Stellate Ganglion Block for the Treatment of COVID-19-Induced Olfactory Dysfunction: A Prospective Pilot Study

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Principal Investigator:

Nyssa Farrell, MD

Department of Otolaryngology – Head and Neck Surgery

Co-Investigators:

Jay F. Piccirillo, MD

Department of Otolaryngology – Head and Neck Surgery

Lara W. Crock, MD, PhD, MSCI

Department of Anesthesiology

Andrew M. Peterson, MD, MSCI

Department of Otolaryngology – Head and Neck Surgery

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A Introduction

A1 Study Abstract

Chronic olfactory dysfunction from the COVID-19 pandemic is a growing public health crisis with up to 1.2 million people in the Unites States affected. Olfactory dysfunction impacts one's quality of life significantly by decreasing the enjoyment of foods, creating environmental safety concerns, and affecting one's ability to perform certain jobs. Olfactory dysfunction is also an independent predictor of anxiety, depression, and even mortality. While the pandemic has increased the interest by the scientific community in combating the burgeoning health crisis, few effective treatments currently exist for olfactory dysfunction. Furthermore, patients impacted by "long COVID," or chronic symptoms after an acute COVID-19 infection, experience impairments other than olfactory and gustatory dysfunction, such as chronic dyspnea, impaired memory and concentration, and severe fatigue. These symptoms have been hypothesized to be a result of sympathetic positive feedback loops and dysautonomia. Stellate ganglion blocks have been proposed to treat this hyper-sympathetic activation by blocking the sympathetic neuronal firing and resetting the balance of the autonomic nervous system. Studies prior to the COVID-19 pandemic have supported a beneficial effect of stellate ganglion blocks on olfactory dysfunction, and recent news reports and a published case series have described a dramatic benefit in both olfactory function and other long COVID symptoms in patients receiving stellate ganglion blocks. Therefore, we propose a single cohort prospective study to generate pilot data on the efficacy and safety of sequential stellate ganglion blocks for the treatment of COVID-19-induced olfactory dysfunction and other long COVID symptoms.

A2 Primary Hypothesis

Stellate ganglion block is effective and safe in improving both objective and subjective olfactory dysfunction in patients with chronic COVID-19-induced olfactory impairment.

A3 Purpose of the Study Protocol

The purpose of this study is to evaluate the efficacy of sequential stellate ganglion blocks for the treatment of chronic COVID-19-associated olfactory dysfunction in order to treat the growing population of people with long-term olfactory dysfunction as a result of the pandemic.

B Background and Rationale

One of the hallmark symptoms of infection with SARS-CoV-2 is olfactory dysfunction, and it is estimated that up to 1.2 million people in the United States will experience chronic olfactory dysfunction from the COVID-19 pandemic.[1] While the majority of patients recover from COVID dysosmia, up to 15%-25% have long-term hyposmia.[2,3] Olfactory impairment can take the form of hyposmia (diminished sense of smell), anosmia (absent sense of smell), or parosmia (distorted sense of smell). Etiologies of olfactory dysfunction include post-viral, traumatic, inflammatory (e.g., chronic rhinosinusitis), neurodegenerative (e.g., Parkinson's disease), and congenital, among others. Prior to the pandemic, post-viral anosmia was the most common cause of olfactory dysfunction, which has further increased as the dominant etiology as a result of COVID-19.[4,5] The proposed pathophysiologic mechanisms of chronic COVID-19-induced olfactory dysfunction include inflammatory cytokine release,[6,7] damage to the supporting environment of the olfactory epithelium,[8] and retrograde propagation to higher order neurons.[9] A unique feature of COVID-19-associated olfactory dysfunction is the high rate of persistent parosmia. In one study of 222 patients with COVID-19-associated olfactory dysfunction, 148 (67%) of these patients experienced parosmia at some point.[10] Of the 148 patients with parosmia at any point, 84 (57%) had persistent parosmia after a mean of 6.5 months, distinguishing COVID-19-induced olfactory dysfunction from any other etiologies of olfactory dysfunction.[10] Patients with olfactory dysfunction have decreased quality-of-life and describe their life as if "living in a box."[11] These patients have concern for environmental safety, decreased enjoyment of their food, depression, anxiety, and even higher risk of mortality.[11-13] The COVID-19 pandemic has highlighted the importance of the sense of olfaction, however, there is a scarcity of effective treatments for olfactory dysfunction. Furthermore, chronic olfactory dysfunction is just one of the constellation of symptoms included in "long COVID," or persistent symptoms after recovery from acute illness due to COVID-19. Other symptoms of long COVID include fatigue, dyspnea, cough, and impaired memory and concentration, among many others.[14] These chronic symptoms are hypothesized to be, at least in part, a result of sympathetic hyperactivity resulting in positive feedback loops.[15] Therefore, the stellate ganglion block, which inhibits the sympathetic nervous system, is hypothesized to reset the balance of the autonomic nervous system and provide relief for long COVID symptoms, including olfactory dysfunction.[15]

