Menopause: The Journal of The North American Menopause Society
Vol. 21, No. 8, pp. 000-000
DOI: 10.1097/gme.0000000000000194

Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized controlled clinical trial in postmenopausal women

David R. Walega, MD,[1] Leah H. Rubin, PhD,[2] Suzanne Banuvar, MPA,[3] Lee P. Shulman, MD,[3] and Pauline M. Maki, PhD[2,4]

Abstract

Objective: Uncontrolled intervention studies, including studies involving breast cancer survivors, have demonstrated improvements in vasomotor symptoms (VMS) after stellate ganglion blockade (SGB) with a local anesthetic. This study presents the first randomized sham-controlled trial of SGB for the treatment of VMS.

Methods: Participants included 40 postmenopausal women, aged 30 to 70 years, with moderate to severe VMS. The study was a randomized sham-controlled trial comparing the effects of SGB versus sham injection on the frequencies of total and moderate to severe VMS, as measured by daily diaries. Image-guided SGB was performed with 5 mL of 0.5% bupivacaine. Sham injection of saline was performed in subcutaneous tissues in the neck. VMS were recorded at baseline and for 6 months thereafter. Objective VMS were recorded using ambulatory sternal skin conductance monitoring during a 24-hour period at baseline and on 3-month follow-up.

Results: There were no significant group differences in overall VMS frequency, but the frequency of moderate to very severe VMS was reduced more in the active group compared with the sham treatment group (event rate ratio, 0.50; 95% CI, 0.35-0.71; $P < 0.001$). The frequency of objective VMS was also reduced to a greater degree in the SGB group than in the sham group (event rate ratio, 0.71; 95% CI, 0.64-0.99; $P < 0.05$). There were no study-related serious adverse events.

Conclusions: SGB may provide effective treatment of VMS in women who seek nonhormonal treatments because of safety concerns and personal preference. The finding that SGB significantly reduces objectively measured VMS provides further evidence of efficacy. A larger trial is warranted to confirm these findings.

Key Words: Menopause – Hot flashes – Hot flushes – Vasomotor symptoms – Stellate ganglion injections – Nonhormonal treatment.

Hot flashes and night sweats (ie, vasomotor symptoms [VMS]) affect 80% of women as they transition through menopause.[1] The severity of VMS is especially high for women who undergo surgical menopause or early menopause because of breast cancer treatments. Hormone therapy (HT) is the most effective treatment of VMS.[2] In a meta-analysis of placebo-controlled trials, HT reduced VMS frequency by 75% and VMS severity by 87% with placebo.[3] Many women, however, seek nonhormonal treatments of VMS because of safety concerns and personal preference. Gabapentin and clonidine are effective nonhormonal treatments for reducing VMS,[4,5] but their use is limited owing to modest symptom improvement and undesirable adverse effects (pedal edema, weight gain, and blurred vision with gabapentin; constipation, orthostatic hypotension, and dry mouth with clonidine). In addition, these agents lack Food and Drug Administration approval for the treatment of VMS. Botanical therapies (eg, phytoestrogens, black cohosh) have shown relative inefficacy,[6,7] and lifestyle interventions are, at best, marginally more effective than placebo in relieving VMS.[8,9]

In 2013, the Food and Drug Administration approved paroxetine, a selective serotonin reuptake inhibitor (SSRI; 7.5 mg), as the first nonhormonal treatment of VMS.[10] As with HT, about a third of women experience a relapse of VMS after discontinuing SSRIs.[11] The product label warns of a possible reduction in the effectiveness of tamoxifen when taken with paroxetine (of obvious concern for women being treated for

Received September 6, 2013; revised and accepted November 26, 2013.

From the [1]Department of Anesthesiology, The Feinberg School of Medicine of Northwestern University, Chicago, IL; [2]Department of Psychiatry, The University of Illinois at Chicago College of Medicine, Chicago, IL; [3]Department of Obstetrics and Gynecology, The Feinberg School of Medicine of Northwestern University, Chicago, IL; and [4]Department of Psychology, The University of Illinois at Chicago College of Medicine, Chicago, IL.

Funding/support: Funding was provided by the Department of Obstetrics and Gynecology, Northwestern University. L.H.R. was supported by grant K12HD055892 from the National Institute of Child Health and Human Development and the National Institutes of Health Office of Research on Women's Health.

Financial disclosure/conflicts of interest: L.P.S. has received honoraria from Shionogi for consulting and speaking engagements on nonhormonal treatment of vulvovaginal atrophy and from Noven Pharmaceuticals for speaking engagements on hormonal treatments in symptomatic postmenopausal women. P.M.M. has received honoraria from Noven Pharmaceuticals and DepoMed for consulting on nonhormonal treatments of vasomotor symptoms. D.R.W., L.H.R., and S.B. declare no conflicts of interest.

Address correspondence to: David R. Walega, MD, Department of Anesthesiology, The Feinberg School of Medicine of Northwestern University, Suite 5-704, 251 East Huron Street, Chicago, IL 60611. E-mail: d-walega@northwestern.edu

breast cancer), in addition to an increased risk of bleeding and a risk of developing serotonin syndrome (ie, confusion, rapid heart rate, and high blood pressure).[11] Indeed, the use of SSRIs for the treatment of VMS is limited by the lower effectiveness of SSRIs when compared with HT, as well as by adverse effects and relapse of symptoms after treatment discontinuation.[12] Identifying safe and effective nonhormonal treatments of VMS remains a priority in women's health research.

