QUERI

Evidence Brief: Effectiveness of Stellate Ganglion Block for Treatment of Posttraumatic Stress Disorder (PTSD)

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Prepared by:
Evidence-based Synthesis Program (ESP)
Coordinating Center
Portland VA Health Care System
Portland, OR
Mark Helfand, MD, MPH, MS, Director

Investigators:
Kim Peterson, MS
Donald Bourne, BS
Johanna Anderson, MPH
Katherine Mackey, MD
Mark Helfand, MD, MS, MPH

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

Posttraumatic stress disorder (PTSD) is the third most common psychiatric diagnosis among Veterans seen in the Veterans Health Administration (VHA). PTSD can be debilitating, leading to a decline in quality of life (QoL) and causing significant medical, mental health, interpersonal, and social impairment. First-line treatments for PTSD include psychotherapy, pharmacotherapy, or their combination; however, several challenges have been identified in their effectiveness and reach. Stellate ganglion block (SGB), also called cervical sympathetic block, has been promoted as an adjuvant in individuals with PTSD who have not fully responded to conventional therapies. One proposed mechanism of action is that SGB might inhibit connections between the peripheral sympathetic nerve system and regions of the cerebral cortex thought to be abnormally activated in PTSD. Some proposed benefits of SGB for PTSD include (1) it may destigmatize treatment by offering a biologic approach to PTSD management, (2) it may offer a fast-acting treatment alternative with improvements reported within minutes to days of the procedure, and (3) it may increase compliance as it does not require continuous daily or weekly administration.

Our objectives were (1) to determine to what extent SGB provides clinically relevant benefits for patients with PTSD, (2) to determine SGB's potential harms, and (3) to identify Veterans who are most likely to benefit from SGB.

In uncontrolled, unblinded, retrospective case series, SGB for PTSD had high rates of rapid clinical improvement in PTSD symptoms (70% to 75%). However, findings from the first randomized trial (RCT) of SGB for PTSD were inconclusive, neither confirming nor refuting findings from case series. In the RCT, the range of mean percent PTSD improvement after one round of SGB was 5.4% to 14.7%, and was 12.1% to 21.2% after the second round, which was no better than an injection of saline. However, certain population characteristics and intervention and comparator techniques used in the RCT were suboptimal for determining efficacy and it was too small to estimate rates of serious complications. The majority of study participants were active-duty military personnel with unknown psychological and medical comorbidities and previous conventional therapy trials.

The pattern of very encouraging results in a few case series, followed by a negative RCT, is quite common. The pattern suggests that, while it is possible that some patients benefit, the response rates seen in case series will not hold up in actual practice. Substantial uncertainty remains about the potential harms of SGB as well. The RCT, as well as RCTs of SGB for complex regional pain syndrome (CRPS), were inadequately powered to support or refute findings from the frequently cited, but methodologically weak, 1992 German questionnaire survey of 45,000 SGBs that found 1.7 instances of severe complications per every 1000 individuals.

Background

The ESP Coordinating Center (ESP CC) is responding to a request from Office of Community Engagement's (OCE) Center for Compassionate Innovation (CCI) for an evidence brief on the effectiveness of stellate ganglion block (SGB) for treatment of posttraumatic stress disorder (PTSD). Findings from this evidence brief will be used to inform Subject Matter Experts' consideration of clinical use and research and program prioritization of SGB for PTSD in the VA.

Methods

To identify studies, we searched MEDLINE®, CINAHL, and more, through December 2016. We used prespecified criteria for study selection, data abstraction, and rating internal validity, and strength of the evidence. See our PROSPERO protocol for our full methods.

Evidence was also insufficient to determine which Veterans are most likely to benefit from SGB for PTSD. Clinical factors that could be used to select patients include failure to respond to, or high risk of noncompliance with, conventional therapies, low risk of bleeding and other complications, patient preference, and availability of SGB.

To determine whether some patients benefit, and which Veterans are most likely to benefit, new RCTs designed to correct the deficiencies of the first trial should be conducted. These trials, as well as a registry that adheres to methodological standards, should also be designed to ascertain the frequency and severity of side effects. If further investigation of SGB for PTSD is prioritized in VA, it should include a clear plan to address the following identified important limitations that are also characteristic of research on conventional treatments for PTSD as a whole: (1) adequately powering studies to measure clinically relevant benefits and harms; (2) improved documentation of predominant PTSD symptom types, index trauma types, and comorbidities; (3) improved documentation of prior and concomitant PTSD treatments; and (4) use of longer follow-up periods to determine sustainability. We did not investigate whether SGB should be a higher priority than other innovative treatments for PTSD, such as ketamine, MDMA (±3,4-Methylenedioxymethamphetamine)-assisted psychotherapy, and cranial electrical stimulation, or comparative costs.

