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Effect of Stellate Ganglion Block Treatment on Posttraumatic Stress Disorder Symptoms
A Randomized Clinical Trial

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IMPORTANCE This is the first multisite, randomized clinical trial of stellate ganglion block (SGB) outcomes on posttraumatic stress disorder (PTSD) symptoms.

OBJECTIVE To determine whether paired SGB treatments at 0 and 2 weeks would result in improvement in mean Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) total symptom severity scores from baseline to 8 weeks.

DESIGN, SETTING, AND PARTICIPANTS This multisite, blinded, sham-procedure, randomized clinical trial used a 2:1 SGB:sham ratio and was conducted from May 2016 through March 2018 in 3 US Army Interdisciplinary Pain Management Centers. Only anesthesiologists performing the procedures and the procedure nurses were aware of the intervention (but not the participants or assessors); their interactions with the participants were scripted and limited to the 2 interventions. Active-duty service members on stable psychotropic medication dosages who had a PTSD Checklist–Civilian Version (PCL-C) score of 32 or more at screening were included. Key exclusion criteria included a prior SGB treatment, selected psychiatric disorders or substance use disorders, moderate or severe traumatic brain injury, or suicidal ideation in the prior 2 months.

INTERVENTIONS Paired right-sided SGB or sham procedures at weeks 0 and 2.

MAIN OUTCOMES AND MEASURES Improvement of 10 or more points on mean CAPS-5 total symptom severity scores from baseline to 8 weeks, adjusted for site and baseline total symptom severity scores (planned a priori).

RESULTS Of 190 screened individuals, 113 (59.5%; 100 male and 13 female participants; mean [SD] age, 37.3 [6.7] years) were eligible and randomized (74 to SGB and 39 to sham treatment), and 108 (95.6% of 113) completed the study. Baseline characteristics were similar in the SGB and sham treatment groups, with mean (SD) CAPS-5 scores of 37.6 (11.2) and 39.8 (14.4), respectively (on a scale of 0-80); 91 (80.0%) met CAPS-5 PTSD criteria. In an intent-to-treat analysis, adjusted mean total symptom severity score change was −12.6 points (95% CI, −15.5 to −9.7 points) for the group receiving SGB treatments, compared with −6.1 points (95% CI, −9.8 to −2.3 points) for those receiving sham treatment (P = .01).

CONCLUSIONS AND RELEVANCE In this trial of active-duty service members with PTSD symptoms (at a clinical threshold and subthreshold), 2 SGB treatments 2 weeks apart were effective in reducing CAPS-5 total symptom severity scores over 8 weeks. The mild-moderate baseline level of PTSD symptom severity and short follow-up time limit the generalizability of these findings, but the study suggests that SGB merits further trials as a PTSD treatment adjunct.

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Supplemental content

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Posttraumatic stress disorder (PTSD) is a source of considerable long-term morbidity and expense in military and civilian populations.[1,2] Treatment is challenging, requiring a multidisciplinary approach and active patient involvement, and it remains suboptimal because of chronicity, the long duration of therapy, and stigma.[3-7]

Stellate ganglion block (SGB) has been performed to treat sympathetically mediated pain conditions since the 1940s. The procedure involves injection of local anesthetic in and around the stellate ganglion (located at the base of the neck) to temporarily block its function. A 1990 report described a case of reflex sympathetic dystrophy co-occurring with PTSD[8] in which right-sided SGB treatments reduced PTSD symptoms. Mulvaney et al first reported using SGB to treat combat-associated PTSD in a small case series in 2010[9] and subsequently in 166 patients with a 3-month follow-up in 2014.[10] Multiple other case series showed promising results with anxiety symptoms associated with PTSD.[11-13] However, the first pilot, randomized clinical trial (RCT) of SGB for combat-associated PTSD[14] did not find a significant difference between the SGB group and the saline-injection control group. There have been procedural and methodologic criticisms of this study.[15] The mechanism by which temporary interruption of the cervical sympathetic chain could improve PTSD symptoms is not well understood. In the absence of level 1 evidence, we designed and conducted this RCT.

Key Points

Question How does stellate ganglion block compare with sham treatment in reducing the severity of posttraumatic stress disorder symptoms over 8 weeks?

