STUDY TITLE: Stellate Ganglion Blockade to Reduce Posttraumatic stress disorder Symptoms in Cardiac Arrest Survivors: A Pilot Randomized Clinical Trial

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Lay Abstract:
Recent advances in cardiac arrest (CA) treatment have allowed patients to survive neurologically intact, but 1 in 3 screens positive for Posttraumatic stress disorder (PTSD) symptoms at hospital discharge, increasing their risk for poor health-related quality of life and secondary cardiovascular events and mortality. Current treatments for PTSD include both psychotherapeutic and medication-based treatments, with little existing evidence for effectiveness or are associated with severe side-effects which leads to non-adherence. Sympathetic blockade via stellate ganglion block (SGB) has been shown to be effective, fast-acting, with appealing safety profile and good patient acceptability and adherence in combat-related PTSD. SGB treatment has never been tested to treat PTSD induced by acute medical events such as CA. This will be the first prospective, feasibility, and safety study of the stellate ganglion blockade employed as an early, in-hospital intervention to treat PTSD after a life-threatening CA. This pilot study will obtain essential data to support a phase 2 adaptive design dose-escalation clinical trial assessing the efficacy of SGB for treating early PTSD in CA patients. The findings of this trial could revolutionize the management of psychological complications and could potentially improve health-related quality of life and event-free survival after CA and other acute medical events like acute coronary syndrome and stroke. The trial leverages the expertise of an interdisciplinary team with representation from the School of Medicine (neurology, anesthesiology, psychology, and internal medicine), School of Public Health (epidemiology), and the School of Nursing.

1. Study purpose and rationale

Every year in the U.S., 500,000 people experience sudden cardiac arrest (CA),[1] caused by electrical disturbances across cardiac tissue, leading to marked arrhythmia that ultimately result in the heart ceasing to pump blood to the brain, lungs, and other organs. Due to advances in bundled post-arrest care, cardio-cerebral resuscitation, and effective cooling protocols, **a substantial proportion of patients who receive guideline based care (nearly 1 in 3 for out-of-hospital and ~50% for in-hospital CA) now survive this once universally fatal condition.[1-5]** While most survivors retain their cognitive function and physical independence, many grapple with CA's psychological consequences in the context of learning that they were "clinically dead."[6-8] In particular, many describe the CA experience as traumatic,[6,8] and **up to 1 in 3 CA survivors subsequently develop posttraumatic stress disorder (PTSD).**[8,9] Not only is PTSD common in CA patients, but there is now evidence that PTSD after CA may influence prognosis. In the first prospective study of psychosocial determinants of prognosis after CA (n= 114), we found that 32% screened positive for early PTSD at hospital discharge.[10] Patients who developed early PTSD symptoms after CA were at very high risk for cardiovascular disease (CVD) events/mortality in the subsequent year (61% with PTSD vs 24% without PTSD; (HR =3.2; 95% CI, 1.7–6.0).[10] Thus, **intervening on early PTSD symptoms holds promise not only for improving quality of life but for improving prognosis in CA survivors.**

Treatment of early PTSD symptoms after CA requires a timely intervention.[11,12] From the perspective of prevention research, since medical event-induced PTSD presents itself in medical settings compared to other traumas, it constitutes an opportunity for facilitating early intervention. In our recent systematic review on early interventions for early PTSD symptoms in survivors of acute medical conditions, there was low strength of evidence for early psychological PTSD treatments.[13] A separate review of PTSD pharmacologic treatments found that medications were associated with severe side-effects and varying onset of action leading to high dropout rates, and non-adherence.[14] Accordingly, there is a pressing need to explore additional treatment options for PTSD induced by acute medical events such as CA.

Sympathetic blockade via stellate ganglion block (SGB) represents a promising PTSD intervention for early PTSD in CA survivors. The SG is a major sympathetic switching and transit station for the "fight-or-flight" response; interrupting this complex circuitry with a local anesthetic has observable effects on conditions mediated by similar responses, such as PTSD.[15,16] A recent sham-controlled

randomized clinical trial (RCT) of active-duty service members with PTSD symptoms showed that two SGB treatments were effective in reducing Clinician-Administered PTSD Scale (CAPS) for DSM-5 total symptom severity scores over 8 weeks.[17] It confirmed the observational data (n=200) showing rapid and clinically significant improvement in combat-related PTSD from a single SGB treatment[18,19] and persisted beyond 3 months.[19] SGB is shown to be safe,[20,21] with good patient acceptability and adherence, particularly in combat veterans.[22] SGB treatment has never been tested to treat PTSD induced by acute medical events such as CA.

