Stellate Ganglion Block for the Treatment of COVID-19-Induced Parosmia: Double-Blinded, Placebo-Controlled Randomized Clinical Trial

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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TABLE OF CONTENTS

A Introduction

A1 Study Abstract

Chronic olfactory dysfunction, both hyposmia and parosmia, from the COVID-19 pandemic is a growing public health crisis with up to 1.2 million people in the United 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 loss is also an independent predictor of anxiety, depression, and even mortality. Recent research by our group (unpublished data) suggests that parosmias, moreso than hyposmias, can result in increased rates of anxiety, depression, and even suicidal ideation. 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. Persistent symptoms after an acute COVID-19 infection, or "Long COVID" 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. A previous pilot study using stellate ganglion blocks of 20 participants with persistent COVID-19 olfactory dysfunction resulted modest improvements in subjective olfactory function, smell identification, and olfactory-specific quality-of-life, but it lacked a control group. Therefore, we propose a double-blinded, placebo-controlled randomized clinical trial assessing the efficacy of a stellate ganglion block versus saline injection in a total of up to 140 participants with persistent COVID-19-associated olfactory dysfunction.

A2 Primary Hypothesis

Stellate ganglion block (SGB) is effective and safe in improving olfactory dysfunction in patients with chronic COVID-19-induced parosmia.

A3 Purpose of the Study Protocol

The purpose of this study is to evaluate the efficacy of stellate ganglion blocks for the treatment of chronic COVID-19-associated parosmia 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 (OD). While the majority of patients recover from COVID dysosmia, up to 15%-25% have long-term hyposmia[1,2] and it is estimated that up to 1.2 million people in the United States will experience chronic OD from the COVID-19 pandemic.[3] A unique feature of COVID-19-associated OD is the high rate of persistent parosmia. In one study of 222 patients with COVID-19-associated olfactory dysfunction by Lerner et al, 148 (67%) of these patients experienced parosmia at some point, and estimates of persistent parosmia 6 months after COVID-19 infection range from 25% to 57%.[4-6] Patients with OD have decreased quality-of-life and have described their lives as if "living in a box."[7] These patients have concerns for environmental safety, decreased enjoyment of their food, depression, anxiety, and even a higher risk of mortality.[7-9] Unpublished work by our group has demonstrated a relationship between parosmia and increased risk of screening positive for anxiety, depression, and suicidality.

The COVID-19 pandemic has highlighted the importance of the sense of olfaction, but no standard of care treatment for post-viral OD exists. The most commonly used treatment for post-viral OD is olfactory training; however, a large proportion of patients do not receive benefit and continue to have persistent symptoms.[10] A multitude of other therapies have been tried in randomized clinical trials with minimal success, including theophylline[11], vitamin A[12], sodium citrate[13], and intranasal insulin.[14,15] As a result, there is a critical need for the development of a novel intervention to address the large number of patients with OD due to the COVID-19 pandemic.

The stellate ganglion block (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.[16-19] The SGB has been used successfully in a multitude of disorders, including post-traumatic stress disorder[20], migraine[21], and complex regional pain syndrome.[22] A meta-analysis of 12 clinical trials found that SGB was superior to placebo in reducing pain scores among patients with various sympathetic hyperactivity-associated disorders.[23] Many "long COVID" symptoms, those that persist after recovery from acute COVID-19 infection, are hypothesized to be, at least in part, a result of sympathetic hyperactivity resulting in positive feedback loops.[24] Therefore, the stellate ganglion block (SGB) is hypothesized to reset the balance of the autonomic nervous system and provide relief for long COVID symptoms, including OD.[24]

The SGB was first proposed to treat OD by Lee et al in 2003, where 38 post-viral OD participants were treated with SGB and 13 participants remained untreated as controls.[25] 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. Additional studies by Moon et al noted improvement in OD of various etiologies after repeated SGBs.[26,27] However, each of these studies were limited by their use of unvalidated outcome measures in a heterogeneous OD population in the pre-COVID era, limiting their external validity to the present day.