Uncontrolled open-label intervention studies have demonstrated improvements in the frequency and intensity of VMS after stellate ganglion blockade (SGB) with a local anesthetic, with effects ranging from 34% to 90% reduction 4 weeks to several months after blockade.[13-16] Although the exact mechanism is not fully understood, treatment with SGB is based on the interruption of the sympathetic nervous system; thus, it may affect blood flow and may modulate norepinephrine levels in thermoregulatory areas of the brain. This trial compared SGB with bupivacaine and a sham procedure involving saline injection for VMS in women who underwent natural or surgical menopause during a 6-month follow-up. The primary outcomes were the frequencies of total and moderate to very severe VMS reported at the end of the 6-month follow-up and the frequency of objective VMS measured using ambulatory skin conductance monitors at the end of the 3-month follow-up.

METHODS

Participants

Participants underwent an informed consent process, including provision of a written informed consent form before any study procedure, and were compensated for their time and effort. Women aged 30 to 70 years who had had natural or surgical menopause, had moderate to very severe VMS (defined as ≥25 reported VMS per week—the criterion used in prior VMS studies[7]), and were willing to undergo fluoroscopy-guided SGB were recruited for this study. The study was advertised using institutional review board–approved flyers, Chicago Transit Authority advertising, and the Internet. Participants were initially screened by telephone to evaluate interest and eligibility criteria but consented in person. Participants were confirmed (in paper diaries) to have 25 or more VMS per week for a minimum of 2 weeks before randomization to treatment groups. Exclusion criteria included the following: American Society of Anesthesiologists physical status score higher than 2 (indicating more than one systemic disease); 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 (including stroke; severe brain injury; loss of consciousness; and current use of SSRIs, serotonin norepinephrine uptake inhibitors, or gabapentin); current or past diagnosis of psychosis; current diagnosis of depression, alcohol abuse, or substance abuse; and conditions that invalidate cognitive testing procedures (eg, inability to write, speak, or read in English).

The institutional review boards at Northwestern University and The University of Illinois at Chicago approved this study. The trial study was registered with www.clinicaltrials.gov (NCT00992914).

Randomization and masking

A computer-generated 1:1 block randomization scheme was used to assign participants to receive either an SGB with bupivacaine or a sham injection with saline. Randomization was performed by the injectionist immediately before the injection procedure by opening an opaque envelope to reveal the participant number and group assignment printed on an index card. Participants and all other study personnel were blinded to group assignment. Only the person providing the injection and the statistician were unblinded at the conclusion of the study. A board-certified anesthesiologist (D.R.W.) with 15 years of experience performed all injections.

Procedures

At the time of the injection procedure, a 20-gauge angiocatheter was placed in the hand or arm for peripheral intravenous access as a safety precaution. Participants were positioned supine in cervical extension. The anterior neck was prepared with chlorhexidine and draped in the standard sterile manner. For active SGB, right-sided SGB was performed. With fluoroscopic guidance, the C_6 vertebra was identified, and the skin overlying the tubercle was anesthesized using 2 mL of 1% lidocaine. With the use of digital pressure to laterally retract the carotid artery, a 22-gauge 1.5-in. needle was placed to make contact with the anterolateral portion of the C_6 vertebra, retracted 1 to 2 mm, and secured; contrast material (iopamidol, 1-2 mL) was injected with fluoroscopic guidance to confirm contrast dye spread in the prevertebral fascial plane and to rule out intravascular or intrathecal dye spread. Five milliliters of 0.5% bupivacaine was injected, and the needle was removed. For sham injection, the same positioning, monitoring, sterile preparation, and technique were used with identical visual, auditory, and tactile cues, except that the needle was placed in the superficial tissues overlying the C_6 tubercle. With fluoroscopic guidance, contrast material (iopamidol, 1-2 mL) was injected to confirm contrast dye spread in subcutaneous tissues, not in the plane of the stellate ganglion. Preservative-free saline (5 mL) was injected, and the needle was removed. Participants were transferred to a recovery area and monitored in reclining position for at least 30 minutes to assess potential adverse effects of the injection. The presence of a Horner sign (miosis, ptosis, or anhydrosis) was recorded and validated successful SGB.

Outcome measures

The primary outcomes were the frequencies of total and moderate to very severe VMS (measured by daily diaries) and the frequency of objective VMS (measured using ambulatory skin conductance monitors). Secondary outcomes included sleep quality, depression, and quality of life. Measures were performed in conjunction with cognitive assessments before the injection treatment and again 3 months later. These measures are commonly evaluated in menopause studies.[17-21] For a minimum of 2 weeks before the injection procedure and for 6 months thereafter, participants recorded the frequency and

severity of daily VMS in a paper diary. Participants were instructed to rate each hot flash as "mild" (<5 min, warm, red face, and uncomfortable), "moderate" (<15 min, perspiration, clammy skin, dry mouth, tense muscles, tachycardia, irritation, agitation, embarrassment, and warmth involving the neck, ears, head, and whole body), "severe" (<20 min, warmth described as raging furnace or burning up, weak, faint, headache, chest heaviness, extreme perspiration, prickling sensation on skin, heart irregularities, anxious, and panic attacks), or "very severe" (<45 min, boiling eruption, rolling perspiration, inability to breathe, faint/dizzy, leg/foot cramps, heart irregularities, difficulty functioning, distressed, and nausea).[22] Intensity of daytime hot flashes was calculated using the equation: Intensity = Frequency × Severity = [(frequency of mild × 1) + (frequency of moderate × 2) + (frequency of severe × 3) + (frequency of very severe × 4)] and used as a secondary endpoint.[23] Frequency of night sweats was also recorded daily, via self-report, on the following morning. Baseline VMS frequency was calculated as the mean of daily count totals on diaries during the first two screening weeks. Week 1 VMS frequency was calculated as the mean of daily count totals reported in the first 7 days after injection. VMS frequency on months 1 to 6 was calculated as the mean of daily count totals reported for the 30 days before each visit.