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The ESP Coordinating Center (ESP CC) is responding to a request from Office of Community Engagement's (OCE) Center for Compassionate Innovation (CCI) for an evidence brief on the effectiveness of stellate ganglion block (SGB) for treatment of posttraumatic stress disorder (PTSD). Findings from this evidence brief will be used to inform Subject Matter Experts' consideration of clinical use and research and program prioritization for SGB for PTSD in VA.

BACKGROUND

Posttraumatic Stress Disorder (PTSD) and Its Impact

Posttraumatic stress disorder (PTSD) is a trauma- and stress-related disorder than can develop following exposure to a traumatic event. PTSD can affect survivors not only of combat experience, but any life-threatening event or traumatic emotional experience. According to the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-5), PTSD is defined by 4 clusters of symptoms: (1) intrusive re-experiencing of a traumatic event, (2) avoidance of trauma-related stimuli, (3) negative changes in mood and cognition, and (4) persistent physiological arousal and reactivity. Diagnosis of PTSD requires that the symptoms significantly impair functioning and last for at least one month.[1]

PTSD is the third most common psychiatric diagnosis among Veterans seen in the Veterans Health Administration (VHA).[2] The latest reports on VHA healthcare utilization by Operation Enduring Freedom/ Operation Iraqi Freedom/ Operation New Dawn (OEF/OIF/OND) Veterans shows that 378,993 Veterans have been diagnosed with PTSD at some point between FY 2002 and FY 2015.[3] The lifetime prevalence of PTSD in Veterans (12-30%)[4-9] has consistently been found to be greater than that observed in the general population (7%).[10,11] According to research summarized by the Department of Veterans Affairs National Center for PTSD (NCPTSD), experts estimate that up to 20% of Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) Veterans,[4-6] up to 12% of Gulf War Veterans,[7] and up to 30% of Vietnam War Veterans[8,9] have experienced PTSD. Consequently, the need for PTSD treatment may increase within the Veteran population in the coming years.[12]

PTSD can be debilitating and lead to a decline in quality of life (QoL).[13] Mental health impairments can include increased risk of suicide, depression, other mood/anxiety disorders, eating disorders, and substance use disorders.[14-19] PTSD has also been linked to increased rate of aging and early mortality.[20] Interpersonal and social impairments can include strained marital and family relations, parenting difficulties, and difficulty finding and maintaining employment.[21-26] As a result, overall healthcare service needs are high among people with PTSD.[27] Congressional Budget Office data from fiscal years 2004 through 2009 indicate that, compared to Veterans without PTSD, those with PTSD were more likely to use VHA healthcare services in general – regardless of their relationship to a PTSD diagnosis.[27] In 2015, the RAND Center for Military Health Policy Research reported that for OEF/OIF Veterans with PTSD, the

estimated 2-year costs to society – from healthcare needs and lost productivity – were substantial.[6]

Challenges of Conventional Treatments

Commonly recommended first-line treatments for PTSD include psychotherapy, pharmacotherapy, or their combination.[28-33] Examples of psychotherapy modalities used for PTSD include: Exposure-based therapies (ET), Cognitive-based therapies (CPT), Stress Inoculation Training (SIT), and Eye Movement Desensitization and Reprocessing (EMDR).[28] These psychotherapies include 5 core components: (1) narration, (2) cognitive restructuring, (3) in vivo exposure, (4) stress inoculation skills (*eg*, relaxation), and (5) psychoeducation.[34] Pharmacotherapy for PTSD typically consists of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). If unsuccessful, treatment may expand to mood stabilizers, anticonvulsants, antipsychotics, or other agents.

However, several challenges have been identified in the effectiveness and reach of common psychological and pharmacological treatments for PTSD.[34] The overall success of current PTSD treatments is low and variable, with rates of remission generally ranging from 30% to 40%.[35,36] Whether treatment success differs based on particular clinical characteristics is largely unknown.[35] According to surveys of Veterans with PTSD, barriers to seeking and accessing treatment include concerns about treatment, emotional readiness for treatment, stigma, and logistical difficulties.[37,38] Contributors to poor compliance with common psychological and pharmacological treatments may include the many weeks to months required, potential side effects, and co-morbidities.[39] Due to these limitations, there is a great need for innovative approaches to further improving the health and well-being of people with PTSD.

What is Stellate Ganglion Block (SGB)?

The stellate ganglion, part of the sympathetic nervous system, is a cluster of nerve cell bodies located between the C6 and C7 vertebrae. Injection of local anesthetic to the stellate ganglion, a procedure known as stellate ganglion block (SGB), inhibits sympathetic nerve impulses to the head, neck, and upper extremities. SGB is an outpatient procedure, performed by anesthesiologists or interventional pain management physicians, that has been used to treat various disorders including complex regional pain syndrome, hot flashes, migraines, facial pain, and upper extremity pain.