No standard of care treatment for post-viral olfactory dysfunction exists. The most commonly used treatment for post-viral olfactory dysfunction is olfactory training; however, a large proportion of patients do not receive benefit and continue to have persistent symptoms.[16] A multitude of other therapies have been tried with minimal success, including theophylline, vitamin A, sodium citrate, and intranasal insulin.[17] As a result, there is a critical need for the development of a novel intervention to address the large volume of patients with olfactory dysfunction as a result of the COVID-19 pandemic.

The stellate ganglion block (SGB) involves an ultrasound-guided injection of a local anesthetic to inhibit the stellate ganglion. The SGB is proposed to inhibit the sympathetic neural connections within the head, neck, and upper extremity, improve regional blood flow, reduce adrenal hormone concentration, and even reestablish circadian rhythms through modulation of melatonin.[18-21] The SGB has been used successfully in a multitude of disorders, including post-traumatic stress disorder, cluster headache, complex regional pain syndrome, and peripheral vascular disease.

The SGB was first proposed to treat olfactory dysfunction by Lee et al in 2003, where 38 post-viral olfactory dysfunction participants were treated with SGB and 13 participants remained untreated as controls.[22] Subjective olfactory function improved in 27 (71%) of the treated participants compared to zero (0%) of the controls. Olfactory perception was improved significantly in the SGB group assessed both by the butanol threshold test and odor identification test. There were no complications of SGB in the 38 treated participants. Another study in 2007 by Moon et al found that in 13 participants with various etiologies of olfactory dysfunction, seven (54%) demonstrated improvement with repeated SGBs.[23] The same group conducted a study published in 2013 looking at the long-term results of SGB in treating olfactory dysfunction from various etiologies. Of 37 participants with olfactory dysfunction unresponsive to oral or intranasal steroids who underwent SGB, 15 (41%) were determined to be responsive and 22 (59%) unresponsive to the treatment. Importantly, the responsive group had a mean duration of olfactory dysfunction of 1.6 years vs. a mean duration of olfactory dysfunction of 4 years in the unresponsive group. The study found that in those who respond to SGB, the beneficial effects on olfaction last at least 5 years. Of the 37 treated participants there was only 1 who experienced a complication, which was a temporary brachial plexus block.

Most recently, anecdotal news reports and a published case series point to a possible beneficial effect of SGB on both chronic COVID-19-induced olfactory dysfunction and various other long COVID symptoms. A published case series by Liu et al describes two patients who underwent SGB for long COVID symptoms, including olfactory dysfunction.[24] SGB was performed on the right side then either one or two days later to the left side. Both patients reported significant and durable improvement in symptoms, including fatigue, “brain fog,” and olfactory and gustatory dysfunction that persisted at 60-day follow-up. Nearly all other long COVID symptoms, including cough, chest pain, heart palpitations, and orthostatic dizziness, also improved at the one week and two-month follow-up time points. The authors concluded that although the sample size is limited, SGB may have a significant impact on the dysautonomia caused by COVID-19 and improve long COVID symptoms, giving rationale to conduct a larger study. Therefore, we propose a single cohort prospective study to generate pilot data on the effectiveness and safety of sequential stellate ganglion blocks for the treatment of COVID-19-induced olfactory dysfunction and other long COVID symptoms.