Findings In this sham-controlled randomized clinical trial, 2 stellate ganglion block treatments 2 weeks apart were effective in reducing Clinician-Administered PTSD Scale for *DSM-5* total symptom severity scores over 8 weeks. The adjusted mean symptom change was −12.6 points for the group receiving stellate ganglion blocks, compared with −6.1 points for those receiving sham treatment, a significant difference.

Meaning Stellate ganglion block treatment warrants further study as a posttraumatic stress disorder treatment adjunct.

Methods

Trial Design and Oversight

From May 2016 through March 2018, participants were enrolled in a multisite, blinded, sham procedure–controlled randomized clinical trial to evaluate the effectiveness of right-sided SGB administered at weeks 0 and 2 on the acute symptoms of PTSD. Recruitment was discontinued when enrollment reached the number suggested by projections to yield sufficient statistical power. The primary outcome, the past-month Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5), was assessed at baseline and 8 weeks. Complete details about the trial are delineated in the protocol and statistical analysis plan (Trial Protocol in Supplement 1).

This trial was approved by the institutional review boards at study sites Tripler Army Medical Center (Honolulu, Hawaii) and Womack Army Medical Center (Fayetteville, North Carolina); Landstuhl Regional Medical Center (Landstuhl, Germany) deferred to Womack Army Medical Center, as did the institutional review board of the institution (RTI) of the lead author (K.L.R.O.). Approval was also granted by the US Army Medical Research and Materiel Command's Human Research Protection Office. At enrollment, all participants provided written informed consent. The study was registered at ClinicalTrials.gov (NCT03077919). A research monitor, independent of the investigative team and approved by Human Research Protection Office, served as an advocate for the safety of the study participants. The research monitor reviewed all amendments to the protocol and all adverse events, protocol deviations, and other relevant event reports, providing a summary report for submission to the institutional review board at each continuing review.

Trial Participants

Active-duty military personnel were recruited at 3 US military hospitals with Interdisciplinary Pain Management Centers. Key inclusion criteria included active-duty status, stable psychotropic medication dosing for at least 3 months, and a PTSD Checklist–Civilian Version *DSM-IV* (PCL-C-IV) score of 32 or greater at screening guidelines.[16] We used the PCL-C-IV to establish eligibility, as opposed to the PCL-5 or CAPS-5, because at the time of study design, these instruments did not yet have established cut points, and because a score of 32 was recommended by The National Center for PTSD for Department of Defense screening.[16] Also, the CAPS-5 focuses on symptoms associated with a single traumatic exposure, whereas this study considered total symptom experience (as assessed by the PCL-C and PCL-5). Key exclusion criteria included a prior SGB treatment; a history of schizophrenia, another psychotic disorder, bipolar disorder, or personality disorder; moderate or severe traumatic brain injury; symptoms of moderate to severe substance use disorder in the prior 30 days; suicidal ideation in the prior 2 months; or any ongoing stressor or condition deemed by the clinician to place the participant at risk for injury or a poor outcome (eg, undergoing a medical board evaluation because of concerns regarding fitness for duty or pending negative administrative or legal actions).

Trial Treatment

After completing the initial CAPS-5, participants were assigned to treating physicians with whom they did not have a prior patient-physician relationship. Central stratified block (sizes 3 and 6) randomization to SGB vs sham (a 2:1 ratio) occurred at their first interaction (during the baseline assessment and immediately before the study intervention at week 0). Stratification was by site (3 sites), and allocation was generated by a blinded statistician using SAS version 9.4 (SAS Institute). Only treating physicians and their procedure teams were informed of participants' group assignments, and this occurred immediately prior to interventions. Randomization was 2:1 to ensure adequate numbers of participants in the SGB

group, because the procedure was also offered to active-duty service members outside this study, and we believed prospective participants would be less likely to participate if they were randomized 1:1. Participants received study procedures at week 0 and week 2 and on arrival were administered a variety of instruments by blinded research coordinators.