Because the stellate ganglion is connected to brain regions thought to be abnormally activated in PTSD, such as the amygdala, SGB has been explored as a potential alternative treatment option for PTSD.[40] Studies that have examined brain imaging before and after PTSD treatment provide potential evidence of this biological rationale for the effect of SGB on PTSD. A 2015 study comparing fluorodeoxyglucose (FDG) PET brain scans of 5 Veterans with combat-related PTSD one week before and after undergoing right-sided SGB found that the right amygdala and hippocampal areas were relatively overactive when PSTD symptoms were more prominent.[41] A 2016 longitudinal study comparing functional MRIs and symptom scores of 72 Veterans with and without PTSD during which PTSD patients received trauma-focused therapy suggested that higher baseline dorsal anterior cingulate cortex (dACC), insula, and amygdala activation may predict poor response to PTSD treatment.[42]

SGB has also been associated with biologic markers of sedation. A 2014 study on the effects of SGB in rats found that SGB was associated with decreased EEG activity, suggesting a sedative effect.[43] Similarly, a 2015 study of healthy adult volunteers found that SGB was associated with a sedative effect compared to sham as measured by the bispectral index system (based on EEG) and Observer's Assessment of Alertness/Sedation scores.[44]

The specific mechanism of action by which SGB may mitigate PTSD symptoms remains incompletely understood. SGB results in peripheral vasodilation, but the mechanism by which SGB impacts symptoms of PTSD is likely more complex. A proposed explanation for the prolonged effectiveness of SGB on PTSD, as well as symptoms of hot flashes and complex regional pain syndrome, is that application of local anesthetic to the stellate ganglion leads to a reduction in nerve growth factor and a resulting decrease in sympathetic nerve sprouting and brain norepinephrine levels.[45]

Ropivacaine or bupivacaine, 7 cc of 0.5% solution, are the most common anesthetic types and dosages used in SGB.[39] To avoid potential serious adverse effects of inaccurate needle placement to the anatomy surrounding the stellate ganglion, use of image-guidance techniques such as ultrasound, fluoroscopy, or computed tomography are recommended to help visualize the injection area. SGB performance also requires the availability of continuous vital sign monitoring technology and resuscitative equipment and personnel to monitor and respond to changes in respiration and circulation that may occur as a result of unintentional intravascular injections. Identification of a successful SGB is made by diagnosing temporary Horner's syndrome occurring within 15 minutes of the procedure – a constricted pupil, weak and droopy eyelid, decreased sweating, and potential inset eyeball – which is recommended to be quantitatively graded by a third-party medical professional.[46]

Regulation, Guidance, and Advocacy for SGB

Ropivacaine and bupivacaine are FDA-approved for production of local or regional anesthesia for surgery and acute pain management, including in the head and neck area. Injection of these drugs into the stellate ganglion for PTSD is considered an "off-label" use for a different disease than described in the drug label, which is legal and unregulated. PTSD treatment guidelines from the VA/DoD and other professional societies do not reference SGB,[28,29,33] but in 2015, Lieutenant Colonel Sean W. Mulvaney, MD and colleagues published clinical guidelines in the Journal of Special Operations Medicine.[46] The main source of public advocacy for SGB for PTSD comes from pain management anesthesiologist, Eugene Lipov, MD, who founded the Global Post-Traumatic Stress Injury Foundation (GPTSIF) to facilitate access to innovative biological treatment for PTSD,[47] and who has made numerous network television appearances and authored numerous articles about SGB for PTSD.[48-52] Advocates such as Drs. Lipov and Mulvaney have promoted SGB for PTSD primarily based on the notably high rates of clinically meaningful improvement (70% to 75%) in uncontrolled case series of predominantly males in their early forties who were active-duty military with combat-related PTSD.[39,53,54] Advocates commonly describe SGB as safe, with the most frequently cited supporting evidence coming from a questionnaire survey with a 51% response rate that included responses from 39 West German departments of anesthesiology, representing approximately 45,000 SGBs, that reported low rates (1.7 per 1000) of severe complications such as convulsions.[55]

What Are Possible Roles for SGB for PTSD?

SGB for PTSD has typically been promoted as an adjuvant in individuals who have not fully responded to conventional therapies.[53] Some proposed benefits of SGB for PTSD include (1) it may destigmatize treatment by offering a biologic approach to PTSD management,[39] (2) it may offer a faster-acting treatment alternative with improvements reported within 30 minutes to days of the procedure,[39] and (3) it increases compliance as it does not require continuous daily or weekly administration.[53]

Objectives of this Evidence Review

Our objectives were (1) to determine to what extent SGB provides clinically relevant benefits for patients with PTSD, (2) to determine SGBs potential harms, and (3) to identify patients who are most likely to benefit from SGB.