To measure VMS objectively, we fitted participants with an ambulatory sternal skin conductance monitor (Biolog Model 3991x/2-HFI) featuring two skin conductance electrodes connected to the sternum by adhesive electrode pads (UFI Model 1081-HFD; UFI, Morro Bay, CA). The monitor was placed inside a small pouch that was worn on a belt or slung over the shoulder. Both objective (ie, >2.0 μmho increase in 30 s) and subjective (button press) VMS were recorded with the monitor according to standard procedures.[24] Participants were instructed to push two red buttons on the monitor when

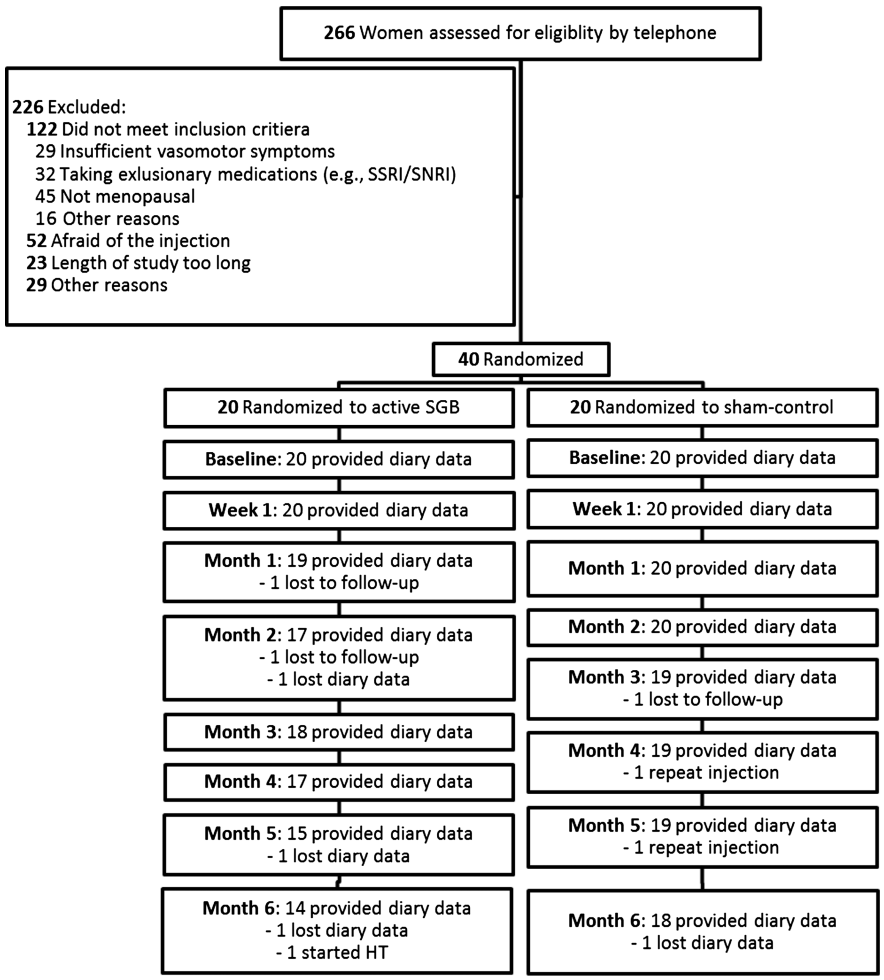

FIG. 1. Participant flow diagram. SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine uptake inhibitor; SGB, stellate ganglion blockade; HT, hormone therapy.

they experienced a hot flash. These events were time-stamped to record the time of a subjective hot flash. Participants also kept a diary of the time, severity, and intensity of the hot flash. Raw hot flash data were transmitted from the monitor to a PC using the Biolog Interface Box. Time series of skin conductance data (in μmho) were presented in a time-based graphical display showing subjective VMS (ie, event markers) and objective VMS (see below) using specialized software (DPS v. 1.5; UFI). Raw objective hot flash data were analyzed by a combination of automated computer software and two trained data coders. According to standard procedures, once an objective hot flash was coded, no other VMS were coded for the next 15 minutes.[25] Data were independently double-scored and double-entered into the database by coders blinded to treatment assignment. The frequencies of objective and subjective VMS during sleeping and waking hours were scored based on reports in hot flash diaries of the time participants went to bed and the time they woke up while being monitored. Depressive symptoms were assessed by the Center for Epidemiological Studies—Depression Scale, a 20-item self-report measure of depressive symptoms during the past week. A score of 16 or higher was considered severe. Sleep quality was assessed with the modified Pittsburgh Sleep Quality Index for the preceding 1-month period.[26] Total sleep score was calculated using an established scoring scheme, with higher scores indicating greater sleep disturbance.[26] Quality of life was measured with the Utian Quality of Life Scale, a validated subjective appraisal of life satisfaction and well-being.[27] Participants rated 23 questions in four life domains (occupational, health, sexual, and emotional) using a 5-point Likert scale (1, "not true of me"; 5, "very true of me") for the preceding 1-month period. The outcome was a total score derived by summing the separate domain scores.