Interventions were performed using real-time ultrasonography with an in-plane technique. For the week-2 visit, the initial procedure (SGB or sham) was reconfirmed to ensure identical reassignment. For the active SGB arm, 7 to 10 mL of ropivacaine, 0.5%, were injected around and into the site of the ganglion at the level of the C6 anterior tubercle. For the sham procedure, 1 to 2 mL of preservative-free normal saline were injected into deep musculature anterolateral to the anterior tubercle of C6. The participant was not informed of which procedure was performed. Although clinicians could not be blinded, their interactions with participants were scripted, and all medical personnel involved in the procedures were trained to avoid unblinding the participant by the setup (eg, both saline and anesthetic and both small and large syringes were available on the sterile tray), descriptions or requests (eg, using the term *medication* rather than *ropivacaine* or *saline*), or allowing observation of the actual procedure via reflecting surfaces (eg, mirrors, cabinets, monitor screens). Participants also were draped to limit their field of view. All other clinical and study personnel were unaware of treatment assignment. Because participants could not be blinded to temporary Horner syndrome (ptosis, miosis, and scleral injection) attributable to SGB, providers informed all participants, regardless of intervention group, of Horner syndrome symptoms.

Posttreatment assessments at weeks 4, 6, and 8 were completed by the participants on their own electronic devices using a secure web-based platform. After 8 weeks, the CAPS-5 was repeated by the same interviewer who conducted the initial CAPS-5.

Outcome Measures

The primary outcome was the change from baseline to week 8 in overall total symptom severity scores (TSSS) on the CAPS-5, which ranges from 0 to 80 points, with higher scores indicating greater PTSD symptom intensity. The CAPS-5 is considered the gold standard in PTSD evaluation.[17] An individual 10-point change in CAPS score from baseline to follow-up 8 weeks after treatment was defined as clinically meaningful (F. Weathers, PhD, written communication, January 12, 2017; P. Schnurr, PhD, written communication, January 26, 2017). We also examined the percentage of participants in each group who achieved a 10-point or greater improvement in TSSS and the percentage of participants by treatment group who met CAPS-5 clinical criteria for a PTSD diagnosis at baseline but no longer met those criteria at 8-week follow-up. We did not capture trauma type.

Secondary outcomes included estimated differences in mean scores at baseline and week 8 for the following symptoms: PTSD-associated symptoms, depression, distress, anxiety, pain, physical functioning, and mental functioning. The current military literature suggests these symptoms are highly correlated with PTSD.[18-21] The symptoms of PTSD were measured with the PTSD Checklist for *DSM-5* (PCL-5)[22] and the PTSD Checklist–Civilian Version (PCL-C-IV).[23] Depression was measured with the Patient Health Questionnaire (PHQ-9).[24] Distress was measured with the K-6 Distress Scale.[25] Anxiety was measured with the Generalized Anxiety Disorder 7-Item Scale.[26] Pain over the past 2 weeks was measured with a pain scale, and physical and mental functioning were measured with the 12-Item Short-Form Survey.[27] For all instruments except the 12-Item Short-Form Survey, higher scores indicated greater symptom severity.