METHODS

The ESP included studies that met the following criteria:

- ***P****opulation:* Adults with posttraumatic stress disorder (PTSD)
- ***I****ntervention*: Stellate ganglion block (SGB)
- ***C****omparator*: Any
- ***O****utcomes:*
  - *Clinical health outcomes:* Remission and % of patients achieving minimally important difference in PTSD symptom scores (% responding). Although no definitive guidance has been established for prioritization of instruments and thresholds to use to best measure clinically significant improvement in PTSD symptoms, we used these as our general guideposts: ≥ 15-point reduction on the Clinically-Administered PTSD Scale (CAPS),[56] a ≥ 10-point reduction on the PTSD Checklist (PCL)[57] and a ≥ 30% reduction in general[58]
  - *Intermediate benefits:* Change in symptom scale scores for PTSD, depression, functional status, quality of life
- *Harms:* Complications including arrhythmia; hypotension; hematoma due to injury to adjacent vascular structures; thoracic duct injury; injection of local anesthetic into the intravascular, intrathecal, epidural space, or brachial plexus; direct spread of local anesthetic to the recurrent laryngeal or phrenic nerves; soft tissue infection; osteitis; and meningitis
- ***T****iming:* Any study follow-up durations
- ***S****etting*: Any
- ***S****tudy design:* Systematic reviews, randomized controlled trials, or concurrently controlled cohort studies. Case series will be briefly discussed to provide frequently cited context, but will not be formally evaluated due to their inherent weaknesses[59,60]

To identify articles relevant to the key questions, we searched MEDLINE®, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, CINAHL, PsychINFO, and PILOTS on 12/30/2016 and updated on 2/7/2017, using terms for *stellate ganglion block* and *PTSD*. (See Appendix A in the supplemental materials for complete search strategies.) We limited the search to articles involving human subjects available in the English language. We sought additional citations through hand-searching reference lists, relevant journals, and consultation with content experts. Study selection was based on the eligibility criteria described above. We searched numerous other sources to identify unpublished and less-accessible forms of data (Appendix A in supplemental materials). Titles, abstracts, and full-text articles were reviewed by one investigator and checked by another. All disagreements were resolved by consensus.

Four reviewers (KP, DB, JA, KM) independently assessed the internal validity of the randomized controlled trial using criteria established by the Drug Effectiveness Review Project.[61] This approach involves assigning ratings of good, fair, or poor quality to reflect the adequacy of methods for randomization, allocation concealment, blinding, outcome measurement and analysis, and acceptability of levels of adherence and attrition. One reviewer abstracted data from the randomized controlled trial on its design, patient characteristics, and results for each included outcome and these were then checked by another. All disagreements were resolved by consensus.

We graded the strength of the evidence based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.[62] This approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Strength of evidence is graded for each key outcome measure and ratings range from high to insufficient, reflecting our confidence that the evidence reflects the true effect. Strength of evidence grades were first completed by one reviewer and checked by another and all disagreements were resolved using consensus.

A draft version of this report was reviewed by 3 technical experts and clinical leadership. Their comments and our responses are presented in the supplemental materials.

