Stellate Ganglion Block for the Treatment of Hot Flashes in Patients with Breast Cancer: A Literature Review

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Background: Currently, hormone replacement therapy (HRT) is the only US Food and Drug Administration-approved treatment for hot flashes, resulting in clinical improvement in 80%-90% of symptomatic women. However, HRT is not recommended for patients with breast cancer. Current data regarding the use of stellate ganglion block (SGB) for the treatment of vasomotor symptoms in symptomatic women with a diagnosis of breast cancer are promising.


Results: Five articles described the physiology of hot flashes and the hypothesis of why SGB would be a treatment option, and 6 were clinical articles.

Conclusion: The available results of SGB efficacy are promising but demonstrate significant variability. A large prospective randomized controlled trial is required to determine the exact success of SGB on hot flashes and quality of life in breast cancer survivors.

Keywords: Breast neoplasms, hot flashes, postmenopause, stellate ganglion, vasomotor system

INTRODUCTION

An estimated 75% of postmenopausal women experience hot flashes.1 In addition, between 60%-80% of patients with breast cancer suffer from them as a result of chemotherapy.2 Currently, hormone replacement therapy (HRT) is the only US Food and Drug Administration-approved treatment for hot flashes. Although HRT results in clinical improvement in 80%-90% of symptomatic women,3 it is not recommended following the diagnosis of breast cancer.4

Various pharmacologic agents have been used to treat hot flashes: clonidine, gabapentin, selective serotonin reuptake inhibitors, and selective norepinephrine reuptake inhibitors. However, randomized controlled trials have produced mixed results.5

The pathophysiology of hot flashes is not entirely understood. Researchers suspect that the vasomotor symptoms occur in response to the rapidly diminishing production of estrogen.6,7 Current data regarding the use of stellate ganglion block (SGB) for the treatment of vasomotor symptoms in symptomatic women with a diagnosis of breast cancer are promising.2,8 We believe that SGB is a reasonable alternative to HRT for vasomotor symptoms secondary to breast cancer treatment, providing improved efficacy compared to pharmacologic and alternative treatments.

METHODS

We searched PubMed for recent articles on SGB used to treat hot flashes in patients with breast cancer, using the following keywords: stellate ganglion block, hot flashes, and breast cancer. We limited our review to English-language articles.

RESULTS

Eleven articles published between 2005-2014 met our search criteria (Figure 1). Five articles described the physiology of hot flashes and the hypothesis of why SGB would be a treatment option. Six were clinical articles.

Basic Science Articles

Table 1 provides an overview of the 5 articles1,5,9-11 that describe the physiology of hot flashes and the hypothesis of why SGB would be a treatment option. The 2007 article by Lipov et al described evidence of central sympathetic involvement in hot flashes and concluded that part of the effect of SGB may be centrally mediated.9

According to Freedman et al, the hypothalamus maintains core body temperature within a certain thermoneutral zone. Small temperature variations seen in diurnal human body temperature patterns trigger a hot flash with vessel dilatation and increased sweat if the upper limit of the
Table 1. Articles Reporting the Basic Science of Hot Flashes and Stellate Ganglion Block (SGB) Treatment