C Study Objectives

C1 Primary Aim

1. The effectiveness of a sequential SGB in improving both self-reported and objective olfactory dysfunction

C2 Secondary Aim

2. The effectiveness of a sequential SGB in improving other self-reported long COVID symptoms, including fatigue, dyspnea, cough, impaired memory and

concentration, muscle pain, headache, heart palpitations, depression/anxiety, fever, orthostatic dizziness, and post-exertional malaise

3. The safety and tolerability of a sequential SGB

C3 Rationale for the Selection of Outcome Measures

University of Pennsylvania Smell Identification Test (UPSIT, Sensonics, New Jersey). The UPSIT is a test of olfactory identification and consists of four 10-page booklets, with a total of 40 items. On each page, there is a different "scratch and sniff" strip and four choice options. Subjects are asked to scratch each strip with a pencil to release the scents, detect the smell, and identify the smell from the four choice options. The UPSIT comes from a scoring rubric that identifies the normalcy benchmark based on age and gender, which is >34 in women and >33 in men.[25,26] The UPSIT is commercially available, takes 10-15 minutes to complete, and is the gold standard test to assess smell identification. The minimal clinically important difference of the UPSIT is 4.

Olfactory Dysfunction Outcomes Rating (ODOR). The ODOR is a new disease-specific questionnaire that assesses for physical problems, functional limitations, and emotional consequences of olfactory dysfunction secondary to any etiology. The instrument contains 28 total items with each scored on a 5-point Likert scale from 0 to 4. The MCID for the instrument is currently being calculated. See Appendix for full instrument.

Smell and Taste Questionnaire. The smell and taste questionnaires will include a series of questions regarding the severity and change in each participant's olfactory and gustatory dysfunction. Questions will be derived from the Clinical Global Impression – Severity and Clinical Global Impression – Improvement scales and administered at all 3 visits. See Appendix for the questionnaires.

> **Clinical Global Impression – Severity Scale (CGI-S).** The current severity of olfactory and gustatory dysfunction will be measured with the *CGI-S* scale.[27] The CGI-S scale measures disease severity based on a 5-point Likert scale and will be modified as seen in the Appendix.
>
> **Clinical Global Impression - Improvement Scale (CGI-I)**. The overall response to treatment will be measured with the *CGI-I* scale. The *CGI-I* Scale measures response to treatment for a number of disorders and has good internal consistency and validity.{Dunlop, 2017, Transdiagnostic Clinical Global Impression Scoring for Routine Clinical Settings} The CGI-I scale measures change in clinical condition based on a 7-point Likert scale and will be modified as seen in the Appendix. The primary outcome measure of the study will the proportion of participants within each CGI-I for smell loss group at 1 month. Responders will be indentified as those reporting moderate improvement or greater.

Long-COVID Questionnaire. We will assess the following 11 symptoms of Long COVID other than olfactory and gustatory dysfunction: tiredness/fatigue, shortness of breath, brain fogginess, headache, cough, depression, low-grade fevers, palpitations, dizziness,

muscle pain, and joint pains. All 11 symptoms will be asked to rank the level of severity with answer choices from *No problem* to *Severe problem*. The Long-COVID questionnaire will be administed at all 3 visits. See Appendix for questionnaires.

Patient Satisfaction with Treatment. Patients will be asked at the final visit, "Overall, how satisfied were you with the stellate ganglion block treatment for your smell loss?" Possible answer choices: 1) Completely dissatisfied, 2) Mostly dissatisfied, 3) Somewhat dissatisfied, 4) Neither satisfied or dissatisfied, 5) Somewhat satisfied, 6) Mostly satisfied, 7) Completely satisfied. Patients will also be asked at the final visit, "Would you recommend this treatment to a family member or close friend who also suffers from chronic smell loss due to COVID-19?" Possible answer choices: 1) Yes, 2) No.

Adverse Events. Participants will be asked to describe any adverse events experienced after both SGB procedures. Additionally, any adverse events noted at the time of SBG will be noted.