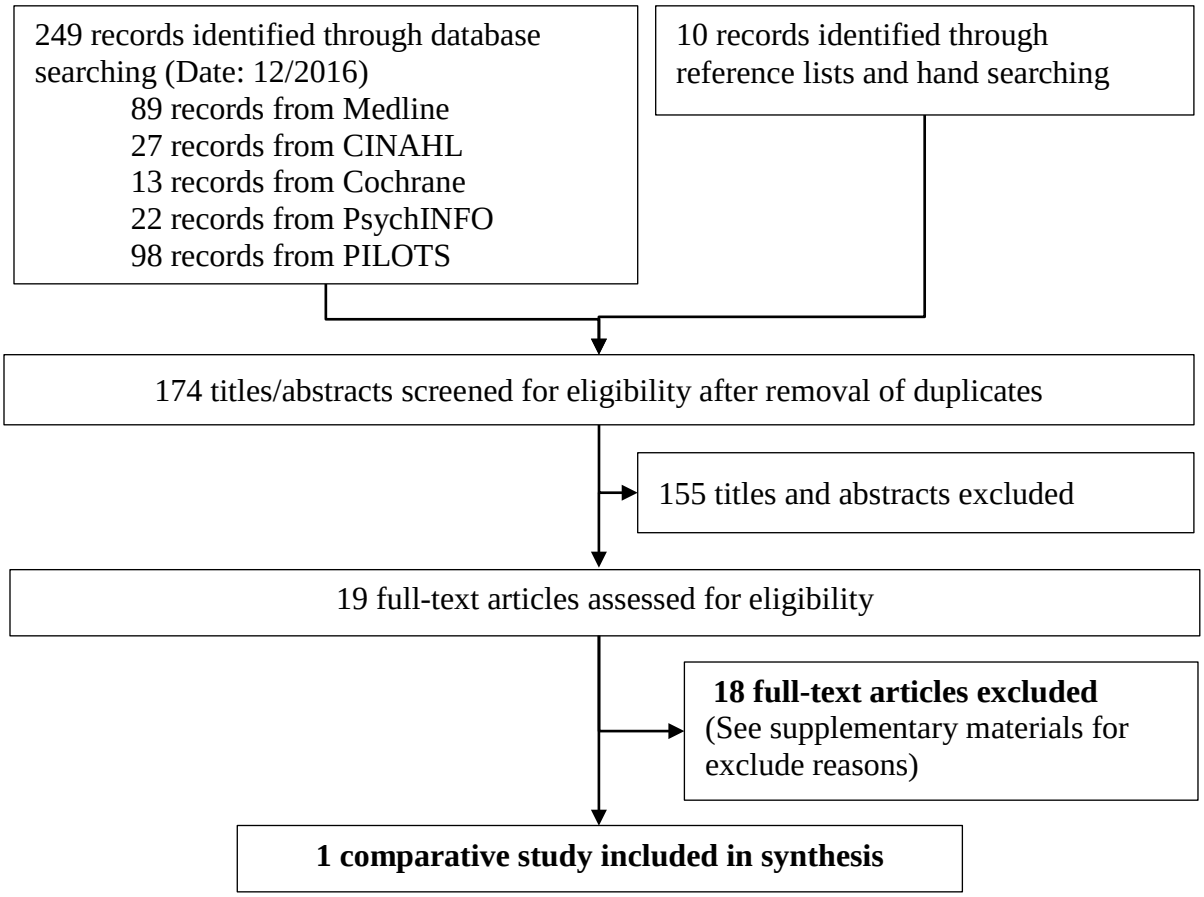
The complete description of our full methods can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42016053908).

RESULTS

LITERATURE FLOW

Searches resulted in 174 potentially relevant articles after removal of duplicates (Figure 1). Of these, we identified one study with a concurrent comparison group, which was an RCT.[63] Detailed reasons for exclusion are provided in Appendix B of the supplemental materials.

Figure 1: Literature Flowchart



TO WHAT EXTENT DOES SGB PROVIDE CLINICALLY RELEVANT BENEFITS FOR PTSD?

Case Series

Uncontrolled case series of predominantly males in their early forties who were active-duty military with combat-related PTSD (N=202) have found high rates of clinically meaningful improvement with SGB (70% to 75%),[39,64,65] including in those with extreme PTSD.[65] Case series can be valuable in providing an initial indication of promise. However, their lack of a control group is a major drawback that prevents drawing conclusions regarding treatment effect.[60] For example, it is quite common to see very encouraging results in a few case series, followed by smaller benefits or contradictory findings in subsequent RCTs.[66]

Randomized Trials

To date there is only one published randomized trial on SGB for PTSD.[63] This study compared ultrasound-guided SGB with 5 cc of 0.5% ropivacaine to an inactive sham procedure with normal saline, in 42 primarily limited-duty male military participants with both combat and noncombat PTSD.[63] SGB was administered on the right side of the neck, generally at the C6 level. The main finding of this RCT was that at one week and one month after the first round of treatment, the magnitude of mean reduction in PTSD symptoms for SGB and sham neither met the proposed criteria for clinical relevance nor were different between groups, regardless of whether they were measured based on the Clinically-Administered PTSD Scale (CAPS) or the PTSD Checklist (PCL) (Table 1). In the subset of patients who received a second round of SGB or sham, the SBG group reached a clinically significant reduction after one week based on the CAPS, but not the PCL, but again there were no significant differences between SGB and sham.

