

Evidence for stellate ganglion block (SGB) as a novel management strategy for anxiety disorders

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ABSTRACT:

Background: Post-Traumatic Stress Disorder (PTSD) is a disabling psychiatric disorder associated with functional and cognitive impairments that results following exposure to either real or perceived physical or mental injury or threat. Generalized Anxiety Disorder (GAD) is a category of anxiety disorders in which excessive, persistent, and unrealistic fear, worry, and feeling of being overwhelmed is accompanied by nonspecific physiological symptoms. GAD and PTSD are common comorbid conditions with an estimated 50% comorbidity rate in civilian populations and up to 91% in veterans. GAD and PTSD pathogenesis have been associated with hyperactivity or dysregulation of the sympathetic nervous system and evidence suggests a significant functional overlap in the neurocircuitry responsible for executing the stress and fear/anxiety responses in these conditions. **Methods:** We highlight results from case studies and applicable randomized controlled trial secondary outcomes when these were available. **Results:** Stellate Ganglion Blocks (SGB) modulate sympathetic signaling and have been shown to provide significant and long-lasting symptom relief for patients with PTSD and trauma-related anxiety. Assuming GAD and PTSD are in some measure driven by abnormal sympathetic signaling, then SGB may have an impact on GAD symptoms. **Limitations:** Additional clinical studies are required to accurately describe the clinical symptom-relieving benefits observed following SGB in PTSD management prior to contingent clinical applications of SGB in anxiety disorder treatment plans. **Conclusions:** Considering the overlapping pathophysiology and high comorbidity of PTSD and GAD, therapeutic applications of SGB for GAD may be feasible.

KEYWORDS: Stellate Ganglion Block, Anxiety Disorders, Generalized Anxiety Disorder, Post-Traumatic Stress Disorder, PTSD, Autonomic Dysfunction.

BACKGROUND:

Introduction

PTSD is a disabling psychiatric disorder associated with functional and cognitive impairments which results following exposure to real or perceived physical or mental injury or threat (Price et al., 2019). Numerous studies have evidenced that patients with PTSD exhibit overactive sympathetic reactivity and activity both during mental stress and under resting conditions (Price et al., 2019, Teed et al., 2022, Wenner, 2018). Clinical manifestations of overactive sympathetic reactivity are also characteristic PTSD symptoms, including

hyperarousal, heightened physiological responses to stressors and increased startle responses (Park et al., 2017).

Anxiety is one of the most common psychiatric disorders in the United States (DeMartini et al., 2019). GAD is a category of anxiety disorders in which excessive and unrealistic fear, worry, and feeling of being overwhelmed is accompanied by nonspecific physiological symptoms (increased heart rate, hyperventilation, etc), cognitive symptoms (fear of losing control, fear of physical injury), and behavioral symptoms (restlessness, pacing) (DeMartini et al., 2019). Evidence of sympathetic system involved in GAD is corroborated by studies of Li et al. by which psychotropic medication usage was discontinued in over half of patients after endoscopic thoracic sympathectomies (ETS), with correlating postoperative improvements in Hyperhidrosis Impact Questionnaires and Liebowitz Social Anxiety Scales (Li et al., 2018).

