ganglion block, the mean hot flash frequency and score at week 6 decreased from baseline week values by 44% and 45%, respectively. This resulted in the mean daily hot flash frequency decreasing from 10.1 to 5.4 and mean daily hot flash score decreasing from 17.6 to 9.8. Weekly changes in hot flash scores for individual patients are illustrated in Table 2 and Fig. 2. Six of the patients who returned diaries had a marked reduction in hot flashes by 1–3 weeks. In three of these patients, the hot flash reduction appeared to be sustained for all 6 weeks of follow-up, while in three of them, hot flashes became more prominent between the 4th and 6th week (Fig. 2). During nurse follow-up phone calls, the patient whose booklet was lost in the mail did note that she had benefited from the procedure with decreased hot flashes.

Of the nine procedures that were done, there were seven reported cases of prominent Horner's syndrome. Six of these resolved in less than 24 h and one resolved in 24–48 h. There was one patient with a mild case of Horner's syndrome (slight ptosis and miosis), who did have a significant decrease in her hot flashes. There was one patient who did not get Horner's syndrome and did not appear to have any apparent hot flash reduction, but she did

have a significant increase in her right hand skin temperature (change from 88.3° F to 93.4° F after the procedure), a change in the ipsilateral hand skin temperature by 1° to 3° F above baseline being another marker supporting a successful sympathetic blockade [7].

Data from questionnaires showed changes in several potential benefits of the stellate ganglion block from baseline to the 6th week of the study. Trends towards improvements in four variables were seen in the 6th week of the study compared to baseline. These improvements were in the areas of face redness, facial warmth, nasal congestion, and satisfaction with hot flash control. In addition, one patient with right-sided lymphedema after right total mastectomy noted reduction in her lymphedema and associated pain within 1 week of the procedure. The pain, however, did return by week 6 post procedure.

Potential adverse events included one case of a person who presented to an emergency department for dyspnea approximately 8 h following the procedure. This dyspnea lasted approximately 5 h and the patient was dismissed from the hospital that night. She denied chest pain or cough, and a chest X-ray was unremarkable. At a follow-up call 6 weeks later, the patient reported a similar reaction after a dental procedure where lidocaine was used. The patient reported that her doctor believed that she has an allergy to these types of anesthetics. This patient had a history of Sjögren's syndrome and has had multiple other emergency department visits prior to and following her stellate ganglion block.

Another patient was noted to have an asymptomatic bradycardia about a month after the stellate ganglion block, with a pulse of 42. Subsequent evaluation of this patient revealed that she had a prolonged QT segment on her electrocardiogram. She subsequently tested positive for type 3 long QT syndrome, a rare genetic cause for prolonged QT [15]. This patient was also taking tamoxifen.

Two patients noted headache starting the day of the procedure that resolved within 24 h. Other noted potential side effects included watery eyes and transient changes in facial warmth.

Discussion

Stellate ganglion blocks are relatively commonly used for the treatment of chronic regional pain syndromes, vascular insufficiency, post-herpetic neuralgia, and other forms of neuropathic pain [7]. However, there are limited data on the use of stellate ganglion blocks to treat hot flashes, with the only known published manuscripts on this subject, to date, coming from Lipov et al.; these investigators have reported a significant decrease in hot flashes in patients who undergo this therapy [16,19]. In addition, a recent abstract from a different group of investigators reported similar benefits [14].

Overall, data from the current pilot trial further support the pre-study hypothesis that stellate ganglion blocks are helpful in reducing hot flashes, noting that mean hot flashes decreased by over 60% during some study weeks. This is based on a previous model which supported that a reduction in hot flashes of 50% or more suggested that a treatment was providing more benefit than would be expected with just a placebo [35]. The trend seen in this present study, for hot flashes to become more prominent after an initial reduction, has been seen in previous studies done by Lipov et al. In their reports, many of the patients received a second block 2–10 weeks after the first [19]. This use of two blocks led to reported benefit lasting for many months [16,19,20]. Therefore, it is possible that more than one stellate ganglion block would provide added benefit. The need for more than one stellate ganglion block is consistent with the use of stellate ganglion blocks for other clinical situations, where the first block is often followed by more blocks, based on the clinical response [9].

Overall, stellate ganglion blocks are considered to be relatively safe procedures, with severe complications being quite rare. The more common side effects include temporary hoarseness, neuralgia along the chest wall, and CNS effects from injection into a vertebral artery. More serious and less common complications include brachial plexus injury, phrenic nerve injury, pneumothorax, infection, allergy, and hematoma [2,44]. These complications are much less likely in a fluoroscopic guided procedure, which was used in this current study. The few reported potential toxicities observed in this trial may have been caused by the stellate ganglion block, or may have been placebo effects.

With regards to the patient in the current study who developed dyspnea, respiratory distress can occur as a result of a blockade of the phrenic nerve or from a pneumothorax [2,7,44]. Nonetheless, there was no good evidence that either of these problems occurred in this patient.