A multitude of anecdotal news reports and published case series[28-30] point to a possible beneficial effect of the SGB on both chronic COVID-19-induced OD and various other

long COVID symptoms. Numerous pain management clinics across the country are offering the SGB for long COVID with thousands of dollars of out-of-pocket costs to patients without adequate evidence to justify its use. One case series of 195 parosmic patients noted up to a 75% response rate after SGB.[31]

Recently, our study team completed a prospective, pilot single-arm trial of 20 participants with persistent COVID-19-associated OD who underwent bilateral stellate ganglion blocks and were followed for 1 month post-procedure. At 1-month, 10 (50%) participants experienced at least slight subjective improvement in their OD, 11 (55%) attained a clinically meaningful improvement in smell identification using the UPSIT, and 7 (35%) achieved a clinically meaningful improvement in olfactory-specific QOL. Therefore, we propose a double-blinded, placebo-controlled randomized clinical trial assessing the efficacy of a stellate ganglion block versus saline injection in a total of 140 participants with persistent COVID-19-associated parosmia.

C Study Objectives

C1 Primary Aim

1. To determine the efficacy of a SGB in improving parosmia-related quality of life compared to saline injection

C2 Secondary Aim

1. To determine the efficacy of a SGB in improving self-reported parosmia compared to saline injection

2. To determine the safety and tolerability of a SGB

3. To determine if subjects who catastrophize their parosmia smell loss are more likely to respond to SGB

4. To determine if subjects who screen positive for anxiety/depression are more likely to respond to SGB

5. Explore if there is variation of SGB effect dependent on injection laterality (right versus left SGB)

C3 Rationale for the Selection of Outcome Measures

Parosmia Olfactory Dysfunction Outcomes Rating (DisODOR). The DisODOR is a disease-specific questionnaire that assesses for physical problems, functional limitations, and emotional consequences of parosmia secondary to any etiology. The instrument contains 29 total items with each scored on a 5-point Likert scale from 0 to 4.

Clinical Global Impression - Severity Scale (CGI-S). The baseline severity of parosmia will be measured with the *CGI-S* scale. The *CGI-S* scale measures disease severity in clinical condition based on a 5-point Likert scale.

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.[32] The CGI-I scale measures change in clinical condition based on a 7-point Likert scale. The CGI-I for parosmia asks, “Compared to before your stellate ganglion block, how would you describe your parosmia (things do not smell the same as you remember)?" Response options for each are: (1) Much better now than before, (2) Moderately better now than before, (3) Slightly better now than before, (4) About the same, (5) Slightly worse now than before, (6) Moderately worse now than before, and (7) Much worse now than before. Responders are defined as those who report “slightly better now than before” or greater.

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.[33,34] 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.

Long-COVID Questionnaire (LCQ). Symptoms assessed via the LCQ are derived from the Symptom Burden Questionnaire for Long Covid[35], which included tiredness/fatigue, shortness of breath, brain fogginess, headache, cough, depression, low-grade fevers, palpitations, dizziness, muscle pain, and joint pains. At baseline, participants are asked to rank the current severity of each problem on a 5-point Likert scale. At each follow-up visit, participants are asked to rank their overall improvement in each of the 11 symptoms compared to their symptoms prior to their first SGB. The improvement options are based on the CGI-I 7-point Likert scale.

Olfaction Catastrophizing Scale (OCS). The pain catastrophizing scale (PCS) was developed to measure the negative mental response to actual or anticipated pain. The OCS was derived from the validated PCS to similarly measure the negative mental response to smell dysfunctionloss. Multiple thoughts/feelings will be assessed on a 5-point likert scale with a maximum score of 52. At each visit, subjects will be asked to complete the OCS.

Hospital Anxiety and Depression Scale (HADS). The HADS was developed for screen for anxiety and depression in the general population. It consists of 7 questions for anxiety and 7 questions for depression each ranked on a 4-point Likert Scale. A score of 0-7 is considered normal, 8-10 is borderline abnormal anxiety or depression, and a score of 11-21 corresponds with screening positive for anxiety or depression. Subjects will be screened for anxiety and depression at eachtheir initial visit.

Pre-Intervention Expectations. A significant number of social media and news stories have discussed anecdotal success of stellate ganglion blocks for COVID-19-induced olfactory dysfunction. As a result, we propose that participants may have a distorted pre-operative expectation that may affect their subjective rating of improvement in olfaction. Therefore, participants will be asked at baseline, “How confident are you that the stellate ganglion block will improve your smell loss or smell distortion?” Possible answer choices: Not at all, Slightly confident, Somewhat confident, Very confident, Extremely confident.