2. Research Question(s)/Hypothesis(es):

We propose to conduct a pilot RCT to gain preliminary evidence regarding the acceptability, tolerability, safety and efficacy of SGB blockade in patients exhibiting early PTSD symptoms before discharge after CA. We will further explore mechanisms of SGB treatment effect and whether it may promote favorable physiology in the form of engagement in healthy behaviors, such as physical activity and sleep. We will leverage the infrastructure of an ongoing longitudinal cohort study of CA patients[10] at Columbia University (PACE Study: "Positive and Negative Psychological Predictors of Long-Term Recovery after Cardiac Arrest," IRB# AAAT4053, PI Agarwal) to identify eligible CA patients with high in-hospital PTSD symptoms (PCL-5>32).[23,24] We will also utilize questionnaire data collected as part of the PACE study, including but not limited to, GENEActive accelerometry data, PCL-5 scores and CQI scores. Consenting patients (N=15) will be randomized in a 2:1 ratio to a single SGB Intervention or sham control saline injection in an inpatient, monitored setting. Patients, and assessors, i.e. the coordinators administering the questionnaires, will be blinded to group assignment. The operator will fill a procedure-related safety questionnaire, and patients will take a comfort and satisfaction survey.[25] Depression (PHQ-8),26 anxiety (GAD-7)27 will be assessed prior to the procedure, and again, in person or by phone, at 1-week, 4-weeks, and 12-weeks post-procedure. In addition, PCL-5 and CQI questionnaires will be administered at the 1-week and 12-week follow-up calls. Patients will be screened for adverse events at all follow-up visit time points. The primary outcome will be change in PCL-5 score from baseline to 4-weeks, which will be assessed by utilizing data collected as part of the PACE study (PI Agarwal, IRB# AAAT4053). The SGB study will assess physical activity and sleep duration post-discharge by utilizing wrist-worn accelerometer data collected as part of the PACE study (PI Agarwal, IRB# AAAT4053). Patients may enroll and participate in both the PACE study and SGB study concurrently.

Primary Aim 1: Gain preliminary evidence regarding the acceptability, tolerability, and effect of a single SGB treatment in CA patients on PTSD symptoms 1 week, 4-weeks, and 12-weeks post-treatment.

Secondary Aim 1: Test whether SGB treatment in CA patients with clinically significant PTSD symptoms is associated with improved health behaviors (physical activity and sleep duration) assessed objectively by a wrist-worn accelerometer post-discharge.

3. Study Design

This is a single center, randomized, double blinded, sham-procedure-controlled study to evaluate the effectiveness of unilateral right-sided stellate ganglion block (SGB) on the acute symptomatology of PTSD, evaluated by the PCL-5 pre-treatment and at 1, 4 and 12 weeks. Pre-treatment and 4-week PCL-5 scores will be assessed by utilizing data collected as part of the PACE study (PI Agarwal, IRB# AAAT4053).

During the in-clinic session 1 the procedure will be performed at the bedside while in-patient or in the clinic by a single operator using NYP standard operating procedure with safe ultrasound techniques. For the active SGB arm, 0.5% 8 cc of ropivacaine and 2 cc of saline, will be injected around and into the site of the ganglion at the level of the C6 anterior tubercle. For the sham procedure, 10 cc of preservative-free normal saline will be injected into deep musculature anterolateral to C6 anterior tubercle.