Studies have shown that a right stellate ganglion block induces a significant increase in the QT interval and QT dispersion (dispersion being a measure of the differences in QT intervals between different leads of a 12-lead ECG) [6,34]. QT interval prolongation is correlated with ventricular arrhythmia, while QT dispersion (commonly seen in patients with diabetes, myocardial infarction, and subarachnoid hemorrhage) is correlated with electrical instability [34]. In the above noted studies, the EKG changes were temporary, resolving within 60 min of the block [6,34]. Tamoxifen, being utilized in the one patient in the current study with bradycardia, also is associated with QT prolongation [36]. Interestingly, left stellate ganglion blocks induce a significant decrease of the QT interval and have been employed as a treatment for individuals with a diagnosis of a long QT syndrome [34].

With regard to the patient with bradycardia in the present study, bradycardia is not a usual reported side effect for right stellate ganglion block, but has been seen in patients with bilateral stellate ganglion blocks [37]. In addition, having EKG abnormalities that persisted a month after the block is not expected and may well have been influenced by her underlying predisposition for QT prolongation.

Another predominant side effect was Horner's syndrome, clearly seen in seven of the patients who underwent a stellate ganglion block, while one patient developed a mild Horner's syndrome. Horner's syndrome consists of facial anhidrosis, enophthalmos, ptosis, swelling of the lower eyelid, miosis, and blood-shot conjunctiva. The presence of Horner's syndrome is often used as a marker of a successful stellate ganglion block. However, it does not always indicate complete interruption of the sympathetic flow [7].

With regards to the one patient in the study who noted a reduction in her ipsilateral lymphedema and associated pain within 1 week of the procedure, stellate ganglion blocks have been reported to be helpful in the treatment of poor lymphatic drainage and local edema after mastectomy [7]. However, the literature in this area is limited.

Although a stellate ganglion block is a relatively safe procedure, it does have a financial cost, ranging from US \$1,000 to 3,000 per procedure, which can be considered a limitation [24].

The exact mechanism of action of the stellate ganglion block and why it might decrease hot flashes is unclear. Hot flashes are thought to result from a narrowing of the thermo-neutral zone so that normal biphasic variations in body temperature can trigger a hot flash [10]. Based on this theory, increases in core body temperature are associated with an increase in sympathetic activation and brain norepinephrine levels [21]. In a study using functional MRI, Freedman et al. found that the insular and anterior cingulate cortex were activated

during hot flashes [11]. Using pseudorabies virus, Westerhaus and Lowey identified connections of the stellate ganglion to multiple areas of the brain known to modulate temperature, including the hypothalamus, amygdala, and insular cortex [43]. In addition, it has been shown that the local anesthetic in a stellate ganglion block reduces nerve growth factor (NGF) at the stellate ganglion's connection to the sympathetic system that modulates temperature, specifically the insular cortex and possibly the hypothalamus. This reduction in NGF reportedly leads to a decrease in sympathetic sprouting and a reduction of norepinephrine in the brain, subsequently leading to a reduction of oversensitivity of the temperature response and, hypothetically, a reduction in hot flashes [18,19,21]. It is worth noting that intra-brain injections of norepinephrine in a rat model leads to hot flashes. Also of note is that tamoxifen increases nerve growth factor by a factor of 14 [17,18]. Further research is required to clarify and elucidate further this novel hypothesis.

Pulsed radiofrequency may provide a more permanent lesion to the stellate ganglion and is not associated with Horner's syndrome [7,19,42]. Lipov et al. have suggested pulsed radiofrequency to the stellate ganglion as an alternative to a stellate ganglion block and have reported some anecdotal experience with pulsed radiofrequency to the stellate ganglion in women with severe hot flashes, with positive-appearing results [19].

The results of this current pilot trial, in conjunction with the work of Lipov et al., support the conduct of a prospective placebo-controlled clinical trial to clearly define the true efficacy of stellate ganglion block for treating hot flashes. Work on such an effort is presently ongoing.

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Fig. 1.
Mean hot flash frequency and score changes from baseline (*error bars* represent 95% confidence intervals for the means)

Fig. 2.
Individual subject hot flash score changes from baseline

Table 1

Patient characteristics at the time of study entry

	Total (N=9)
Age	
Median	53
Range	(38–70)
Tamoxifen	
Yes	4 (44%)
No	5 (56%)
Current raloxifene	
No	9 (100%)
Hot flash number per day	
4 to 9	2 (22%)
≥10	7 (78%)
Hot flash duration	
<9 months	1 (11%)
≥9 months	8 (89%)
Breast cancer history	
Yes	9 (100%)
Antidepressant treatment	
Yes	6 (67%)
No	3 (33%)
Gabapentin therapy	
Yes	3 (33%)
No	6 (67%)

Table 2

Mean percent hot flash reduction from baseline by study week

Week	Baseline	1	2	3	4	5	6
Frequency (%)	0	50	62	56	52	39	44
Score (%)	0	52	64	61	57	42	45