Patient Satisfaction with Treatment. Participants will be asked at the 1-month virtual visit, “Overall, how satisfied were you with the stellate ganglion block treatment for your parosmia?” 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.

Assessment of the Blind. Immediately after the initial injection, participants will be asked, “Which intervention do you think you received?” Answer choices: 1) Mepivacaine (active medication) 2) Saline (placebo).

Parosmia Trigger Question. “How many different items trigger parosmia?" This will be assessed on a 5-point Likert scale.

D Investigational Agent

D1 Clinical Data to Date

The SGB was first proposed to treat OD by Lee et al in 2003, where 38 post-viral OD participants were treated with SGB and 13 participants remained untreated as controls.[25] 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. Additional studies by Moon et al noted improvement in OD of various etiologies after repeated SGBs.[26,27] However, each of these studies were limited by their use of unvalidated outcome measures in a heterogeneous OD population in the pre-COVID era, limiting their external validity to the present day.

A multitude of anecdotal news reports and published case series[28-30] point to a possible beneficial effect of the SGB on both chronic COVID-19-induced OD and various other long COVID symptoms. Most recently, a case series of 195 patients with parosmia noted up to 75% response rate after SGB.[31] Numerous pain management clinics across the country are offering the SGB for long COVID with thousands of dollars of out-of-pocket costs to patients without adequate evidence to justify its use. Recently, our study team completed a prospective, pilot single-arm trial of 20 participants with persistent COVID-19-associated OD who underwent bilateral stellate ganglion blocks and were followed for

1 month post-procedure. At 1-month, 10 (50%) participants experienced at least slight subjective improvement in their OD, 11 (55%) attained a clinically meaningful improvement in smell identification using the UPSIT, and 7 (35%) achieved a clinically meaningful improvement in olfactory-specific QOL.

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.[36] A temporary Horner's syndrome is an expected outcome of SGB and improves over the course of a few hours.

Our 20-participant pilot study demonstrated the following safety data for the SGB. There were no serious adverse events and all adverse events were transient. A total of 11 (55%) of the participants reported being satisfied with the SGB and 17 (85%) said that they would recommend the treatment to a close friend or family member.

Adverse Effect[a]	**No. (%)** **All completed procedures (n = 40)**
Horner syndrome	39 (97.5)
Hoarseness	17 (42.5)
Globus	14 (35)
Brief lightheadedness	9 (22.5)
Numbness of the face	8 (20)
Mild shortness of breath	7 (17.5)
Nasal congestion	6 (15)
Pain at the injection site	6 (15)
Fatigue[b,c]	5 (12.5)
Cough	2 (10)
Weakness of the arm	2 (10)
Weakness of the neck/back	2 (10)
Tightness of the neck	2 (10)
Arm heaviness	1 (5)
Bruising of the injection site	1 (5)
Chest heaviness	1 (5)
Headache	1 (5)
Palpitations	1 (5)
Tightness of the shoulder[b]	1 (5)

[a] Displayed adverse effects were all found to be at least possibly related to the study, three additional adverse effects, bruising of the eyelid, persistent numbness of the neck, and photosensitivity, were also reported but their relatedness to the study was determined to be unlikely
[b] Adverse effect was determined to be unexpected and was reported to the institutional review board

[c] One instance of persistent fatigue was reported and was determined to be unexpected; all other instances of fatigue were brief and were determined to be expected

E Study Design

E1 Overview or Design Summary

The study will be a single center, double-blinded, placebo-controlled randomized clinical trial 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 6 months prior to study enrollment with self-reported parosmia
3) Ability to read, write, and understand English
4) Score of at least 40 on DiSODOR during screening and at least 25 during Visit 1

2.a Exclusion Criteria

1) History of smell loss or change prior to COVID-19 infection
2) History of conditions known to impact olfactory function:
    a. Chronic rhinosinusitis
        i. If individual notes a history of chronic rhinosinusitis or prior endoscopic sinus surgery, they may be eligible if they can a note from their otolaryngology (ENT) physician stating the following:
            1. Patient's chronic rhinosinusitis is controlled
            2. There are no polyps/masses/scarring of the olfactory cleft
            3. The otolaryngologist feels that the patient's parosmia is secondary to COVID-19
    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, including > 81mg aspirin
7) Allergy to local anesthetic
8) Inability to extend the neck for any reason (e.g., severe arthritis)
9) History of prior stellate ganglion block