GAD and PTSD comorbidity

GAD and PTSD are among the most common co-occurring mental health conditions, with at least an estimated 50% comorbidity rate in civilian populations and up to 68-91% in veterans (Knowles et al., 2019, Price et al., 2019). The quadripartite model of psychopathology, a model widely used to explain comorbidity of psychiatric conditions, proposes that psychiatric disorders are defined using two measurements, general distress and specificity (Price et al., 2019). In accordance with this model, GAD and PTSD have high levels of general distress, the measurement which describes negative affect and externalizing symptoms, thus contributing to this particularly high observed comorbidity (Price et al., 2019). Additionally, evidence from a longitudinal clinical study of physical trauma survivors suggests that anxiety sensitivity predicts the severity of subsequent PTSD symptoms, and the severity of PTSD symptoms later predicts sensitivity to anxiety, providing further evidence of a highly interconnected relationship between anxiety and PTSD pathophysiology (Marshall et al., 2010). Autonomic dysfunction has been hypothesized to contribute to the development of similar characteristic manifestations of GAD and PTSD (e.g. impaired relaxation response, hyperarousal, irritability) (Fonkoue et al., 2020, Knowles et al., 2019). Although there are many contributing factors to the development of PTSD and GAD, such as biopsychosocial and genetic factors, it is possible that abnormal sympathetic signaling may also be involved (DeMartini et al, 2019, Ho et al., 2020, Price et al., 2019, Wenner, 2018). Multiple peer-reviewed publications suggest that recurrent PTSD trauma-related symptoms may arise from enhanced, prolonged, and/or inappropriate activation of the sympathetic stress response (Ho et al., 2020, Wenner, 2018). Similarly, GAD is associated with numerous physiological abnormalities that reflect a dysfunctional autonomic state, such as decreased vagally-mediated heart rate variability, which is indicative of cardiac autonomic dysfunction (Carnevali et al., 2019, Park et al., 2017, Teed et al., 2022). As such, dysfunctional sympathetic signaling may be involved in the maintenance and/or development of both PTSD and GAD (Fonkoue et al., 2020, Ho et al., 2020, Lipov et al., 2013, Lynch et al., 2016, 2020, 2021, Mulvaney et al., 2014).

Clinical evidence of the effect of SGB on PTSD symptom severity

For many years, SGB has been safely used as a minimally-invasive treatment for various autonomic nervous system-related medical conditions. More recently, however, SGB has been shown to provide significant and long-lasting PTSD symptom relief, including anxiety, negative mood, and hyperarousal (Lipov et al., 2013, Lynch et al., 2016, Mulvaney et al., 2014, Rae Olmsted et al., 2022). When used in conjunction with trauma-focused psychotherapy, SGB has been shown to have a 70%-80% success rate in treating PTSD symptoms (Lipov et al., 2013, Lynch et al., 2016, Mulvaney et al., 2014, Rae Olmsted et al., 2022). Results from a randomized control study (Rae Olmsted et al., 2022) support a strong efficacy profile of SGB for PTSD as the improvement in CAPS-5 total symptom severity scores was twice as large in the SGB group compared to the sham group. Additionally, the results from a quality assurance assessment of SGB for PTSD showed that 100% of patients surveyed were satisfied with the procedure and would recommend SGB to a friend, indicating SGB is well-tolerated amongst PTSD patients (McLean, 2015). At present, there are four ongoing clinical trials investigating the impact of SGB on PTSD.

Clinical evidence of the effect of SGB on anxiety symptom severity

Across various clinical reports, SGB has been demonstrated to significantly reduce PTSD symptoms, including anxiety (Lipov et al., 2013, Lynch et al., 2020, 2021, Mulvaney et al., 2014, 2021, Rae Olmsted et al., 2020). A clinical case study involving 166 active duty service members investigated the effect of SGB treatment on symptoms associated with PTSD, including anxiety symptoms, indicate that patients who received SGB had significantly improved scores on assessments of PTSD compared with patients receiving sham procedures, as measured through at least a 10 point reduction in PCL-5 scores post-procedure compared to baseline (Mulvaney et al., 2014). Furthermore, of the 166 patients who received a SGB, over 70% had a clinically significant improvement in anxiety symptoms associated with PTSD, as measured by a mean reduction of 21.8 points in PCL-5 scores compared to baseline, which persisted beyond 3 to 6 months post-procedure (Mulvaney et al., 2014). Results from a multisite, blinded, sham-procedure, randomized clinical trial published in *JAMA Psychiatry* (Rae Olmsted et al., 2020) reported a significant reduction in anxiety symptoms associated with PTSD following two SGBs at the C6 level, as measured by a reduction in Generalized Anxiety Disorder 7-Item Scale scores following intervention. At 8 weeks post-procedure, those who received SGB had significantly improved scores on assessments of PTSD symptoms as measured through numerous secondary outcomes (anxiety, depression, pain symptoms, distress, physical functioning, and mental functioning) compared to those who received sham treatment (Rae Olmsted et al., 2020). The beneficial effects demonstrated in these clinical findings warrant further investigation of SGB for management of anxiety symptoms.