Because these findings come from a single study with imprecise findings, moderate methodological limitations, and did not directly focus on clinically relevant outcomes or use the most common administration techniques, they provide an insufficient basis upon which to draw conclusions about SGB for treatment of PTSD in Veterans. Although this study did well in using blinded outcome assessors, we rated the methodological quality of this trial as fair because there were more active-duty participants in the SGB group (96% vs 73%), attrition was high overall (57%) – primarily due to "lost to follow-up at 3 month post treatment or completed outside of 3 month post treatment window" – and was higher in the SGB group (67% vs 40%), and the study did not report on or account for potential between-group differences in concurrent PTSD treatments. Although no definitive guidance has been established for prioritization of instruments and thresholds to use to best measure clinically significant improvement in PTSD symptoms, this trial did not report on the key outcomes that have been suggested as general guideposts: ≥ 10- to 15-point reduction on the CAPS,[56] a ≥ 10-point reduction on the PCL,[57] and/or a ≥ 30% reduction in general.[58] Although in previous case series the most commonly used anesthetic type and dosage used have been 7 cc of ropivacaine, or bupivacaine 0.5% solution, this trial used 5 cc ropivacaine, a 28%-lower dose, and provided no rationale for doing so. Also, it is unclear whether the ropivacaine injection actually reached the stellate ganglion in all patients. Although the stellate ganglion is typically located at C6 to C7, the level of target needle placement was C5 to C6 in this study. Although the study author confirmed that the injection was "typically" at C6, some could have been at C5 and missed the stellate ganglion. Other commonly criticized limitations of this trial that may have altered SGB effects include that (1) it used an inappropriate population who were in the process of disability evaluation and may have had secondary financial incentives to resist treatment,[63,67] and (2) the use of saline instead of an active control that mimicked the side effects of SGB was potentially inadequate and may have reduced the effectiveness of the blinding, as patients may have been able to easily tell if they received SGB or sham based on the occurrence of the Horner's syndrome eye droop. Effectiveness of the blinding was not formally assessed.

Table 1. Mean Change from Baseline for SGB versus Sham in the RCT

	First Round				Second Round			
	One week		One month		One week		One month	
Scale	SGB	Sham	SGB	Sham	SGB	Sham	SGB	Sham
CAPS	-12.7 N=27	-11.3 N=15	-6.6 N=27	-8.8 N=14	-17.8 N=18	-9 N=12	-7.8 N=14	-4.3 N=12
PCL	-3.6 N=26	-4.1 N=15	-2.0 N=27	-2.4 N=13	-7.9 N=17	-4.6 N=12	-6.5 N=12	-6.3 N=12

Abbreviations: CAPS = Clinically-Administered PTSD Scale; PCL = PTSD Checklist; SGB = Stellate Ganglion Block

WHAT ARE SGB'S POTENTIAL HARMS?

Substantial uncertainty remains about the potential serious harms of SGB due to a lack of adequately powered studies using clearly reliable and valid assessment methods. Although the frequently cited 1992 West German questionnaire survey of approximately 45,000 SGBs from 39 anesthesiology departments appears to provide the most precise estimates of serious complications, it has important methodological weaknesses that seriously limit our confidence in its findings. At 1.7 per 1000, rates of severe complications, such as convulsions, were reportedly low in this questionnaire survey.[55] However, we have no information about what methods were used to collect and analyze these data, such as the rating criteria used, how they were implemented, what the time period was between the procedure and outcome assessment, what data monitoring standards were used to reduce error, the level of which and how missing data were handled, and how consistent these factors were across departments. Without this information, we cannot be sure of the reliability and validity of these data. Compared to the "blind" technique used in the West German SGBs from the survey, we agree that the modern standard of using image-guidance techniques has the potential to increase needle placement accuracy and result in lower severe complications than reported in this survey. However, we have no way of knowing how much or in what direction the potential limitations in the outcome assessment methods may affect the reported rates.

Although RCTs of SGB for PTSD,[63] and CPRS,[68] and case series of SGB for PTSD,[39,54,69] may have used stronger assessment methods, their findings are limited by imprecision and do not importantly improve our knowledge about the risk of serious complications. In the RCT and case series of SGB for PTSD,[63] there were no instances of serious complication such as arrhythmia, hypotension, hematoma due to injury to adjacent vascular structures, thoracic duct injury, injection of local anesthetic into the intravascular, intrathecal, or epidural space or brachial plexus, direct spread of local anesthetic to the recurrent laryngeal or phrenic nerves, soft tissue infection, osteitis, or meningitis. In the RCT,[63] after one month post-injection, 28 mild adverse events were recorded, resulting in a potential complication rate of 33%. An IRB-designated scientific reviewer categorized the adverse events as "Unrelated," "Remote," "Possible," or "Related." Ten of the events were classified as "Related" or "Possible," for a complication rate of 12%. There was no significant difference in the rate of complications between the SGB and sham injection groups. Complications included increased injection site pain, which could potentially have been reduced by using a smaller needle such as in prior studies (20 gauge in RCT vs 22-25 gauge in case series). The most notable event was prolonged eye drooping, which was observed in one patient and resolved after 4 days.