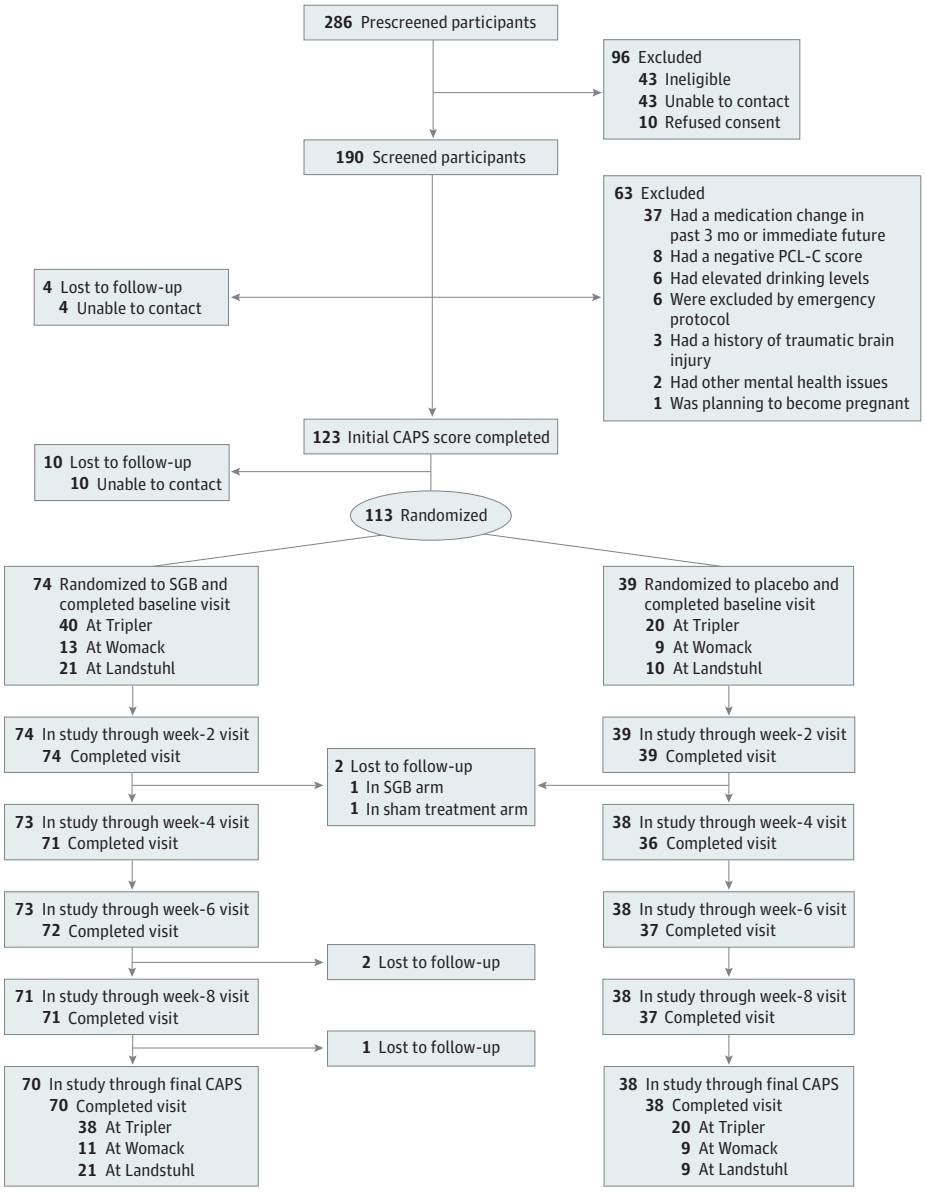
Information on adverse events was collected by participant report, with all reported adverse events simply tabulated. No formal statistical analyses of these events were planned.

Statistical Analysis

Sample-size calculations were based on detecting a 10-point difference in the CAPS-5 TSSS change from baseline to week 8 between the treatment groups, with a 2-sided α of .05 and an estimated SD of 15. Power to detect this 10-point difference ranged from 83% with an enrollment of 90 participants to 95% with an enrollment of 135 participants. All primary data analyses were performed according to the intent-to-treat principle, and an analogous secondary analysis was conducted on the primary outcome using a per-protocol population, defined during a masked data review as the subset of participants who adhered strictly to protocol interventions and end point assessments. Individuals were excluded if they withdrew or were lost to follow-up before completing the study, received an intervention that was not centrally randomized, knew the intervening physician, completed visits outside of the prespecified window, or had a screening-to-baseline interval of more than 31 days. A secondary analysis was performed with only participants who initially met diagnostic criteria for PTSD according to the CAPS-5, because investigators considered this population of particular clinical relevance. Missing data for both the primary and secondary outcomes were treated as missing at random for all analyses. Multiple imputation was used for missing data in the primary analysis; linear mixed models were used for to account for missing data in secondary analyses. All analyses were conducted using SAS version 9.4 (SAS Institute Inc) or more recent versions.

The correlations between the primary and secondary outcomes measured at baseline were assessed using the Pearson correlation coefficient. As specified in the protocol in Supplement 1, the primary outcome was assessed using linear models accounting for site (consistent with the randomization process) and initial CAPS-5 score effects (as a covariate to increase power). Residual plots were used to confirm models were appropriate for the study data. Analysis including an interaction term for site by treatment found no evidence of heterogeneity of treatment effect; therefore, no such interaction term is included in analysis of the primary outcome. The *P* value for the primary outcome is 2-sided and unadjusted for multiple comparisons. Any *P* value less than .05 was considered significant for the planned primary analysis. Further details of statistical analysis are available in the eAppendix in Supplement 2.

Figure 1. Study Screening, Enrollment, and Loss to Follow-up at Each Stage



Exclusion by emergency protocol indicates patients who were excluded because of suicidal ideation at a screening visit. Other patients were ineligible because of having previously received a stellate ganglion block (SGB), not being on active duty, not expecting to be stationed at their current location for at least 2 months, not having personal access to email and the Internet, or undergoing medical board/retirement or legal action at the time of the assessment. CAPS indicates Clinician-Administered PTSD Scale for *DSM-5*; PCL-C, PTSD Checklist–Civilian Version.