D Investigational Agent

D1 Clinical Data to Date

The SGB was first proposed to treat olfactory dysfunction by Lee et al in 2003, where 38 post-viral olfactory dysfunction participants were treated with SGB and 13 participants remained untreated as controls.[22] Subjective olfactory function improved in 27 (71%) of the treated participants compared to zero (0%) of the controls. Olfactory perception was improved significantly in the SGB group assessed both by the butanol threshold test and odor identification test. There were no complications of SGB in the 38 treated participants. Another study in 2007 by Moon et al found that in 13 participants with various etiologies of olfactory dysfunction, seven (54%) demonstrated improvement with repeated SGBs.[23] The same group conducted a study published in 2013 looking at the long-term results of SGB in treating olfactory dysfunction from various etiologies. Of 37 participants with olfactory dysfunction unresponsive to oral or intranasal steroids who underwent SGB, 15 (41%) were determined to be responsive and 22 (59%) unresponsive to the treatment. Importantly, the responsive group had a mean duration of olfactory dysfunction of 1.6 years vs. a mean duration of olfactory dysfunction of 4 years in the unresponsive group. The study found that in those who respond to SGB, the beneficial effects on olfaction last at least 5 years. Of the 37 treated participants there was only 1 who experienced a complication, which was a temporary brachial plexus block.

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heart palpitations, and orthostatic dizziness, also improved at the one week and two-month follow-up time points. The authors concluded that although the sample size is limited, SGB may have a significant impact on the dysautonomia caused by COVID-19 and improve long COVID symptoms, giving rationale to conduct a larger study. Therefore, we propose a single cohort prospective study to generate pilot data on the effectiveness and safety of sequential stellate ganglion blocks for the treatment of COVID-19-induced olfactory dysfunction and other long COVID symptoms.

D2 Dose Rationale and Risk/Benefits

The stellate ganglion block has been used for decades with the assistance of fluoroscopy and has been modified in the present day by using ultrasound to improve visualization. Substantial data has been generated on the safety and tolerability of the procedure in other conditions, such as post-traumatic stress disorder (PTSD). One study of 250 SGBs for PTSD performed by an experienced pain management provider resulted in zero post-procedural or delayed complications. Of 110 participants in the study who returned completed surveys, 100% of the patients said they would recommend the procedure to a friend, and 95% stated that they would be willing to undergo as many repeat procedures as necessary based on the minimal discomfort and tolerable side effects.[28] A temporary Horner's syndrome is an expected outcome of SGB and improves over the course of a few hours.

Risks of lidocaine injection include: drowsiness, dizziness, nausea, vomiting, feeling hot or cold, confusion, ringing in your ears, blurred vision, or double vision. However, these side effects are all rare when used at the maximum total combined dose of 4.5mg/kg lidocaine and 4.5mg/kg mepivacaine. We will strictly following this dosing guideline.

E Study Design

E1 Overview or Design Summary

The study will be a single center, unblinded, prospective cohort study conducted at Washington University School of Medicine.

E2 Subject Selection

2.a Inclusion Criteria

1) Adults age 18 to 70
2) Diagnosis of COVID at least 12 months prior to study enrollment with self-reported olfactory dysfunction
3) Objective olfactory dysfunction due to COVID-19 that has persisted despite viral recovery, as defined by the UPSIT (≤ 34 in women, ≤ 33 in men)

4) Ability to read, write, and understand English

2.a Exclusion Criteria

1) History of smell loss prior to COVID-19 infection
2) History of conditions known to impact olfactory function:
   a. Chronic rhinosinusitis
   b. History of prior sinonasal or skull base surgery
   c. Neurodegenerative disorders (Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, Lewy body dementia, frontotemporal dementia)
3) Currently using concomitant therapies specifically for the treatment of olfactory dysfunction
4) Inability to tolerate a needle injection into the neck
5) History of coexisting conditions that make SGB contraindicated:
   a. Unilateral vocal cord paralysis
   b. Severe COPD (FEV1 between 30-50% of predicted)
   c. Recent myocardial infarction within the last year
   d. Glaucoma
   e. Cardiac conduction block of any degree
6) Currently taking blood thinners or antiplatelet agents
7) Allergy to local anesthetic
8) Inability to extend the neck for any reason (e.g., severe arthritis)

2.b Ethical Considerations

Patients will be informed in the informed consent process that they may or may not personally benefit from the study and that the data obtained from the study will be used to inform the future care patients with chronic COVID-19-induced olfactory dysfunction. There will be phone assistance available 24/7 during the study period to report any possible adverse reactions. There are no financial conflicts of interest.