<u>Ultrasound-Guided SGB Detailed Procedure Protocol</u>

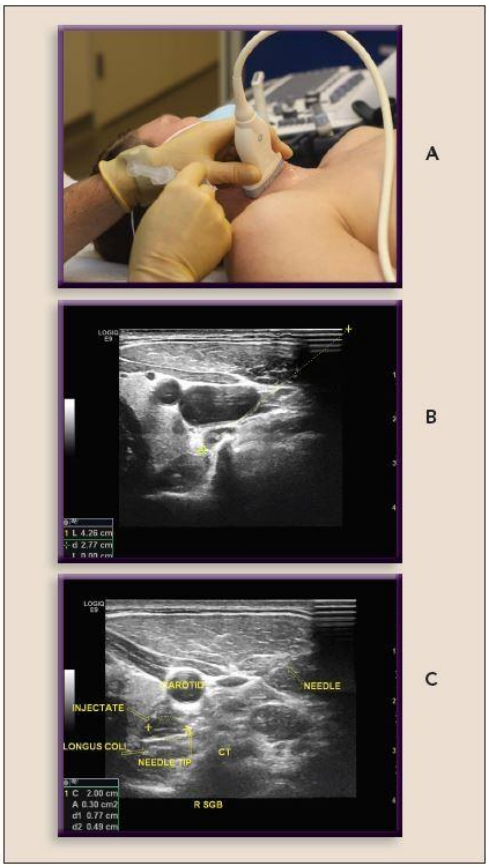
1. General preparation: We will confirm that advanced cardiac life support (ACLS) equipment and capability are current and available in the procedure room. We will also ensure that midazolam, which is

required to rapidly abate a seizure in the event of an inadvertent vascular injection, is on the ACLS cart.

2. Procedure preparation: Secure an intravenous saline lock in a peripheral vein, connect noninvasive physiologic monitors, and place the patient in the supine position with their head rotated slightly to the left. Do not use a pillow under the head or neck. A bolster may be placed under the knees for patient comfort. Widely prepare the skin over the anterior and right side of the neck with an alcohol and chlorhexidine solution, and allow the solution to dry for 1 minute. Perform a “time out” to confirm correct patient, correct procedure, and correct side.

3. Ultrasound positioning: Apply a small amount, approximately 2 grams, of sterile ultrasound gel to the anterior neck at the level of the cricoid membrane. While seated on the right side of the patient, place a cleaned and prepared high-frequency linear transducer transverse at the level of the cricoid membrane (i.e., sixth cervical vertebra, or C6, level). Raising the procedure table to about the level of the provider's chest usually facilitates proper ergonomics. The depth of the ultrasound unit is set to visualize the ventral border of the C6 vertebral body (usually 4 cm in male patients). Identify the anterior tubercle of the C6 vertebra. The anterior tubercle of C6 has a distinct peaked appearance, and the level can be confirmed by being both at the level of the cricoid membrane and by it being the most caudad anterior tubercle (which can be confirmed with a short-axis slide in a caudad direction towards the clavicle). Identify key landmarks: the common carotid artery, interior jugular vein (facilitate viewing the entire internal jugular vein by having the patient perform the Valsalva maneuver), ventral portion of the C6 vertebral body, longus coli muscle overlying the vertebral body, longus capitus muscle (usually) overlying the anterior tubercle of C6. (*Note:* there is a high degree of anatomic variation in the anterior neck.) While in this transverse view, use power Doppler or color Doppler to scan and identify vascular structures, especially looking for the well-documented anatomic variation of a vertebral artery coursing anterior and medial to the anterior tubercle of C6.

Figure 1 *Ultrasound-guided, right-sided stellate ganglion block (SGB).* **(A)** *Transducer positioning during a long-axis (in-plane) approach to the stellate ganglion.* **(B)** *Path of the needle, going through the sternocleidomastoid, under the internal jugular vein, through the longus capitus muscle just ventral to the anterior tubercle of C6, and into the ventral fascia of the longus coli muscle, laying immediately ventral to the body of the C6 vertebra.* **(C)** *Long-axis needle approach, with the needle tip in the ventral fascia of longus coli.*