Results

Participants

A total of 286 individuals were prescreened to determine basic eligibility. Of the 243 determined to be eligible, 190 individuals were screened, and 113 individuals (59.5%; 100 men and 13 women; mean [SD] age, 37.3 [6.7] years) were randomized to treatment (74 to SGB treatment and 39 to sham treatment). Of these, 108 individuals (95.6%) remained in the study through the 8-week assessment (**Figure 1**).

Baseline Characteristics

Baseline characteristics were similar in the 2 treatment groups (**Table 1**). In particular, initial CAPS-5 TSSS were similar (**Figure 2**). Baseline PCL-5 mean (SD) scores (SGB group, 41.5 [14.0]; sham treatment group, 43.2 [18.1]) and the percentage of participants who met CAPS-5 criteria for a PTSD diagnosis (SGB group, 60 of 74 participants [81.1%]; sham treatment group, 31 of 39 participants [79.5%]) were also similar between the arms. There was no difference in CAPS-5 score by treatment site (eFigure in Supplement 2).

Primary End Point

Table 2 presents the primary and selected secondary outcomes by group. The mean change in CAPS-5 TSSS at 8 weeks among participants treated with SGB was greater than the reduction in participants treated with sham (Cohen *d*, 0.56 [SD, 0.09; 95% CI, 0.38-0.73]). The unadjusted

Table 1. Baseline Characteristics by Treatment Group

Characteristic	Patients, No. (%)	
	Stellate Ganglion Block Treatment (n = 74)	Sham Treatment (n = 39)
Male	64 (86.5)	36 (92.3)
Married	67 (90.5)	33 (84.6)
Military rank		
Junior enlisted	3 (4.1)	3 (7.7)
Noncommissioned officer	27 (36.5)	11 (28.2)
Senior enlisted	28 (37.8)	19 (48.7)
Warrant officer	5 (6.8)	3 (7.7)
Commissioned officer	11 (14.9)	3 (7.7)
Age at screening, mean (SD), y	37.4 (6.8)	37.0 (6.5)
Study site		
Womack	13 (17.6)	9 (23.1)
Tripler	40 (54.1)	20 (51.3)
Landstuhl	21 (28.4)	10 (25.6)
Concurrent behavioral therapy, yes	38 (51.4)	20 (51.3)
Time since PTSD diagnosis or onset of symptoms to enrollment, mean (SD), mo	48.1 (46.6)	49.8 (48.5)
Medication		
Antidepressant	30 (40.5)	14 (35.9)
Anxiolytic	13 (17.6)	8 (20.5)
Opioid	2 (2.7)	2 (5.1)
Other[a]	19 (25.7)	10 (25.6)
Clinician-Administered PTSD Scale for *DSM-5* total symptom severity scores, mean (SD)[b]	37.6 (11.2)	39.8 (14.4)
Met Clinician-Administered PTSD Scale for *DSM-5* criteria for PTSD, yes	60 (81.1)	31 (79.5)
PTSD checklist for the *DSM-5*, mean (SD)[c]	41.5 (14.0)	43.2 (18.1)
Symptoms, median (IQR)		
Depressive[d]	13.0 (8.0-17.0)	12.0 (8.0-18.0)
Anxiety[e]	13.0 (8.0-16.0)	13.0 (7.0-18.0)
Physical functioning, mean (SD)[f]	41.2 (11.3)	40.2 (9.8)
Mental functioning, mean (SD)[f]	41.0 (8.2)	42.0 (7.9)
Pain scale, median (IQR)[g]	5.0 (3.0-6.0)	5.0 (4.0-6.0)

Abbreviations: IQR, interquartile range; PTSD, posttraumatic stress disorder.

[a] Includes antipsychotic, stimulant, sleeping, anticonvulsant, nicotine, antismoking, and antihypertensive medications.

[b] On the Clinician-Administered PTSD Scale for *DSM-5*, the range for total symptom severity scores is 0 to 80, with higher scores indicating worse PTSD symptom intensity.

[c] On the PTSD Checklist for *DSM-5*, the range is 0 to 80 points, with higher scores indicating worse PTSD symptom intensity.

[d] Assessed by the Patient Health Questionnaire–9; the range is 0 to 27 points, with higher scores indicating worse depression symptom intensity.