TABLE 1. *Demographic and clinical characteristics by treatment group at baseline*

	Treatment group		
	SGB (n = 20)	Sham control (n = 20)	*P*
Demographics			
Age, mean (SD), y	51.70 (2.36)	52.90 (4.09)	0.26
Body mass index, mean (SD), kg/m^2	28.20 (5.45)	28.05 (5.09)	0.93
Race, n (%)			0.24
White	6 (30)	11 (55)	
Black	11 (55)	8 (40)	
Hispanic	3 (15)	1 (5)	
Menopause, n (%)			0.15
Natural	17 (85)	13 (65)	
Surgical	3 (15)	7 (35)	
Postmenopause status, n (%)			0.75
<5 y since last LMP	12 (60)	13 (65)	
Menopausal symptoms, mean (SD)			
CES-D depressive symptoms	11.11 (7.06)	12.40 (8.92)	0.62
PSQI global score	8.63 (3.70)	10.55 (4.87)	0.18
UQOL total score	80.53 (9.77)	82.26 (11.03)	0.61
Vasomotor symptoms (daily count), mean (SD)			
Subjective (via diaries)			
Mild	1.20 (1.46)	1.99 (2.14)	0.18
Moderate to very severe	4.75 (2.28)	5.73 (3.66)	0.31
Night sweats	2.13 (1.74)	2.07 (1.73)	0.92
Total[a]	8.08 (3.08)	9.89 (5.82)	0.22
Intensity	12.52 (5.69)	15.90 (11.18)	0.24
Objective (via monitor)[b]			
Total	15.07 (12.41)	10.10 (9.94)	0.22
Awake	12.32 (10.65)	7.34 (7.68)	0.14
Asleep	2.75 (2.12)	2.75 (3.96)	0.99

SGB, stellate ganglion blockade; LMP, last menstrual period; CES-D, Center for Epidemiological Studies—Depression Scale; PSQI, Pittsburgh Sleep Quality Index; UQOL, Utian Quality of Life.
[a]Mild, moderate, severe, and very severe vasomotor symptoms, and night sweats.
[b]Valid objective data were available for 35 of 40 women (SGB, 18; sham control, 17). Refer to the text for the definition of intensity.

Statistical analysis

Baseline characteristics were compared between treatment groups using *t* tests or χ^2 tests for categorical variables. A modified intent-to-treat (ITT) analysis, including all randomized participants who provided diary data, was performed using a series of mixed-effects regression (random intercept only). This method is consistent with previous approaches used in randomized controlled trials of escitalopram and paroxetine for the treatment of VMS.[10,28] Specifically, mixed-effects Poisson regression was used for count data (eg, mean daily count of subjective and objective VMS). Exponentiation of unstandardized β coefficients from these models yields event rates/event rate ratios. Event rates provide information on the expected number of events occurring during a given period. From each model, an event rate ratio is computed for each group using the following equation: (Expected number of VMS at baseline − Expected number of VMS at a subsequent time point) / Expected number of VMS at baseline. The ratio of event rate ratios provides a statistical comparison of the expected change in VMS from baseline to a subsequent time point between the SGB group and the sham control group. Specifically, the ratio of event rate ratios simply divides the event rate ratio for the SGB group by the event rate ratio for the sham control group. Mixed-effects regression was used for continuous outcomes (eg, subjective VMS intensity). For subjective VMS and menopausal symptoms, independent predictors included treatment group (active SGB vs sham control); dummy variables for week 1 (vs baseline), months 1 to 3 (vs baseline), and months 4 to 6 (vs baseline); and interactions between treatment group and each dummy variable. For menopausal symptoms, the dummy variables reflected week 3 (vs baseline) and month 3 (vs baseline). For objective VMS outcomes, independent predictors included treatment group, a dummy variable for month 3 (vs baseline), and their interaction.

SAS statistical software version 9.2 (SAS Institute Inc, Cary, NC) was used for statistical analyses. Significance was set at $P < 0.05$.

Power for total subjective hot flashes was calculated using Power Analysis and Sample Size 11.0 software and was based on a mixed design with one between-subjects factor (Treatment: sham control and SGB) and one within-subjects factor (Time: baseline and posttreatment) and a Geisser-Greenhouse corrected *F* test with 5% significance level, using data from a

TABLE 2. *Modified intent-to-treat analysis: estimated RRs (95% CI) as a function of time for subjective vasomotor symptoms in women randomized to active SGB or sham control*

	Treatment group		
	SGB	Sham control	Treatment × Time
Primary outcomes	RR (95% CI)	RR (95% CI)	RRR (95% CI)
Baseline to week 1			
Total	0.76 (0.61-0.96)[a]	0.75 (0.61-0.93)[b]	1.01 (0.74-1.39)
Moderate to very severe	0.73 (0.54-1.00)[c]	0.74 (0.56-0.98)[a]	0.99 (0.65-1.50)
Baseline to months 1-3			
Total	0.68 (0.57-0.83)[d]	0.68 (0.56-0.80)[d]	1.03 (0.80-1.34)
Moderate to very severe	0.62 (0.48-0.80)[d]	0.69 (0.55-0.87)[b]	0.90 (0.64-1.27)
Baseline to months 4-6			
Total	0.66 (0.54-0.81)[d]	0.82 (0.69-0.98)[a]	0.81 (0.62-1.03)[e]
Moderate to very severe	0.48 (0.36-0.63)[d]	0.96 (0.77-1.20)	0.50 (0.35-0.71)[d]

Results are reflective of mixed-effects Poisson regression (random intercept only).
RR, event rate ratio; SGB, stellate ganglion blockade; RRR, ratio of event rate ratios.
[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P = 0.05$.
[d] $P < 0.001$.
[e] $P = 0.10$.

previously published pilot study.[13] A sample size of 20 participants in each treatment group provided at least 80% power to test the two-way interaction between treatment and time.