4. Procedure: Envisioning a long-axis (or in-plane) lateral approach, mentally ensure the needle can reach the target area from the lateral neck **(Figure 1**). Place a skin wheal of 0.5 mL buffered 1% lidocaine at the needle entry site. Using a 3.5-in long 22-gauge needle (or other appropriate needle), enter the neck with the needle in long axis to the ultrasound transducer ("in-plane" approach) going through sternocleidomastoid, continuing just ventral to the tip of the anterior tubercle of C6, then continuing on until the needle tip has just penetrated the ventral fascia of longus coli, just medial to the longus capitus muscle and dorsal to the common carotid artery. The cervical sympathetic chain usually courses along the ventral fascia of longus coli at this level, and it is sometimes, but not always, clearly visible on ultrasound. Initially aspirate to check for no blood in the hub of the needle, then slowly inject 0.5% 8 cc of ropivacaine and 2 cc of saline (over 2 minutes in 0.5 cc aliquots) to mitigate risk associated with potential intravascular injection. The (anechoic) injectate should flow just dorsal to the ventral fascia of longus coli. There is significant anatomic variation in the anterior neck and slight variations of this description may be required. Let the patient know that they can talk during the injection if needed. Periodically ask the patient during the injection if they are doing well, and let the patient know that questioning them is just another way to monitor how they are doing. It is absolutely critical to constantly keep the needle tip in view. If the needle tip cannot be visualized, stop the injection, reacquire needle tip visualization, aspirate while checking for no blood in the hub of the needle, and only then restart the injection.

5.Observation and monitoring: Observe and monitor the patient for at least 30 minutes after completion of the injection. Have the patient remain in the supine position (a pillow may be used at this time). The first sign of a successful block will often be a sensation change on the right side of the face. Once signs and symptoms of Horner's syndrome are evident, the patient may sit reclined at a 20° angle for the remaining observation period. These positions may facilitate productive anesthetic spread. Record the patient's initial response to the injection, the time at which an obvious Horner's response was evident, and the quantitative score of the Horner's syndrome. Re-emphasize appropriate precautions to the patient before discharge.

Behavioral: Psychoeducation on trauma symptoms and stellate ganglion blockade: All participants will complete a single, 30-minute psychoeducation session with the study PI, Dr. Sachin Agarwal. Dr. Agarwal will be assisted by a research coordinator for fidelity and note-taking purposes. For Spanish-speaking subjects, a fluent, Spanish-speaking research coordinator will serve as the translator for Dr. Agarwal as he conducts the psychoeducation session. Dr. Agarwal will use a checklist (attached in RASCAL documents) to ensure that all components of the psychoeducation session are fully addressed. The session will be focused on providing the patient with information on the following:

(1) Establish therapeutic relationship and rapport with the subject and provide a general overview of stellate ganglion blockade treatment.

(2) Rationale for stellate ganglion blockade treatment in the context of cardiac arrest-induced PTSD symptoms by explaining how the body has a fight-or-flight system that is controlled in part by the stellate ganglion. Further, explaining how blocking the action of this part of the body can calm down the fight-or-flight part of the body and help reduce the feelings of anxiety that commonly occur.

(3) Explain the goals of the intervention.

(4) Review common misconceptions about anxiety and fear after cardiac arrest, and description of empirical research showing how distress is associated with interoceptive bias and avoidance of health behaviors. Explain how many of these feelings are common in cardiac arrest survivors, and they are often unrelated to their risk of cardiac arrest recurrence or other types of cardiac events. Further, help the patient identify anxious situations, thoughts, and bodily feelings related their recent cardiac arrest.

(5) Provide education about safety behaviors (e.g., monitoring bodily processes, reassurance-seeking, preventive healthy behaviors).

During the psychoeducation session, Dr.Agarwal will review with the subject, important health and safety guidelines related to their heart health, for the duration of participation in the study. Safety will be a core focus of this pilot trial. Dr. Agarwal will review what a subject should do, should they experience any chest pain or other concerning medical symptoms including but not limited to: calling 9-1-1, seeking help at the Emergency Department and calling their doctor.

To further ensure proper execution of the psychoeducation sessions, Dr. Agarwal will review and discuss any participant issues with SGB study investigator, Jeffrey Birk, PhD.