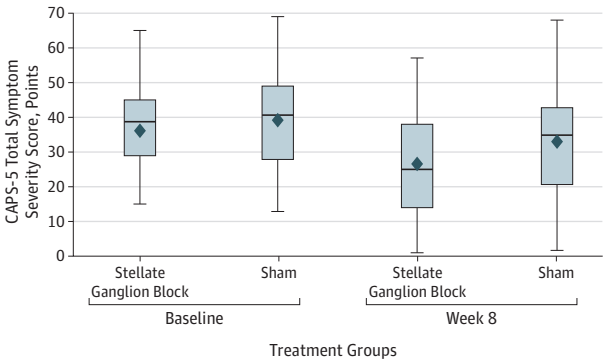
[e] Assessed by the Generalized Anxiety Disorder 7-Item Scale; the range is 0 to 21 points, with higher scores indicating worse anxiety symptom intensity.

[f] Assessed by the 12-Item Short-Form Survey T score with a mean of 50 and an SD of 10. Higher scores indicate better physical and mental health.

[g] Assessed by a pain rating in the past 2 weeks; the range is 0 to 10 points, with higher scores indicating more intense pain.

mean (SD) change in TSSS for the SGB group was −12.2 (12.9) points compared with −5.8 (8.2) points for the sham group.

Figure 2. Unadjusted Clinician-Administered Posttraumatic Stress Disorder Scale for *DSM-5* (CAPS-5) Total Symptom Severity Score at Baseline and Week 8 by Treatment Group



Within each box plot, the top of the box represents the 75th percentile, the diamond represents the mean, the horizontal line within the box represents the median, and the bottom of the box represents the 25th percentile. The upper and lower ends of the whiskers correspond to the highest value and the lowest value, respectively.

There was no evidence of a study-site effect and no significant site-by-treatment interaction (eTable 1 in Supplement 2). For each 1-point increase in initial CAPS-5 score, the model estimated an additional 0.2-point reduction at 8 weeks. Results from analyses of the per-protocol population and with those who fulfilled CAPS-5 diagnostic criteria for PTSD at baseline were consistent with those from the intent-to-treat analyses (eTable 2 in Supplement 2).

Secondary End Points

Evaluation of the secondary outcome measures, which were shown to have a strong correlation with the primary outcome (eTable 3 in Supplement 2), provides evidence of the effects of SGB for other outcome measures of clinical interest (Table 2). For all secondary outcomes, the estimated mean difference between arms at 8 weeks is consistent with the magnitude and direction of the CAPS-5 difference. Those receiving SGB had significantly improved scores on assessments of PTSD-associated symptoms (sham treatment group: mean [SD], −5.16 [13.99]; SGB group, mean [SD], −12.63 [14.34]; effect size [SD], 0.53 [0.20]), depression (sham treatment group: mean [SD], −12.69 [6.61]; SGB group, mean [SD], −12.57 [6.05]; effect size [SD], 0.60 [0.20]), distress (sham treatment group: mean [SD], −0.16 [4.59]; SGB group, mean [SD], −2.52 [4.86]; effect size [SD], 0.49 [0.20]), anxiety (sham treatment group: mean [SD], −1.22 [4.93]; SGB group, mean [SD] −4.42 [5.80]; effect size [SD], 0.58 [0.20]), pain symptoms (sham treatment group: mean [SD], −0.03 [1.44]; SGB group, mean [SD] −0.56 [1.65]; effect size [SD], 0.34 [0.20]), physical functioning (sham treatment group: mean [SD], −0.37 [7.02]; SGB group, mean [SD] −2.56 [8.15]; effect size [SD], −0.38 [0.20]), and mental functioning (sham treatment group: mean [SD], −0.66 [7.21]; SGB group, mean [SD] 1.74 [7.58]; effect size [SD], −0.32 [0.20]) compared with those receiving the sham procedure.