Because of the limited data on harms for SGB in PTSD, we looked to the larger literature on its use for CRPS. A 2016 Cochrane review on sympathetic blockades for CRPS identified 3 studies that provided specific data regarding adverse effects of SGB for CRPS (N=115).[68] Adverse event rates ranged from 0% to 14.3% and included significant nausea and emesis, paresthesia during needle positioning, pain at the injection site, varying rates of drowsiness, dizziness, or hoarseness based on the anesthetic used, increased pain, headache, dysphagia, hematoma, dyspnea, shivering, cold feeling, face swelling, mouth numbness, and blurred vision. The most prevalent complaint was pain at the injection site. Due to the small size of the included studies, Cochrane review authors could not draw conclusions regarding the safety of sympathetic blockades.

WHO IS MOST LIKELY TO BENEFIT?

There is insufficient information to determine which Veterans, if any, are most likely to benefit from SGB for PTSD. We found no studies that compared outcomes between subgroups of patients with different demographics, predominant PTSD symptom clusters, or comorbidities. Findings from a case series of 30 active-duty military service members with combat-related PTSD suggest that people with predominantly hyperarousal and avoidance types of symptoms may be more likely to benefit from SGB.[70] Evidence for this effect is very weak as it is based on inference from evaluation of which symptoms are most impacted after SGB, rather than from direct comparison of response rates between people with different levels of these symptoms at baseline.

SUMMARY AND DISCUSSION

Emergence of an intervention's first randomized trial is always a highly anticipated event. For SGB, however, findings from its first randomized trial for PTSD proved to be disappointing. In uncontrolled, unblinded, retrospective case series, SGB for PTSD had high rates of rapid clinical improvement in PTSD symptoms (70% to 75%). In the RCT, the range of mean percent PTSD improvement after one round of SGB was 5.4% to 14.7%, and was 12.1% to 21.2% after the second round, which was no better than an injection of saline. The RCT was too small to estimate complication rates and did not report the number of patients in each group, if any, who responded to treatment. Instead it reported group averages. What do we make of this? It is not surprising that SGB's benefits were less impressive in the RCT than in the case series, as empirical evaluation has shown that, on average, benefits are generally larger in observational studies.[66] However, what was surprising is that by using a somewhat lower than usual dose of ropivacaine (5 cc versus 7 cc) and a population that may have been motivated to resist treatment, design features may have limited the RCT's chances of generating meaningful data on efficacy.[71] Substantial uncertainty remains about the potential harms of SGB as well, as the RCT and previous case series in PTSD, as well as RCTs for CRPS,[68] were inadequately powered to support or refute findings from the 1992 German questionnaire survey of 45,000 SGBs. We agree with the conclusions of previous reviews that further research is needed to more precisely determine the balance of benefits and harms of SGB for PTSD.[39,52,72]

LIMITATIONS

Overall, a key limitation of the evidence on SGB is that it is based primarily on uncontrolled, unblinded studies. Also key is that evidence on SGB for PTSD has unclear applicability to Veterans. Although most studies have been conducted in military populations, the majority were

active-duty military members. In the largest case series (N = 166), a majority of participants continued exposure to combat after treatment.[54] The majority of study participants were male, as in VA, but mean age was late thirties to early forties and prevalence of depression, anxiety, pain, and other medical comorbidities was unclear.

The limitations of the evidence base for SGB for PTSD are similar to those for other PTSD treatments.[35] First, SGB studies have generally been underpowered to adequately measure the most clinically important outcomes of remission, response, and serious adverse events. Second, although SGB has been recommended for use as an adjuvant for other therapies,[53] evidence is insufficient to support recommendations about specifically when to initiate SGB in the order of recommended conventional pharmacotherapies and psychotherapies. How much failed conventional therapy is "enough" before trying SGB? Although likely many study participants had already failed "gold standard" therapy and their lack of success suggests the need for an innovative approach, the studies' lack of specific criteria for establishing "failure" of conventional therapy, and/or dose and duration and order of conventional therapies makes it difficult for readers to compare their patient with those in the studies. For example, in the largest case series of N = 166, only 3% of patients were taking psychotropic medication before SGB and there was no information about dose and duration and no information about any psychotherapy.[54] In the RCT, the only information about other mental health treatments was that 9.5% participated since deployment, 26% during deployment, and 69% after deployment, but no details were provided about type or duration.[63] Third, there was insufficient information to determine applicability to and which Veterans, if any, are most likely to benefit from SGB for PTSD, due to inadequate documentation of predominant PTSD symptom types, index trauma types, comorbidities, optimization of prior dose, and duration of prior treatments. Fourth, evidence is insufficient to fully assess the clinical relevance of the benefits of SGB for PTSD. Although the studies consistently used the recommended tools – the CAPS and the PCL – none assessed remission (loss of PTSD diagnosis). Although the largest case series measured proportion of patients who were "responders" using the recommended PCL criteria of a $\geq$ 10-point reduction, the RCT did not measure the proportion of patients meeting any clinically relevant threshold. Finally, we could not assess long-term sustainability of response as follow-up was generally limited to 3 months post-SGB.