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Hypothesis/Theme</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Lipov et al, 2007&lt;sup&gt;9&lt;/sup&gt;</td>
<td>SGB relieves hot flashes by interaction with the sympathetic nervous system.</td>
<td>Hot flashes may be centrally mediated because of an increased activity of central nervous system nuclei linked to sympathetic nervous system and norepinephrine release.</td>
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<td>Lipov et al, 2009&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Theory links the efficacy of SGB for treatment of complex regional pain syndrome, hot flashes, and posttraumatic stress disorder.</td>
<td>Estrogen decrease leads to a nerve growth factor increase that increases brain norepinephrine that is affected by SGB, resulting in a reduction of nerve growth factor and a decrease in norepinephrine. This interaction leads to a reduction of many symptoms associated with these conditions.</td>
</tr>
<tr>
<td>Pachman et al, 2010&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Authors review current treatment options.</td>
<td>Hormonal therapy is most effective but carries increased risk of breast cancer. Venlafaxine and SGB show promising data as future treatments.</td>
</tr>
<tr>
<td>Kontos et al, 2010&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Authors review treatment of hot flashes after breast cancer.</td>
<td>The majority of non–hormone replacement therapy treatments are little better than placebo, but early results from randomized trials of venlafaxine and pilot studies of SGB suggest that it is worthwhile to test their efficacy specifically in cancer survivors.</td>
</tr>
<tr>
<td>Lipov and Kelzenberg, 2011&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Authors provide clinical evidence and neurobiology for treatment of hot flashes.</td>
<td>SGB has a significant effect on relief of hot flashes per the mechanism described by Lipov et al in 2009. Understanding the neurobiologic mechanism of action underlying the SGB effect may offer additional insight into the etiology and treatment of hot flashes.</td>
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</table>
Stellate Ganglion Block for Hot Flashes in Breast Cancer Patients

The thermoneutral zone is crossed or shivering if the lower limit is traversed.12-14 Women suffering from hot flashes show increases in core body temperature with significant increases in the plasma levels of a metabolite of brain norepinephrine but not of a peripheral metabolite, leading to the conclusion that hot flashes are driven by a central noradrenergic mechanism. Also, Freedman et al used functional magnetic resonance imaging (MRI) to identify the regions of brain activation associated with hot flashes and found that the insula and anterior cingulate cortex showed significantly more activation than the hypothalamus.12-14

Westerhaus and Loewy used pseudorabies virus injections as an anatomical labeling technique to provide evidence of connections between the stellate ganglion and other brain nuclei.15 They found that the stellate ganglion interacts with several key structures known to modulate core body temperature, including the hypothalamus, amygdala, and regions of the prefrontal cortex, in particular the insular cortex. Westerhaus and Loewy’s data correspond directly with the functional MRI results provided by Freedman et al.

In 2009, Lipov et al published a theory linking the efficacy of SGB with the treatment of complex regional pain syndrome, hot flashes, and posttraumatic stress disorder (PTSD).10 Their theory involves an interaction between the effects of estrogen, nerve growth factor, and norepinephrine. Estrogen is known to regulate the production of nerve growth factor in sympathetic neurons.16 Estrogen decrease may lead to anxiety and depression similar to the symptoms of PTSD.17 It was also evident that nerve growth factor increases in pathologic states with chronic stress.18 Nerve growth factor has been shown to increase nerve growth and sprouting of uterine sympathetic fibers in the rat uterus, leading to increased norepinephrine production in sympathetic neurons. It has also been shown that increased brain levels of norepinephrine lead to hot flashes in rats.19

Local anesthetics decrease nerve growth factor and sympathetic nerve sprouting.20 Lipov et al postulated that the decreased levels of estrogen in menopause allow for increased nerve growth factor and increased norepinephrine production in sympathetic neurons. Under sympathetic stimulation, this increase could lead to increased brain levels of norepinephrine, triggering the hot flash. The increase in brain norepinephrine in turn is affected by SGB, leading to a reduction of nerve growth factor and eventually a decrease in norepinephrine.10

In 2010, Pachman et al reviewed all the current treatment options for menopause-associated vasomotor symptoms.1 They reported that HRT is the most common and most effective treatment for hot flashes and is associated with an increased risk of breast cancer. The HABITS (Hormonal Replacement Therapy After Breast Cancer—Is It Safe?) trial, a randomized study involving 434 women diagnosed with breast cancer, had to be abandoned because of the increased incidence of breast cancer events found in the HRT group.4 Farquhar et al stressed that HRT has been shown to be the most effective treatment but reported a significant increase in risk of breast cancer.21 Most pharmacologic drugs studied had significant side effects that frequently outweighed the benefits, leading many patients to discontinue the medications. Pachman et al reported that nonhormonal therapies (bellergal, clonidine, methyldopa, and veralipride) have significant adverse side effects with moderate efficacy and are not recommended for the treatment of hot flashes. Clonidine, gabapentin, various selective serotonin reuptake inhibitors, and selective norepinephrine reuptake inhibitors have been tested in randomized trials with mixed results. The authors concluded that of all the treatments, venlafaxine and SGB showed enough promise to warrant further study.