2.c Subject Recruitment Plans and Consent Process

Adult patients with chronic COVID-19-induced olfactory dysfunction will be recruited from the Washington University School of Medicine/Barnes Jewish Hospital and the EPIC electronic medical record. Advertisements describing the study will be posted in the WU Department of Otolaryngology - Head & Neck Surgery clinic and on the Department of Otolaryngology – Head and Neck Surgery Twitter and Instagram pages.

Eligible patients who present to clinic or respond to advertisements will be approached by a research team member to review the informed consent process and thoroughly discuss the research protocol, potential benefits, and risks of the study. The informed consent discussion will take place with the patient and any available family members over the phone or in person, whichever the potential participant prefers. Any subsequent questions or concerns from the potential participant and any family members will also be addressed at that time. After discussion, the patient will be asked to re-summarize the steps involved in the study to ensure understanding. If interested, written consent in

person will be obtained prior to undergoing SGB. Patients will be reminded that study participation is voluntary and will in no way affect their current or future care.

2.d Randomization Method and Blinding

No randomization or blinding will take place.

2.e Risks and Benefits

2.f Early Withdrawal of Subjects

During the informed consent process, participants will be informed that they may withdraw at anypoint during the study, including before, during, or after their first SGB. Participants will face no penalty or negative consequences for withdrawaling from the study.

E3 Study Drug

3.a Description

3.b Treatment Regimen

The ultrasound-guided stellate ganglion blocks (SGBs) will be performed by Dr. Lara Crock, a board-certified anesthesiologist and pain management specialist who has extensive experience performing SGBs.

Patients will remain NPO for 8 hours prior to the block. If needed, they can take morning medications with a small sip of water. Using ultrasound guidance, the transverse process of C6 will be identified and confirmed. A 27-gauge needle will be used to localize the superficial skin with 1% lidocaine. Color-doppler will be used to identify vessels. Then, a 21-gauge ultrasound needle will be advanced using an in-plane technique from lateral to medial. After negative aspiration, a test dose of 2 ml of 1% lidocaine will be injected. If tolerated, 6-8 ml of 1% mepivacaine local anesthetic will be deposited beneath the prevertebral fascia and above the longus coli muscle.
Total local anesthetic will be determined using a maximum total combined dose of 4.5mg/kg lidocaine and 4.5mg/kg mepivacaine.

The presence of Horner's syndrome (ipsilateral ptosis, miosis, anhydrosis) will be recorded post-procedure. They should remain NPO for 2 hours post-block if they have a feeling of a lump in their throat.

The first SGB at the initial visit will be performed on the right side, and the second SGB at the Week 1 visit will be on the left side, given that the patient tolerated the first SGB.

F Study Procedures

F1 Screening for Eligibility

To determine potential eligibility for the study, the research team will query the medical record and our team's pre-existing databases of COVID-19-induced olfactory dysfunction patients based on the inclusion/exclusion criteria. The two study databases we will assess are the SCENT2 and GRACE studies within the department of otolaryngology - head and neck surgery. For those meeting the selection criteria, we will access name, telephone number, age, sex, and date/time of any upcoming clinic visits.

F2 Schedule of Measurements

The first two visits will be completed at the Clinical and Translational Research Unit (CTRU). The third visit will be completed virtually.

Role of the CTRU: Nursing staff will be needed for assistance in completion of the SGB. Additionally, all subjects will have vital signs monitored with serial blood pressures and pulse oximetry within the CTRU for 1 hr after completion of the block.

Visit 1

At the initial visit, demographic information, including age, sex, race, and length of time of dysosmia will be collected from each enrolled patient. Prior to undergoing the first SGB, participants will complete the UPSIT, ODOR questionnaire, Long-COVID Questionnaire I, and Smell and Taste Questionnaire I.

Visit 2

At one week, prior to undergoing a SGB on the contralateral side to their initial SGB, participants will be asked again to fill out the UPSIT and ODOR. They will also complete the Smell and Taste Questionnaire II, Long-COVID Questionnaire II, and describe any adverse events experienced after the first SGB.