Publication bias is the primary potential limitation of our review process. We attempted to minimize the risk of publication bias by specifically searching for unpublished studies, and we did not find any negative case series or previously unreported outcomes. Nonetheless, we may have missed such data.

CLINICAL AND RESEARCH IMPLICATIONS

SGB for PTSD has been recommended for use as an adjuvant in individuals who have not fully responded to conventional therapies.[53] Other practical considerations that may guide treatment decisions include access to, contraindications for, and patient preference for SGB. Access to SGB may require efforts to increase psychiatrists' education about SGB and promote development of partnerships between psychiatry and anesthesiology and pain management specialists.[39] Contraindications for SGB may include a history of an anesthetic allergy, and because of the potential risks of ocular, cardiac, and circulatory adverse events, SGB should be avoided in individuals with coagulopathy, a recent cardiac infarction, a severe conduction block, or glaucoma.[73] Finally, although those who have undergone SGB have found it highly

acceptable,[69] the invasive nature of SGB may be a barrier for some candidates to try it in the first place.

SGB for PTSD is currently supported only by evidence from uncontrolled, unblinded case series which was neither confirmed nor refuted by a single RCT with imprecise findings, moderate methodological limitations, and which did not directly focus on clinically relevant outcomes. In currently used evidence grading systems,[62] such evidence is considered "insufficient" for estimating an effect. More rigorous studies are needed to more precisely determine the balance of benefits and harms of SGB for the treatment of PTSD. Both randomized trials and observational studies can contribute to our knowledge of SGB for PTSD. RTI International is conducting a U.S. Army-funded randomized trial that will compare SGB to placebo in a planned enrollment of 204 active-duty military personnel with PTSD (US Army Medical Research Acquisition Activity, grant number W81XWH-15-2-0015).[74] This trial will help answer the overarching question of whether SGB is effective, but follow-up is only 8 weeks and it is not expected to address all of the gaps in the existing evidence.

We agree with Dr. Lipov[53] that the VA could be an ideal setting to perform further practice-based research on SGB for PTSD to evaluate remission, response, and serious complication rates, with follow-up longer than 8 weeks. An observational design could be appropriate, but it should be incorporate precautions against bias that were lacking in prior studies. In particular,

1) Rigorous standards for registry studies should be followed (see below);

2) Assessment of preferences as part of the research protocol;

3) Inclusion of Veterans with PTSD who are offered (and either do or do not undergo) conventional treatments, followed prior to and after consideration of SGB; and

4) Outcome assessment and data analysis should be conducted by research or quality improvement personnel who do not have strong prior views of the effectiveness of SGB.

In addition, future VA research on SBG should include a clear plan to address shortcomings of previous research through use of the following rigorous standards for registry studies: (1) sufficient sample size to assess the clinically relevant benefits and harms; (2) improved documentation of predominant PTSD symptom types, index trauma types, and comorbidities; (3) improved documentation of prior and concomitant PTSD treatments; and (4) longer follow-up periods.

A controlled observational study designed in this way could provide better justification for conducting another RCT to strengthen our certainty about the benefits. If a future RCT is undertaken, we also suggest considering adding functional magnetic resonance imaging (fMRI) assessment both to improve our understanding of SGB's neural mechanisms and to help clarify the impact of inadequate blinding. Differences in fMRI results between SGB and control group participants could help refute an argument that clinical differences were due to knowing whether or not they got SGB.

We did not investigate whether SGB should be a higher priority than other innovative treatments for PTSD. Examples of other potentially rapid and innovative treatments include ketamine,

MDMA (±3,4-Methylenedioxymethamphetamine)-assisted psychotherapy, and cranial electrical stimulation. Each has their own unique set of potential harms, such as addiction and neurotoxicity, which would have to be considered in relation to SGB's net benefits. Cost of these innovative treatments compared to conventional psychotherapy and pharmacotherapies should also be assessed in the prioritization process. SGB costs have been estimated to be lower than conventional PTSD therapies ($2,000 for two SGB injections vs a range of $6,000 to $30,000).[75] However, we have not formally evaluated comparative costs or how these estimates apply to the current VA environment.

For additional related evidence review work, we recommend that a review of the state of the science of PTSD outcome assessment methods, such as has been done in the field of chronic pain outcome assessment,[76] could be useful in informing the direction of future research for PTSD as a whole.

CONCLUSIONS

Findings from the first RCT of SGB for PTSD were inconclusive, neither confirming nor refuting findings of rapid and high rates of clinically relevant improvement and low risk of serious adverse events from unblinded, uncontrolled case series. It is appropriate to listen to criticism of the RCT, envision a better study of SGB for PTSD, and investigate whether SGB should be a higher priority than other innovative treatments for PTSD.

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