Kontos et al concluded that non-HRT treatments with response rates <50% are no more beneficial than placebo but identified venlafaxine and SGB as promising treatments worth studying in breast cancer survivors.5 As Pachman et al, Kontos et al, and Loprinzi et al report, the most promising data on possible treatments for hot flashes in cancer survivors involve newer antidepressant agents such as venlafaxine that reduce hot flashes by about 60%.1,5,22 Currently, strong evidence to support complementary/alternative therapies (phytoestrogens, black cohosh, vitamin E, dehydroepiandrosterone, and other herbal remedies) and mind-body/behavior therapies (behavioral modifications, exercise, yoga, relaxation training, hypnosis, and acupuncture) is lacking because of limited effectiveness.1,23

The 2011 article by Lipov and Kelzenberg concentrated on the neurobiology underlying SGB.11 The authors summarized the results from previous trials, stating that the perimenopausal estrogen decrease causes increased concentrations of nerve growth factor that, in turn, lead to sympathetic nerve sprouting in the cortex and increased brain norepinephrine. SGB is known to reduce nerve growth factor, leading to the reversal of the process and thereby leading to symptom resolution of hot flashes. Lipov and Kelzenberg concluded that understanding the neurobiologic mechanism of action underlying the SGB effect may offer additional insight into the etiology and treatment of hot flashes.11

Clinical Articles

Four of the clinical trials and the one case series were not blinded and enrolled highly symptomatic subjects. The sixth article reported a randomized controlled clinical trial that included only moderately to severely symptomatic patients. Table 2 provides an overview of these clinical articles.8,24-28 The SGB techniques used were almost identical—blocking the anterolateral aspect of the C6 vertebra on the right side under fluoroscopy after confirmation of location with contrast dye (Figures 2, 3, and 4). Successful sympathetic blockade was confirmed by transient Horner syndrome and/or change in temperature in all of the subjects analyzed. No adverse events resulting from SGB were reported for any of the studies.

A 2005 case series by Lipov et al included 6 women without breast cancer with severe hot flashes.24 All had complete relief of symptoms for 2-5 weeks after the first SGB. Five patients returned for a second SGB when their hot flash symptoms increased and received relief for 4-18 weeks. A third SGB was performed on 2 of these 5 patients who reported relief for 15-48 weeks.