RESULTS

Two hundred sixty-six women expressed their interest to participate and contacted the site between February 2009 and November 2012 (Fig. 1). Of these, 61 women enrolled and provided a written informed consent form. Twenty-one women failed screening primarily because of an insufficient number of hot flashes, and 40 participants were randomized. Participants were followed for 6 months after the injection procedure. There were no statistically significant group differences in baseline demographic characteristics, VMS symptoms, or menopausal symptoms (Table 1).

The mean (SD) daily frequency of total subjective VMS at baseline was 9.85 (8.58), with 63% of VMS rated as moderate to very severe. The modified ITT analysis of the mean daily count of all VMS (mild, moderate, severe, and very severe VMS, and night sweats) showed no significant treatment group differences in VMS frequency from baseline to week 1 or from baseline to months 1 to 3 after injection (Table 2, Fig. 2A). The sham control group showed a significant placebo effect of 34% until 3 months after injection. On months 4 to 6, total VMS were notably reduced in the SGB group (34% reduction) compared with the sham control group (18% reduction), but this difference did not reach statistical significance ($P = 0.10$). In the modified ITT analysis of moderate to very severe VMS, SGB-treated women showed significantly greater reductions (52%) from baseline to months 4 to 6 compared with the sham control group (4%; Fig. 2B). This same pattern of effects was observed for VMS intensity (Fig. 3). SGB-treated women showed significantly greater reduction (38%) from baseline to 4 to 6 months

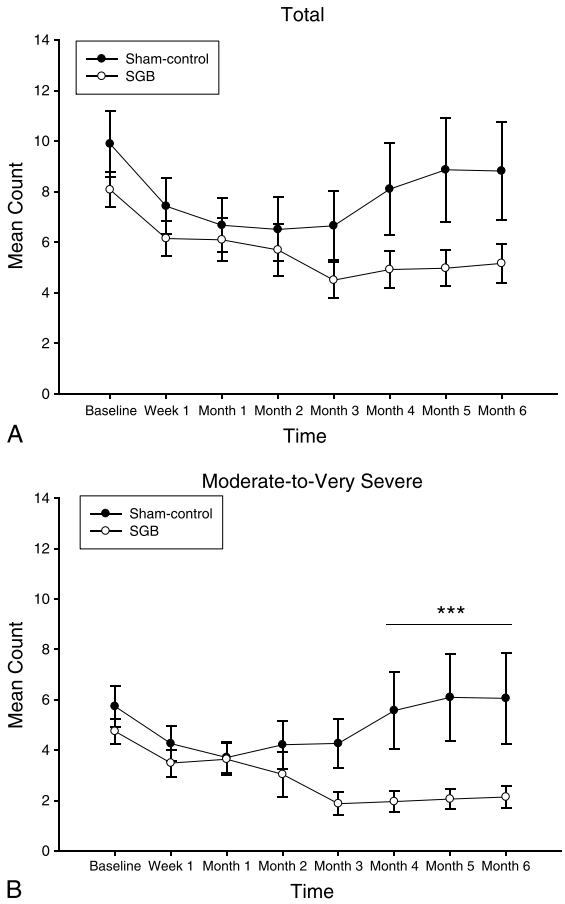

FIG. 2. Modified intent-to-treat analysis of the mean daily count of (**A**) total subjective vasomotor symptoms and (**B**) moderate to very severe vasomotor symptoms. Data points represent the mean and standard error at each time point. Results are reflective of a mixed-effects Poisson regression model for count data. *** $P < 0.001$, Treatment × Time interaction (baseline to months 4-6). SGB, stellate ganglion blockade; Total = mild, moderate, severe, and very severe vasomotor symptoms, and night sweats.

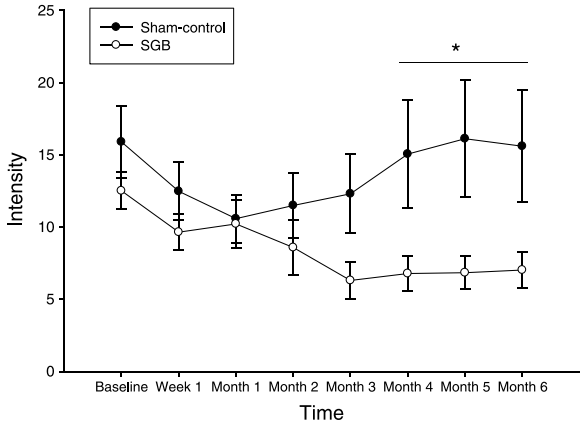

FIG. 3. Modified intent-to-treat analysis of vasomotor symptom intensity (Frequency × Severity) as a function of treatment (active SGB vs placebo) over 12 months of follow-up. Data points represent the mean and standard error at each time point. Results are reflective of a mixed-effects regression model for continuous data. There were no treatment group differences in vasomotor symptom intensity from baseline to 1 week (Treatment × Time: $\beta = 0.54$, SE = 2.09, $P = 0.80$) or from baseline to 1 to 3 months (Treatment × Time: $\beta = 0.96$, SE = 1.74, $P = 0.58$) after injection. However, SGB-treated women showed significantly greater reductions in vasomotor symptom intensity from baseline to 4 to 6 months ($\beta = -4.80$, SE = 1.23, $P < 0.001$) compared with the sham control group ($\beta = -1.30$, SE = 1.28, $P = 0.31$; Treatment × Time: $\beta = -3.50$, SE = 1.78, $P = 0.04$). SGB, stellate ganglion blockade. *$P < 0.001$.