METHODS:

There are currently no randomized trials of SGB for anxiety disorders. We highlight results from case studies and applicable randomized controlled trial secondary outcomes when these were available. Specifically, we used secondary outcome data from the study by Rae Olmstead et al., a sham-controlled randomized clinical trial of 100 male and 13 female participants with mean CAPS-5 scores of 37.6 and 39.8, respectively (on a scale of 0-80), to generate our hypothesis that SGB may reduce anxiety symptoms (Rae Olmstead et al., 2020). Clinical applications of SGB for psychiatric disorders beyond PTSD have not been rigorously studied. Further, CAPS-5 is not specifically designed to assess anxiety symptoms and we note these limitations.

DISCUSSION:

Conventional treatments for PTSD and GAD often utilize cognitive behavioral therapy as a first-line therapy, which may be implemented in combination with pharmacological treatments (i.e. antidepressants, antipsychotic drugs, benzodiazepines and/or mood stabilizers). Although this management approach provides adequate symptom relief or even symptom remission in many patients, others continue to experience symptoms despite seeking care. As such, SGB may represent a novel therapeutic avenue for both PTSD and GAD. Although the exact mechanisms by which SGB exerts its anxiety-relieving effects remains unknown, it has been hypothesized that SGB may effectively “reset” sympathetic nervous system signaling (Lipov et al., 2013, Lynch et al., 2020, 2021, Mulvaney et al., 2014.). Previous literature has indicated that inappropriate stress signaling may contribute to PTSD and GAD pathogenesis and has revealed significant overlap of neurocircuitry involved in stress responses and fear/anxiety responses (Bremner et al., 1996). Similarly, biomarker profiles reflecting an exaggerated stress response in PTSD and GAD have also been previously described (Bremner et al., 1996, Carnevali et al., 2019). Our interpretation of these findings is that autonomic dysfunction may underscore some shared abnormalities in GAD and PTSD pathophysiology and may suggest an explanation for the mechanism by which SGB might alleviate anxiety symptoms in PTSD (Carnevali et al., 2019). One would anticipate that selective anesthetization of the C6 stellate ganglion may relieve clinical symptoms of anxiety disorders (Lipov et al., 2013, Lynch et al., 2020, 2021, Mulvaney et al., 2014). In the case that autonomic dysfunction contributes to GAD and PTSD pathogenesis, therapeutics like SGB which aim to restore autonomic function may serve not only these patient populations but also may have therapeutic potential in numerous other mental health disorders with anxiety-related symptoms. Although available clinical data on the effects of SGB on GAD are currently limited, they do suggest that SGB may optimize clinical outcomes of treatment for GAD with or without comorbid PTSD. Thus, investigating the effects of SGB on reducing GAD symptoms through further clinical studies may be warranted (Fonkoue et al., 2020, Ho et al., 2020, Lynch et al., 2016, Mulvaney et al., 2021, Price et al., 2019, Rae Olmsted et al., 2020, Teed et al., 2022).

LIMITATIONS:

Further insight into the pathophysiology contributing to PTSD and GAD is needed to accurately describe the clinical symptom-relieving benefits observed following SGB. Although the safety profile for SGB in PTSD management has been well-documented, additional clinical studies are required for a comprehensive review of the safety implications of SGB for GAD treatment. Similarly, supplementary clinical data underscoring appropriate SGB frequency and duration of symptom relief are necessary to justify the use of SGB for GAD management.

CONCLUSION:

In addition to the reports from numerous case studies highlighting the efficacy of SGB for PTSD and trauma-related anxiety, our clinical experience with SGB as a management strategy for PTSD and trauma-related anxiety has been markedly positive. At present, we are gathering further data on the effects of SGB on PTSD and trauma-related anxiety to establish a potential indication for a future study on SGB for GAD. Despite the previously mentioned clinical data which support the hypothesis that SGB may reduce anxiety symptoms in patients with GAD based on the evidence that SGB may reduce trauma-related anxiety symptoms in PTSD patients, further information about SGB long-term efficacy and number of SGB treatment sessions necessary to achieve symptom relief is required before initiating clinical trials with GAD patients. Additionally, more extensive studies exploring physiological parallels between GAD and PTSD etiology are also necessary to validate the hypothesis that many symptoms experienced by patients with these mental health conditions stem from autonomic dysfunction.

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