Measures

To determine eligibility, we will use a cut point of 32 on The PTSD Checklist for *DSM-5*-Specific for CA (PCL-5) or cardiac-specific anxiety measure (CQI scale score≥1.81), to categorize participants as likely having PTSD as suggested by the National Center for PTSD for provisional PTSD diagnosis[25] or severe cardiac-specific anxiety per previous studies on cardiac arrest patients. The PCL-5 and CQI will be implemented at the 1-week and 12-week follow-up visits to measure symptoms. General anxiety and depressive symptoms assessments, adverse events, Attitudes and perception questionnaire[26] will be administered by an RA in-person before discharge and via telephone or secure NYP virtual visit system at 1, 4, and 12 weeks follow-up visits **(Figure 2).**

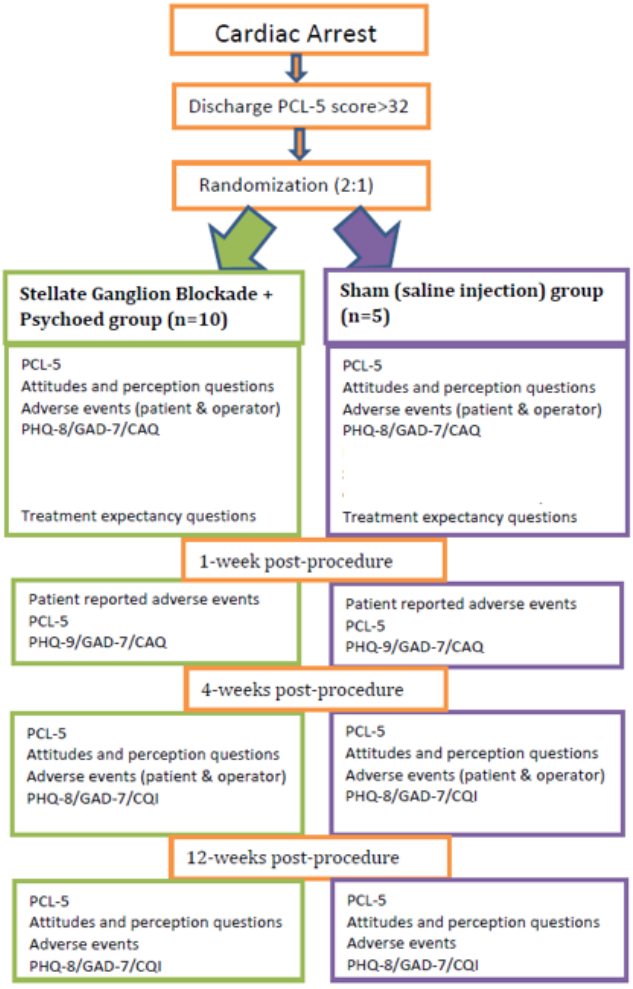


Figure 2. Study Schema

Study procedures

Prior to completing the written informed consent process, an SGB study team member will recruit adult subjects, that are more than 18 years of age, inclusive, with a clinical diagnosis of Post-Cardiac Arrest that have been hospitalized in one of the ICUs at the Milstein Hospital Building and meet the inclusion/exclusion criteria for the STELLATE study, and have been identified to have elevated symptoms of psychological distress tested by the approved IRB "PACE Study: Positive and Negative Psychological Predictors of Long-Term Recovery after Cardiac Arrest" study IRB # AAAT4053. Previously the SGB study enrolled subjects from the approved IRB "CANOE Study: Cardiac Arrest Neuropsychological Outcomes Evaluation" study IRB # AAAR8497, but effective 6/2/2021 the SGB study will only enroll from PACE. Please note, only PACE subjects who also gave permission to be contacted for future research opportunities will be contacted to discuss participation in SGB. Further, PACE subjects who decline participation in SGB will not be contacted a second time to participate in the same study.

Potential participants will be asked to review a screening verbal consent form with the SGB study team member. After reviewing the document, the participant will provide verbal consent to complete screening procedures and then will answer the questions outlined in the attached document titled, "SGB Screening questions 11_23_2020." Participants who meet all screening eligibility will then review the informed consent form with the SGB study team member and provide written consent to participate.