($\beta = -4.80$, SE = 1.23, $P < 0.001$) compared with the sham control group (8%; $\beta = -1.30$, SE = 1.28, $P = 0.31$; Treatment × Time: $\beta = -3.50$, SE = 1.78, $P = 0.04$).

Valid objective VMS data were available for 18 women in the SGB group and for 17 women in the sham control group. The total number of objective VMS from baseline to 3 months was reduced by 21% in the SGB group, whereas the sham control group showed no reduction, for a significant group difference ($P < 0.05$; Table 3).

The SGB group showed trends toward improvement in depressive symptoms on week 3 ($\beta = -2.25$, SE = 1.31, $P = 0.09$) and month 3 ($\beta = -2.45$, SE = 1.26, $P = 0.069$), whereas the sham control group showed no improvement (Table 4, Fig. 4). The group difference on month 3, however, did not meet statistical significance ($P < 0.10$). There were no improvements in either treatment group on sleep or quality of life from baseline to week 3 or month 3.

There were no study-related serious adverse events. All participants who underwent SGB developed Horner syndrome (miosis, ptosis, and anhydrosis) immediately after the injection, confirming successful sympathetic blockade. No sham controls exhibited Horner syndrome. Only one injection was given to those in the SGB group. Two women in the placebo group opted to receive a second SGB injection 3 months after the first injection, as allowed by study protocol.

DISCUSSION

In this randomized sham-controlled trial, SGB led to a 52% reduction in the diary-reported frequency of moderate to very severe VMS. In addition, a 38% reduction in VMS intensity (a measure that reflects both frequency and severity) was found in the SGB group as compared with sham controls—findings that were durable through the 6-month follow-up. As expected, the sham control group showed a notable initial improvement in reported VMS frequency (akin to a placebo effect), but the effect of SGB was significantly greater and longer-lasting. SGB reduced the frequency of all VMS, regardless of severity, by 19% more in the treatment group compared with the control group, but this difference was not statistically significant. Objective measures of hot flash frequency were 21% lower in women who received SGB as compared with sham controls.

These findings are consistent with nonrandomized studies of SGB in women with severe VMS and a history of breast cancer. In an observational study of 13 breast cancer survivors with severe VMS, SGB reduced total VMS by nearly 90% during a 12-week follow-up period.[13] SGB decreased the mean hot flash frequency by 44% at 6 weeks in 10 breast cancer survivors who failed conventional VMS treatment.[14] SGB led to a 47% decrease in hot flash scores at 24 weeks in 34 women with nonrecurrent early-stage postmenopausal breast cancer and severe VMS, with a positive effect on sleep observed during the 24-week follow up.[15] In another uncontrolled trial of SGB in 19 postmenopausal women, a 34% decrease in hot flash scores was seen at 4 weeks after SGB in "responders," although 10 of the 19 women were "nonresponders," with a 0% to 11% reduction in hot flash

TABLE 3. *Estimated mean counts (95% CI) and estimated RRs (95% CI) as functions of time for objective vasomotor symptoms in women randomized to active SGB or sham control*

	Treatment group						
	SGB (n = 18)			Sham control (n = 17)			
	Baseline	3 mo after		Baseline	3 mo after		
	Mean (95% CI)	Mean (95% CI)	RR (95% CI)	Mean (95% CI)	Mean (95% CI)	RR (95% CI)	RRR (95% CI)
Total	7.21 (3.68-14.1)	5.74 (2.92-11.3)	0.79 (0.64-0·98)[a]	5.60 (2.85-11.0)	6.24 (3.12-12.5)	1.11 (0.86-1.43)	0.71 (0.64-0.99)[a]
Awake	5.84 (2.93-11.6)	4.33 (2.17-8.66)	0.74 (0.59-0·94)[a]	3.95 (1.97-7.96)	4.48 (2.19-9.17)	1.13 (0.84-1.52)	0.66 (0.45-0.96)[a]
Sleep	1.66 (0.84-3.29)	1.66 (0.84-3.30)	1.00 (0.63-1.60)	1.36 (0.67-2.77)	1.45 (0.69-3.04)	1.06 (0.63-1.71)	0.94 (0.48-1.83)

Results are reflective of mixed-effects Poisson regression (random intercept only).
RR, event rate ratio; SGB, stellate ganglion blockade; RRR, ratio of event rate ratios.
[a]$P < 0.05$.

TABLE 4. *Estimated means (SE) and estimated change scores across time for menopausal symptoms in women randomized to SGB or placebo*

	Treatment group					
	SGB (n = 20)		Sham control (n = 20)			
Outcomes	Δ Baseline to 3 wk	Δ Baseline to 3 mo	Δ Baseline to 3 wk	Δ Baseline to 3 mo	Treatment × Time (Δ baseline to 3 wk)	Treatment × Time (Δ baseline to 3 mo)
Depressive symptoms (CES-D)[a]	−2.25 (1.31)[b]	−2.45 (1.26)[c]	0.05 (1.38)	1.06 (1.29)	−2.30 (1.91)	−3.51 (1.81)[c]
UQOL total score[d]	2.42 (1.91)	0.53 (1.84)	−0.34 (2.01)	−1.85 (1.88)	2.76 (2.77)	2.39 (2.63)
PSQI global score[a]	0.51 (0.79)	−0.97 (0.76)	−0.12 (0.86)	−0.59 (0.76)	0.63 (1.17)	−0.38 (1.08)