Visit 3

The final visit will occur virtually, 1 month after the 2nd SBG, where participants will complete the UPSIT, ODOR, Smell and Taste Questionnaire II, Long-COVID Questionnaire II, and the Participant Satisfaction with Treatment questionnaire. Participants will also be asked to describe any adverse events experienced since the second SGB.

	Screening/Visit 1	**Visit 2**	**Visit 3**
		(1 Week post 1st SGB)	**(1 month post 2nd SGB)**
Written informed consent	X		
Demographics	X		

Inclusion/Exclusion Criteria	X		
UPSIT	X	X	X
ODOR Questionnaire	X	X	X
Long-COVID Questionnaire I	X		
Long-COVID Questionnaire II		X	X
Smell and Taste Questionnaire I	X		
SGB	X	X	
Smell and Taste Questionnaire II		X	X
Participant Satisfaction with Treatment Questionnaire		X	X
Adverse Events	X	X	X

F3 Safety and Adverse Events

3.a Safety and Compliance Monitoring

The specific monitoring plan for this study is based on the potential risk of participation and size and complexity of the planned investigation. Based on these considerations, this study will have a monitoring board comprised of Dr. Farrell, Dr. Crock, Dr. Piccirillo, Ms. Kukuljan, and Dr. Kallogjeri, the study biostatistician. The monitoring board will meet to review data after enrollment of 10 participants. All reports of a Serious Adverse Event (SAE) or an Unexpected Adverse Event will be investigated by the monitoring team and reported to Washington University HRPO according to the reporting requirements.

3.b Adverse Events

Adverse events will be tracked from the time of dose administration through post dose and at the follow up visit 3 for drug-related adverse events. All adverse events will be documented and assessed for relatedness to the study medication. The study team will monitor for adverse events on an ongoing basis. Once the team becomes aware of an adverse event, the AE will be reported according to institutional guidelines.

G Statistical Plan

G1 Sample Size Determination and Power

Sample size estimate for the proposed study is based both on feasibility and previous data on the use of SGB for non-COVID-19 post-viral olfactory dysfunction.

A power analysis was performed using Fisher's exact test in G-Power 3.1.2. With a positive response based on the previous study expected in 71% of participants,[22] we estimate that a total sample size of 20 participants will result in a 95% confidence interval of 0.71 (+/- 0.21), resulting in a true response rate likely between 50% and 92%. A total of 20 participants are needed to allow us to detect with 80% power at the 2-sided alpha level of 0.05 a within-subjects response rate of 50% or more in the percent of subjects who experience a clinically meaningful change in CGI-I score.

G2 Analysis Plan

Standard descriptive statistics will be used to describe distribution of baseline characteristics in each of the study groups. The effect of the intervention will be measured as the proportion of participants reporting that their sense of smell is moderately better or much better than before undergoing a stellate ganglion block. Intention to treat principles will be followed.

The 95% confidence interval around this effect size will be determined to assess the precision of the observed effect and whether a clinically meaningful difference is plausible given the observed results. Appropriate analyses will be performed for the secondary outcome measures.

H Data Handling and Record Keeping

H1 Confidentiality and Security

The secure REDCap database will be used to store data. Only study team members will have access to the database.

I Study Monitoring, Auditing, and Inspecting

I1 Study Monitoring Plan

The specific monitoring plan for this study is based on the potential risk of participation and size and complexity of the planned investigation. Based on these considerations, this study will have a monitoring board comprised of Dr. Farrell, Dr. Crock, Dr. Piccirillo, Ms. Kukuljan, and Dr. Kallogjeri, the study biostatistician. The monitoring board will meet to review data after enrollment of 10 participants. All reports of a Serious Adverse Event (SAE) or an Unexpected Adverse Event will be investigated by the monitoring team and reported to Washington University HRPO according to the reporting requirements.

J Attachments

J1 Questionnaires or surveys

- ODOR questionnaire
- Symptom Burden Questionnaire
- Long COVID
- Smell and Taste Questionnaire I
- Smell and Taste Questionnaire II

K References

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