Table 2. Unadjusted Means and Effect Size for Primary and Secondary Outcomes by Treatment Groups

Outcome Measure	Unadjusted Mean Score (SD)		Effect Size[a] (SD) [95%CI]
	Sham Treatment (n = 39)	Stellate Ganglion Block (n = 74)	
Primary Outcome			
Clinician-Administered PTSD Scale for *DSM-5* total symptom severity scores[b]			
Baseline[c]	39.82 (14.23)	37.61 (11.13)	NA
8-wk follow-up[d]	33.68 (15.6)	25.67 (14.13)	NA
Mean change[d,e]	−5.79 (8.19)	−12.16 (12.86)	0.56 (0.09) [0.38-0.73]
Secondary Outcomes			
PTSD Checklist for *DSM-5*[f]			
Baseline	43.23 (18.13)	41.54 (14.03)	NA
8-wk Follow-up	38.11 (18.23)	29.49 (19.29)	NA
Mean change	−5.16 (13.99)	−12.63 (14.34)	0.53 (0.20) [0.14-0.91]
PTSD Checklist-Civilian Version[f]			
Baseline	54.95 (15.67)	53.30 (13.64)	NA
8-wk Follow-up	50.65 (17.04)	42.41 (17.47)	NA
Mean change	−4.30 (14.17)	−11.45 (13.40)	0.52 (0.20) [0.14-0.91]
Patient Health Questionnaire-9[f]			
Baseline	12.69 (6.61)	12.57 (6.05)	NA
8-wk Follow-up	11.76 (6.25)	8.68 (6.02)	NA
Mean change	−0.92 (4.78)	−4.11 (5.55)	0.60 (0.20) [0.21-0.99]
Generalized Anxiety Disorder 7-Item Scale[f]			
Baseline	12.49 (5.50)	12.39 (5.35)	NA
8-wk Follow-up	11.19 (6.38)	8.11 (6.02)	NA
Mean change	−1.22 (4.93)	−4.42 (5.80)	0.58 (0.20) [0.19-0.97]
K-6 Distress Scale[f]			
Baseline	10.33 (6.01)	10.08 (5.55)	NA
8-wk Follow-up	10.00 (6.25)	7.80 (6.41)	NA
Mean change	−0.16 (4.59)	−2.52 (4.86)	0.49 (0.20) [0.11-0.88]
Pain[f]			
Baseline	4.95 (2.21)	4.61 (2.40)	NA
8-wk Follow-up	4.86 (2.30)	4.10 (2.51)	NA
Mean change	−0.03 (1.44)	−0.56 (1.65)	0.34 (0.20) [−0.04 to 0.72]
12-Item Short-Form Survey			
Mental functioning[f]			
Baseline	40.16 (9.84)	41.24 (11.32)	NA
8-wk Follow-up	40.17 (9.50)	42.83 (10.22)	NA
Mean change	−0.66 (7.21)	1.74 (7.58)	−0.32 (0.20) [−0.71 to 0.06]
Physical functioning[f]			
Baseline	42.01 (7.87)	41.04 (8.16)	NA
8-wk Follow-up	41.28 (8.18)	43.43 (8.33)	NA
Mean change	−0.37 (7.02)	2.56 (8.15)	−0.38 (0.20) [−0.76 to 0.01]

Abbreviations: NA, not applicable; PTSD, posttraumatic stress disorder.

[a] Cohen *d* effect size.

[b] Multiple imputation was performed for missing data on the primary outcome (5 participants did not complete the week-8 Clinician-Administered PTSD Scale for *DSM-5*).

[c] Adjusted for site.

[d] Adjusted for site and baseline Clinician-Administered PTSD Scale for the *DSM-5* total symptom severity score.

[e] Adjusted mean reductions in total symptom severity scores from baseline to week 8 by treatment group from the per-protocol analysis and secondary analysis among those who fulfilled the Clinician-Administered PTSD Scale for the *DSM-5* diagnostic criteria for PTSD at baseline were consistent with those from the intent-to-treat analyses.

[f] Adjusted for site, sex, age, visit, and interaction between visit and treatment.

Of note, the proportions of participants by group who correctly guessed their treatment arm did not differ significantly from 0.5. This would be expected as a random guess of study arm (data not shown).

Adverse Events

Of the 6 adverse events reported, none were serious. Details are provided in eTable 4 in Supplement 2.

Discussion

This RCT involving active-duty service members with PTSD symptoms (with nearly 80% meeting PTSD criteria) showed that 2 right-sided SGBs produced a clinically significant reduction in symptoms at 8 weeks and that this decrease was greater than the symptom reduction experienced by those who

received a sham procedure. Those with higher initial CAPS-5 scores had greater improvements.