In 2008, Lipov et al conducted a pilot study of 13 female survivors of breast cancer with severe hot flashes and night awakenings.8 Both hot flashes and night awakenings
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<thead>
<tr>
<th>Authors, Year</th>
<th>Type of Study, Number of Subjects</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipov et al, 2005&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Case series, 6</td>
<td>• Women without breast cancer</td>
<td>• Medically unstable</td>
<td>Subjectively, all 6 subjects were asymptomatic for 2-5 weeks after the first SGB with more prolonged benefit after second and third SGB.</td>
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<td>• Severe hot flashes &gt;10 per day</td>
<td>• Hormone therapy</td>
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<td>• Blood clotting disorder</td>
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<td>• ASA ≥3</td>
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<td>Lipov et al, 2008&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Pilot, 13</td>
<td>• Female survivors of breast cancer</td>
<td>• Acute infections</td>
<td>90% and 93% reduction in hot flash frequency and night awakenings, respectively, to week 12</td>
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<td></td>
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<td>• Severe hot flashes &gt;15 per day</td>
<td>• Cardiac compromise</td>
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<td>• Hormone treatment</td>
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<td>• Blood clotting disorder</td>
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<td>• ASA ≥3</td>
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<td>Pachman et al, 2011&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Pilot, 8</td>
<td>• Women with breast cancer</td>
<td>• Receiving antineoplastic chemotherapy, androgens, estrogens, or progesterone analogs</td>
<td>44% reduction in hot flash frequency from baseline to week 6 after receiving a single SGB</td>
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<td></td>
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<td>• Bothersome hot flashes &gt;28 per week</td>
<td>• Pregnant, nursing, or of childbearing potential and unwilling to employ adequate contraception</td>
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<td>• Sufficient severity to make patient desire therapeutic intervention</td>
<td>• Anticoagulants, including aspirin, clopidogrel, ticlopidine, and Coumadin (warfarin), or diagnosis of von Willebrand disease or other bleeding disorders</td>
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<td>• Hot flashes present for at least 1 month</td>
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<td>• At least 18 years old</td>
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<td>• Life expectancy of at least 6 months</td>
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<td>• Excellent performance status</td>
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<td>Haest et al, 2012&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Uncontrolled experimental, 34</td>
<td>• Nonrecurrent, early-stage, postmenopause</td>
<td>• Change of antihormonal therapy for breast cancer within 8 weeks of the first SGB</td>
<td>64% and 47% reduction from baseline in hot flash frequency and severity in weeks 1 and 24, respectively</td>
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<td>• Breast cancer diagnosed &lt;5 years ago</td>
<td>• Blood clotting disorders</td>
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<td>• Karnofsky performance status &gt;80</td>
<td>• Use of anticoagulants</td>
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<td>• Severe treatment-resistant hot flashes</td>
<td>• Any acute infection</td>
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<td></td>
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<td></td>
<td>• Cardiac disorders</td>
<td>Odds of better sleep quality 3.36 and 4.26 times higher than baseline at week 1 and week 24, respectively</td>
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<td>• ASA &gt;3</td>
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<td></td>
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<td></td>
<td>• Simultaneous use of systemic therapy for climacteric symptoms</td>
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<td>Authors, Year</td>
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<td>Inclusion Criteria</td>
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| van Gastel et al, 2013<sup>27</sup> | Open uncontrolled, 19           | • Amenorrhea for at least 1 year  
• Serum LH and FSH levels in the postmenopausal range with estradiol levels <100 pmol/L  
• Mean daily hot flash score >15  
• Physical examination revealed no abnormalities. | • Active somatic or psychiatric disease  
• Blood and urine analysis for other known causes of hot flashes  
• Mean daily hot flash score >15  
• Physical examination revealed no abnormalities. | • Mean hot flash frequency and severity decreased by 34% in 4 weeks.  
• Quality of sleep significantly improved by a mean of 23% in 4 weeks. |
| Walega et al, 2014<sup>28</sup> | Randomized controlled, 40       | • Women aged 30-70 years with natural or surgical menopause  
• >25 reported vasomotor symptoms per week | • ASA score >2  
• Anatomic abnormalities of the anterior neck or cervical spine  
• Cardiac/pulmonary compromise  
• Acute illness/infection  
• Coagulopathy/bleeding disorder  
• Allergic reactions/contraindications to a local anesthetic or contrast dye  
• Use of oral or transdermal hormones  
• Conditions or disorders that affect cognitive functioning  
• Current or past diagnosis of psychosis  
• Current diagnosis of depression, alcohol abuse, or substance abuse  
• Conditions that invalidate cognitive testing procedures | • SGB group vs sham control group:  
• Reduction in total subjective vasomotor symptoms, 34% vs 18%  
• Reduction in subjective moderate to severe vasomotor symptoms, 52% vs 4%  
• Reduction in vasomotor symptom intensity, 38% vs 8%  
• Reduction in objectively measured vasomotor symptoms, 21% vs 0% |