First In-Clinic Visit (90 minutes)

Consenting patients will be randomized in a 2:1 ratio to a single SGB intervention or sham control saline injection. Depression (PHQ-8)[27] and generalized anxiety (GAD-7)[28] will be assessed prior to the procedure. Patients, and assessors, i.e. the coordinators administering the questionnaires, will be blinded to group assignment. The anesthesiologist will remain unblinded. A safety questionnaire related to the procedure will be filled by the operator. Post-procedure, patients will complete the Attitudes and perception survey on the comfort and satisfaction associated with it. PTSD (PCL-5) and cardiac-specific anxiety (CQI)[29] collected as part of the PACE study will be used as eligibility criteria for enrollment into the SGB study. These measures will only be asked at the 1-week and 12-week follow-up visits for SGB.

Participation in this study will be documented in each participant's EPIC electronic medical record and study staff will access medical records in order to extract health-related data and ensure participant safety throughout the duration of the study.

Post-Discharge Accelerometry: Sleep and physical activity data will be collected as part of the IRB-approved PACE protocol (PI Agarwal, IRB# AAAT4053), using a GENEActiv accelerometry device. The sleep and physical activity data collected as part of PACE will later be linked with the SGB dataset. SGB subjects recruited from the PACE study will not receive an additional GENEActiv device to wear as part of their participation in SGB.

1, and 12 weeks Post-procedure (30 -60 minutes each)

Participants will complete the PCL-5, PHQ-8, GAD-7, CQI and Attitudes and perception questions at the 1 and 12-week follow up visits. Subjects will be asked about any ED visits or hospitalizations they have experienced since their last contact with the study team. Hospitalization records will be obtained for those reporting events. In addition to asking about ED visits/hospitalizations during each follow-up visit, throughout the duration of participation, research staff will monitor the EPIC EHR system on a weekly basis to review any ED visits/hospitalizations within NYP.

4 weeks Post-procedure (30 -60 minutes)

Participants will complete the PHQ-8, GAD-7, and Attitudes and perception questions at the 4-week follow up visit. Subjects will be asked about any ED visits or hospitalizations they have experienced since their last contact with the study team. Hospitalization records will be obtained for those reporting events. In addition to asking about ED visits/hospitalizations during each follow-up visit, throughout the duration of participation, research staff will monitor the EPIC EHR system on a weekly basis to review any ED visits/hospitalizations within NYP.

Statistical Procedures:
Data analysis for the primary outcome will be performed according to the intent-to-treat principle with an analogous secondary analysis conducted with the per-protocol population. The primary outcome of this study will be tested for differences between arms. The primary outcome will be analyzed using a linear model for continuous variable that accounts for treatment assignment, and baseline PCL-5 score. 95% confidence intervals will be produced for each of the arms. We are establishing a 10-point change in PCL-5 score from baseline to follow-up 4 weeks after SGB as a clinically meaningful change. Consequently, as a part of the primary outcome analyses, point and interval estimates of the change will be generated for each treatment arm to evaluate whether one or both arms reach the level of clinically meaningful change.

4. Compensation

Participants receive $50 at the completion of the first in-clinic visit 60-minute baseline/pre-intervention/intervention session. They receive $25 for completing follow-up phone call 1, $50 for completing follow-up phone call 2 and $50 for completing follow-up phone call 3. Therefore, the total possible compensation for completing the study is $175 for each participant. All compensation will be in the form of a PayCard.

5. Eligibility

Inclusion criteria

1. Age 18 years or older
2. Fluent in English or Spanish
3. A diagnosis of cardiac arrest (CA)
4. Admitted to the NYPH ICUs
5. Enrolled in the PACE study (IRB# AAAT4053) and agreed to be contacted for future research opportunities
6. Elevated symptoms of psychological distress
    a. PCL-5 > 32 at discharge or CQI scale score≥1.81

Exclusion criteria

1. A prior SBG treatment
2. Severe brain injury defined as Cerebral Performance Category Score ≥3, and/or significant aphasia, dysarthria, or cognitive impairment precluding ability to complete study questionnaires as determined by interviewer
3. Terminal non-cardiovascular illness (life expectancy <1 year)
4. Severe mental illness requiring urgent psychiatric hospitalization
5. Alcohol or substance abuse that would impede ability to complete study
6. Unavailable for telephone and in-person follow-up
7. Allergy to amide local anesthetics (e.g., ropivacaine, bupivacaine)
8. Pre-existing contralateral Horner's syndrome
9. Pregnancy
10. Current anticoagulant use
11. History of a bleeding disorder
12. Infection or mass at injection site
13. Prior Recurrent laryngeal nerve injury