Data are presented as β (SE).
SGB, stellate ganglion blockade; Δ, change in score between two time points; CES-D, Center for Epidemiological Studies—Depression Scale; UQOL, Utian Quality of Life; PSQI, Pittsburgh Sleep Quality Index.
[a]Higher scores indicate more severe symptoms.
[b]$P = 0.09$.
[c]$P = 0.06$.
[d]Higher scores indicate less severe symptoms.

scores. Quality of life and sleep measures were also significantly improved in "responders."[16] In contrast to these prior studies, SGB did not improve sleep quality in the present study. However, the observed trend toward improvement in depressive symptoms after SGB warrants further investigation, especially given evidence that SGB improved affective symptoms in patients with posttraumatic stress disorder.[29]

Stellate ganglion injections are considered safe when performed by experienced practitioners. In the current study, none of the participants experienced any serious adverse events. Severe injury related to stellate ganglion injections is rare when they are performed by experienced skilled practitioners. The published incidence of SGB complications—predating the common use of image guidance—is 1.7 per 1,000 procedures and is related to intravascular injection of a local anesthetic, resulting in temporary seizures related to a local anesthetic.[30] It follows that image-guided injections would have far fewer complications, as critical vascular or neural structures can be visualized in real time and thus can be avoided. However, safety concerns may evolve in the future if inadequately trained or inexperienced practitioners perform SGB, given the close proximity of critical structures such as the vertebral artery, internal carotid artery, inferior thyroid artery, and spinal nerves.

The mechanism by which VMS occur with menopause is not well understood, and the mechanism by which SGB modulates these symptoms bears further study. Although the hypothalamus has long been considered as the central thermoregulatory center, functional magnetic resonance imaging studies have confirmed that the brainstem is activated immediately before a hot flash, whereas activity in the insula only rises after the experience of a hot flash.[31] One hypothesis is that the sympathetic nervous system induces activity in those regions. SGB causes increased blood flow in the head, neck, upper extremities, and trunk via temporary sympatholysis. Changes in blood flow to thermoregulatory regions of the brain could decrease VMS. Anatomic studies reveal connections between the stellate ganglion and thermoregulatory regions of the brain, specifically the insular cortex, via second- and third-order synapses.[32] Alternatively, SGB may modulate nerve growth factor and norepinephrine, which increases centrally before and during a hot flash.[33]

To our knowledge, this is the first randomized sham-controlled trial of SGB for VMS. Unlike prior studies, no participants in the active arm underwent more than one SGB during the study. All women in the SGB group exhibited a Horner sign immediately after the injection, confirming successful sympathetic blockade, whereas failure to identify a Horner sign occurred in 5% to 22% of participants in prior studies.[14,15] Nonetheless, our study has several limitations. The sample comprised only 40 women, although this is the largest clinical study, to date, of SGB for the treatment of VMS. A larger sample would probably provide the statistical power necessary to observe an effect of SGB on total VMS given the sizeable placebo effect. Although women in the sham control group showed a 34% placebo effect on reported VMS from baseline to month 3, objective monitoring showed no improvement in VMS in the sham control group during that same time frame compared with a 21% reduction in objective VMS in the SGB group. Other trials also reported a lack of improvement in objective VMS among women randomized to placebo despite an improvement in subjective VMS.[34,35] Further studies of SGB in

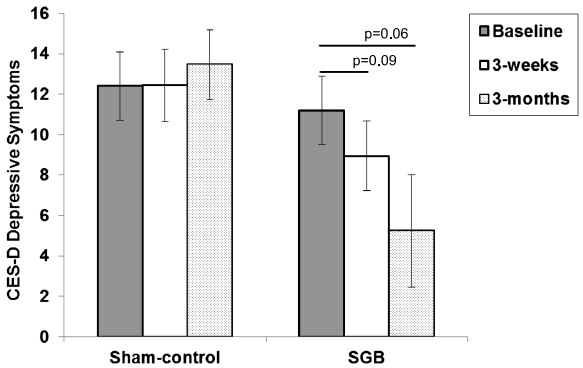

FIG. 4. Changes in depressive symptoms for women randomized to SGB or sham control. Data points represent the mean and standard error at each time point. CES-D, Center for Epidemiological Studies—Depression Scale; SGB, stellate ganglion blockade.

women with moderate to very severe VMS resulting from the natural, surgical, or pharmaceutical initiation of menopausal symptoms are needed to assess the important clinical characteristics of SGB (such as duration of symptom relief) and the comparative effectiveness of other doses and types of sympatholytic agents. Nonetheless, further robust studies showing the benefits of SGB on symptomatic women will corroborate this and earlier observational reports that SGB is an effective nonhormonal intervention for women seeking relief from VMS that are adversely affecting health and well-being.

CONCLUSIONS

SGB may provide effective treatment of VMS in women seeking nonhormonal treatments because of safety concerns and personal preference. The finding that SGB significantly reduces objectively measured VMS provides further evidence of efficacy. A larger trial is warranted to confirm these findings.

Acknowledgments: We would like to thank Dr. Eugene Lipov for his collegial support in our initial discussions of study design for this clinical research.