These results are congruent with case reports and case series that have reported improvements in PTSD symptoms after SGB. Our results expand on 1 prior small, single-site pilot trial of SGB for PTSD in military personnel,[14] which failed to find significant differences between the active-treatment group and the sham-treatment group. The difference in findings may be explained in several ways, including provision of 2 SGBs instead of 1, the larger size of the sample (113 participants vs 42 participants) and increased statistical power, the increased volume of ropivacaine (7-10 mL vs 5 mL), the avoidance of intravenous sedation, and more rigorous exclusion criteria. Our finding of an unadjusted mean change in CAPS-5 TSSS of −12.2 points is similar to mean change scores seen in a 2018 noninferiority trial of written exposure therapy compared with cognitive processing therapy (−12.8 points and −15.7 points, respectively).[28]

This is the first RCT to show effectiveness of right-sided SGB for the treatment of PTSD symptoms. Secondary analysis among those who met clinical criteria for PTSD diagnosis were consistent with our findings among the full group intent-to-treat analysis. Our analysis of scores from the PCL-5, PCL-C, PHQ-9, Generalized Anxiety Disorder 7-Item Scale, the K-6 Distress Scale, and pain scale is relevant for clinical interpretability, because the conditions assessed by these measures are frequently comorbid with PTSD.

We chose the sham intervention because pressure and/or temperature differences associated with administration of saline in close proximity to the stellate ganglion might interrupt nerve transmission. Injections of equal volumes of either normal saline or local anesthetic in and around the stellate ganglion would allow blinding of both the patient and the treating physician, but it would have been impossible to determine if clinical effects were attributable to the placebo effect or a direct action of either injection.

Stellate ganglion block is a safe, routine procedure.[29-31] Usually, a right-side SGB is performed because of the typical neuroanatomical association of the right central autonomic network and the maintenance of chronic sympathetic responses.[32,33] A 1992 survey based on 45 000 SGBs done without fluoroscopic or ultrasonographic guidance found a serious adverse event rate of 1.7 events per 1000 SGBs.[31] The most common serious adverse event was generalized seizures from inadvertent intravascular injection of a local anesthetic. A 2015 publication by McLean showed no adverse outcomes from 250 SGBs conducted under fluoroscopy and suggested that ultrasonographic guidance would be even safer[34]; the widespread adaptation of ultrasonography to perform SGB[29] should reduce complications.[30]

Limitations

This trial supports the effectiveness of SGB treatment, but it should be viewed within its limitations. It benefited from a blinded, sham-procedure-controlled, randomized design. Treating physicians were unable to be blinded to the interventions they performed, but their interactions with the participants were limited to the procedure suite, and their communications with participants were scripted. Stellate ganglion block often causes Horner syndrome, which may be noticed by a participant. All personnel interacting with participants were trained to not draw attention to these potentially unblinding signs. Although there was no evidence of differential unblinding by Horner syndrome between the study arms and the confidence intervals for each of the estimates included 0.5 (data not shown), participants' potential recognition of these signs is a limitation.

This study's population was highly specified, with patients included only if they had stable psychotropic medication usage, were not undergoing administrative evaluations, and did not have a history of moderate or severe traumatic brain injury; this further limits clinical generalizability. The overall severity level of PTSD symptoms in the sample was low to moderate, potentially limiting generalizability to patients routinely seen in outpatient practice. However, we view inclusion of active-duty service members with subthreshold signs as a strength, given emerging evidence suggesting PTSD symptoms may be best seen as a continuum.[35-37] Further, inclusion of these individuals follows our original intention of determining whether SGB is effective in treating PTSD symptoms, even if patients were below a diagnostic threshold. Finally, although overall symptom reduction was clearly shown, a number of participants who fulfilled PTSD diagnostic criteria at baseline still fulfilled those criteria at 8 weeks.

Conclusions

Future studies should explore possible mediating mechanisms, the effectiveness of SGB (single and multiple) beyond 8 weeks, and the effectiveness of the procedure in a more typical clinical population. These results showed those with higher baseline TSSS had greater symptom reduction at 8 weeks, meriting more focused evaluation of active-duty service members with higher symptom scores. Additional research should also focus on any adverse effects, either short term or long term, of the procedure. Finally, establishing a mechanism of action may be important in improving understanding of the causative mechanisms of PTSD. Further investigations could identify individual characteristics (including biomarkers) that are associated with PTSD symptom responsiveness to SGB, as well as the role of SGB in a multimodal, interdisciplinary treatment approach to PTSD.

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