ASA; American Society of Anesthesiologists physical status classification system; FSH, follicle-stimulating hormone; LH, luteinizing hormone.
decreased immediately after the procedure. The decreases were significant when compared with baseline reports, a mean 90% and 93% reduction in hot flash frequency and night awakenings, respectively, up to week 12 among the 13 subjects, 8 of whom received a second SGB. Lipov et al published a 52-week follow-up report that demonstrated significant reductions in the frequency and intensity of hot flashes, as well as marked reductions in night awakenings.29

In 2011, Pachman et al published a pilot study evaluating 8 women with breast cancer who had bothersome hot flashes.25 They showed a 44% reduction in hot flash frequency from baseline to week 6 after patients received a single SGB.

Figure 2. Anatomy of stellate ganglion and surrounding structure. A, artery; M, musculus; N, nerve; V, vein. (Figure printed with permission, Cleveland Clinic Center for Medical Art & Photography © 2014. All Rights Reserved.)

Figure 3. Ultrasound image of stellate ganglion with arrow trajectory for out-of-plane technique for stellate ganglion block. CA, carotid artery; C6, sixth cervical vertebra; M, musculus. (Figure courtesy of Dmitri Souzdalnitski, MD, PhD.)

Figure 4. Ultrasound image of stellate ganglion with arrow trajectory for in-plane technique for stellate ganglion block. CA, carotid artery; C6, sixth cervical vertebra; IJV, internal jugular vein; M, musculus. (Figure courtesy of Dmitri Souzdalnitski, MD, PhD.)
An uncontrolled experimental study by Haest et al. published in 2012 assessed 34 postmenopausal survivors of breast cancer with severe vasomotor symptoms and showed 64% and 47% reductions from baseline in a combined hot flash frequency and severity score from baseline after one or multiple SBGs in weeks 1 and 24, respectively.26 The odds of having better sleep quality were 3.36 and 4.26 times higher in week 1 and week 24, respectively, compared with baseline.

In 2013, van Gastel et al. studied 19 postmenopausal women with severe hot flashes.27 They classified 9 women as responders to SGB with decreases in their flash score of 40%-90% and 10 women as nonresponders with decreases of 0%-11%. The mean combined flash frequency and severity score decreased by 34% 4 weeks after SGB. Quality of sleep significantly improved by a mean of 23% in 4 weeks.

In 2014, Walega et al. published the largest and only randomized sham-controlled clinical trial.28 They randomized 40 moderately to severely symptomatic postmenopausal women to SGB vs sham injection and analyzed the patients’ vasomotor symptoms subjectively and objectively for 6 months. The study showed a notable reduction in total subjective vasomotor symptoms between the SGB group and the sham control group, 34% vs 18%, respectively, in months 4-6. A significantly greater reduction in subjective moderate to very severe vasomotor symptoms from baseline to months 4-6 was reported for the SGB group compared to the sham control group, 52% to 4%, respectively. Also, SGB-treated subjects showed a significantly greater reduction in the reported intensity of vasomotor symptoms from baseline to 4-6 months, 38% vs 8%, respectively. The total number of objectively measured vasomotor symptoms was significantly reduced between the SGB group and the sham control group, 21% and 0%, respectively, from baseline to 3 months. Also, the SGB-treated group demonstrated improvement of depressive symptoms while the sham control group showed none. Neither group had improvement in sleep or quality of life from baseline to week 3 or month 3.28

CONCLUSION

Current evidence suggests that the most effective treatment for hot flashes is HRT, but HRT is not recommended for breast cancer survivors because of the increased rate of breast cancer recurrence. Nonhormonal therapies are associated with significant side effects and mild to moderate effectiveness and are not recommended for treating hot flashes. The available results of SGB efficacy are promising but demonstrate significant variability. A large prospective randomized controlled trial is required to determine the exact success of SGB on hot flashes and quality of life in breast cancer survivors.

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REFERENCES


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