REFERENCES

1. Kronenberg F. Hot flashes: epidemiology and physiology. *Ann N Y Acad Sci* 1990;592:52-86, discussion 123-133.
2. de Villiers TJ, Gass ML, Haines CJ, et al. Global Consensus Statement on menopausal hormone therapy. *Maturitas* 2013;74:391-392.
3. Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev* 2004;4:CD002978.
4. Pandya KJ, Morrow GR, Roscoe JA, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet* 2005;366:818-824.
5. Pandya KJ, Raubertas RF, Flynn PJ, et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med* 2000;132:788-793.
6. Geller SE, Shulman LP, van Breemen RB, et al. Safety and efficacy of black cohosh and red clover for the management of vasomotor symptoms: a randomized controlled trial. *Menopause* 2009;16:1156-1166.
7. Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. *Ann Intern Med* 2006;145:869-879.
8. Morrow PK, Mattair DN, Hortobagyi GN. Hot flashes: a review of pathophysiology and treatment modalities. *Oncologist* 2011;16:1658-1664.
9. Fisher TE, Chervenak JL. Lifestyle alterations for the amelioration of hot flashes. *Maturitas* 2012;71:217-220.
10. Simon JA, Portman DJ, Kaunitz AM, et al. Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. *Menopause* 2013;20:1027-1035.
11. Joffe H, Guthrie KA, Larson J, et al. Relapse of vasomotor symptoms after discontinuation of the selective serotonin reuptake inhibitor escitalopram: results from the menopause strategies: finding lasting answers for symptoms and health research network. *Menopause* 2013;20:261-268.
12. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006;295:2057-2071.
13. Lipov EG, Joshi JR, Sanders S, et al. Effects of stellate-ganglion block on hot flushes and night awakenings in survivors of breast cancer: a pilot study. *Lancet Oncol* 2008;9:523-532.
14. Pachman DR, Barton D, Carns PE, et al. Pilot evaluation of a stellate ganglion block for the treatment of hot flashes. *Support Care Cancer* 2011;19:941-947.
15. Haest K, Kumar A, Van Calster B, et al. Stellate ganglion block for the management of hot flashes and sleep disturbances in breast cancer survivors: an uncontrolled experimental study with 24 weeks of follow-up. *Ann Oncol* 2012;23:1449-1454.
16. van Gastel P, Kallewaard JW, van der Zanden M, de Boer H. Stellate-ganglion block as a treatment for severe postmenopausal flushing. *Climacteric* 2013;16:41-47.
17. Bromberger JT, Matthews KA, Schott LL, et al. Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). *J Affect Disord* 2007;103:267-272.
18. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry* 2006;63:375-382.
19. Carpenter JS, Guthrie KA, Larson JC, et al. Effect of escitalopram on hot flash interference: a randomized, controlled trial. *Fertil Steril* 2012;97:1399-1404.e1.
20. Carpenter JS, Burns DS, Wu J, et al. Paced respiration for vasomotor and other menopausal symptoms: a randomized, controlled trial. *J Gen Intern Med* 2013;28:193-200.
21. Painovich JM, Shufelt CL, Azziz R, et al. A pilot randomized, single-blind, placebo-controlled trial of traditional acupuncture for vasomotor symptoms and mechanistic pathways of menopause. *Menopause* 2012;19:54-61.
22. Finck G, Barton DL, Loprinzi CL, Quella SK, Sloan JA. Definitions of hot flashes in breast cancer survivors. *J Pain Symptom Manage* 1998;16:327-333.
23. Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl H. Methodologic lessons learned from hot flash studies. *J Clin Oncol* 2001;19:4280-4290.
24. Freedman RR. Laboratory and ambulatory monitoring of menopausal hot flashes. *Psychophysiology* 1989;26:573-579.
25. Carpenter JS, Andrykowski MA, Freedman RR, Munn R. Feasibility and psychometrics of an ambulatory hot flash monitoring device. *Menopause* 1999;6:209-215.
26. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193-213.
27. Utian WH, Janata JW, Kingsberg SA, Schluchter M, Hamilton JC. The Utian Quality of Life (UQOL) Scale: development and validation of an instrument to quantify quality of life through and beyond menopause. *Menopause* 2002;9:402-410.
28. Freeman EW, Guthrie KA, Caan B, et al. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA* 2011;305:267-274.
29. Mulvaney SW, McLean B, de Leeuw J. The use of stellate ganglion block in the treatment of panic/anxiety symptoms with combat-related post-traumatic stress disorder; preliminary results of long-term follow-up: a case series. *Pain Pract* 2010;10:359-365.
30. Wulf H, Maier C. [Complications and side effects of stellate ganglion blockade. Results of a questionnaire survey]. *Anaesthesist* 1992;41:146-151.
31. Diwadkar VA, Murphy ER, Freedman RR. Temporal sequencing of brain activations during naturally occurring thermoregulatory events [published online ahead of print June 19, 2013]. *Cereb Cortex*.
32. Westerhaus MJ, Loewy AD. Central representation of the sympathetic nervous system in the cerebral cortex. *Brain Res* 2001;903:117-127.
33. Lipov EG, Joshi JR, Sanders S, Slavin KV. A unifying theory linking the prolonged efficacy of the stellate ganglion block for the treatment of chronic regional pain syndrome (CRPS), hot flashes, and posttraumatic stress disorder (PTSD). *Med Hypotheses* 2009;72:657-661.
34. Carpenter JS, Storniolo AM, Johns S, et al. Randomized, double-blind, placebo-controlled crossover trials of venlafaxine for hot flashes after breast cancer. *Oncologist* 2007;12:124-135.
35. Maki PM, Rubin LH, Fornelli D, et al. Effects of botanicals and combined hormone therapy on cognition in postmenopausal women. *Menopause* 2009;16:1167-1177.