6. Risks

In the most recent data on 113 individuals (100 men; mean [SD] age, 37.3 [6.7] years)[19] who were randomized to SGB treatment vs sham (74 to SGB treatment and 39 to sham treatment), there were total of 3 (0.04%) adverse events, 2 were definitely related and one possibly related, to the SGB treatment (see **Figure 5**). There were no adverse event in the sham treatment. In other RCT and case series of SGB for PTSD,[17,22] there have been no instances of serious complications reported and there was no significant difference in the rate of minor injection related complications between the SGB and sham injection groups. Garneau et al.[32] reported that they encountered no complications in SGB applied under USG guidance to 40 patients including a control group. Wei et al.[33] presented total of 156 SGBs results applied under USG guidance in 16 patients with CRPS. They reported that the frequency of mild complications (such as hoarseness, dysphagia) was 13.5%. Horner's syndrome is a desired effect, and if it does not occur, the injection may have to be repeated.

ID	Adverse Event	Assessment of Causality	Treatment Group
2054[a]	Temporary irritation of larynx which resulted in coughing	Possibly related	SGB
2054[b]	Pain and redness at injection site	Definitely related	SGB
2109[b]	Vasovagal syncope with insertion of the IV	Definitely unrelated	SGB
3008[a]	Detection of nodule or cyst (< 1 cm) in thyroid gland	Definitely unrelated	SGB
3028[a]	Self-resolving episode of bradycardia (30-second duration; minimum heart rate of 32)	Definitely related	SGB
3066[a]	Report of mild, relative increase in pre-existing right tinnitus	Definitely unrelated	Sham

[a] – week 0 procedure.

[b] – week 2 procedure.

Figure 5. Common Adverse events

Inadvertent temporary block of nerves innervating the larynx may occur in up to 15% of cases and may result in a temporary hoarse voice or a sensation that there is something in the back of the throat, and can last up to 10 hours following injection. Although rare, more serious complications include seizure from inadvertent injection of local anesthetic into a blood vessel, or a hematoma or localized collection of blood that could compromise the airway and result in death. If a patient experiences significant and increasing pain in the neck—more than just a mild soreness from the needle—we will immediately seek medical attention, as it could represent a hemorrhage in the neck. Although highly unlikely, pneumothorax has been reported with SGB. It is acceptable for the patient to talk during the injection. The patient should let the provider know if they have any new or strange sensations during the procedure, including tingling of the skin or mouth, ringing in the ears, or just feeling odd.

7. Benefits

There is no direct benefit to participation except that participants in the intervention arm may experience reduction in their anxiety symptoms associated with PTSD. Patients may have some variation of feeling "relaxed, light, and calm." Additionally, the pilot study will contribute to scientific knowledge about stress, emotion, and autonomic nervous system of the human body.

8. Alternatives

The alternative is not to participate in the study.

9. Data and Safety Monitoring

As this study presents risk to participants, data and safety monitoring will be conducted by the study staff as directed by the principal investigator. Thus, there is a plan for a Data Safety and Monitoring Board (DSMB) established to support the Roybal Centers to adjudicate the adverse events. Investigators and research assistants will meet weekly to discuss any problems with the study, in particular, whether there were any unexpected complaints about the study procedures or questionnaires, or whether there were any breaches in data confidentiality (which will be reported to the IRB as required by policy). If unexpected complaints about the procedures or questionnaires are generated, then the study may be stopped or altered prior to recruiting the full sample. An exhaustive checklist of most to least common SGB procedure-related adverse events will be determined from the operator and patients. In the RCT and case series of SGB for PTSD there were no instances of serious complications reported and there was no significant difference in the rate of minor injection related complications between the SGB and sham injection groups.

Investigators and research assistants will meet weekly to discuss any problems with the study, in particular, whether there were any unexpected complaints about the study procedures or questionnaires, or whether there were any breaches in data confidentiality (which will be reported to the IRB as required by policy). If unexpected complaints about the procedures or questionnaires are generated, then the study may be stopped or altered prior to recruiting the full sample.