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

Study recruitment strategies include:

- Approaching adult patients with chronic COVID-19-induced olfactory dysfunction being seen at Washington University Medical Center
    - CARES clinic will provide list of potentially eligible patients to be contacted by the study team
- Searching the electronic medical record (Epic) to identify potentially eligible patients to be contacted by a study team member
- Contacting participants from previous COVID related research studies who agreed to be contacted for future studies
- Distributing study recruitment flier to ENT physicians/offices
- Posting study recruitment flier to social media sites
- WU Volunteer for Health database email blast and Study Search post

Eligible patients who present to clinic, contact the study team, or are contacted by the study team will be approached by a research team member for study screening and, if eligible, to review the informed consent form and thoroughly discuss the research protocol, potential benefits, and risks of the study. The informed consent discussion will take place with the potential participant 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 about the study will also be addressed at that time and they will be reminded that participation is voluntary and will not affect their current or future care. If interested, written consent will be obtained a the initial study visit and prior to commencement of any research activities.

2.d Randomization Method and Blinding

After informed consent, participants will be randomized using permuted blocks of varying sizes to receive either a stellate ganglion block or a placebo saline injection near the stellate ganglion. Randomization will ocurr as 2:1 active versus placebo injection.

Blinding. Blinding will be achieved through two primary means. First, the Barnes Jewish Hospital investigational drug pharmacy will produce identical appearing mepivacaine and saline vials of which the entire research team will be unaware of the participant's intervention assignment. Second, a single-use eye patch will be placed prior to the procedure. Additionally, a cool compress will be applied to each participant's ipsilateral eye prior to the procedure and kept in place throughout the procedure and during the post-procedure recovery for a total of up to 20 min of cool compress application. Once subjects have been approved for discharge from the CTRU, participants will be asked to to wear the single-use eye patch for an additional 2 hours prior to patch removal. All subjects will be informed that Horner's syndrome can occur regardless of injection of mepivacaine or placebo.

2.e Risks and Benefits

Risks of lidocaine/mepivacaine injection (SGB) include:

- allergic reactions like skin rash, itching or hives, swelling of the face, lips, or tongue
- breathing problems
- changes in vision
- chest pain
- feeling faint or lightheaded, falls
- headache
- seizures
- slow, irregular heartbeat
- trembling or shaking
- unusually weak or tired
- confusion
- ringing in your ears

If a participant experiences any side effect listed above following the injection, the post-injection observation period will last up to 2 hours. Vital signs (heart rate and breathing) will be monitored throughout the observation period.

Side effects that are expected, common, usually lasting up to 24 hours and usually do not require medical attention:

- Horner syndrome - constricted pupil (miosis), drooping of the upper eyelid (ptosis), absence of sweating of the face (anhidrosis), and sinking of the eyeball into the bony cavity that protects the eye (enophthalmos).
- anxiety or nervousness
- backache
- feelings of cold, heat, or numb
- irritation at site where injected
- nausea, vomiting
- hoarseness
- mild shortness of breath
- dysphagia (difficulty swallowing)
- globus (feeling of something stuck in the throat)

- congestion- nasal
- temporary weakness in the arm
- blurry vision
- droopy eye lid
- eye redness
- neck pain or pain at injection site

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.

Participants may or may not directly benefit from the stellate ganglion blocks and will be aware that they may receive the saline injection (without active medication). Regardless of the results, our findings will help direct future care of patients with a similar condition.

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 SGB. Participants will face no penalty or negative consequences for withdrawaling from the study.

E3 Study Drug

3.a Treatment Regimen

Stellate Ganglion Block. All SGBs will be performed by a board-certified anesthesiologist and pain management specialist with extensive experience performing SGBs (Dr. Lara Crock). Laterality of the SGB will be randomized between the left and right sides of the neck. Participants will be asked to remain NPO for 8 hours prior to the SGB. Using ultrasound-guidance, the transverse process of the C6 vertebra is identified. Color-doppler is used to identify blood vessels. A 27-gauge needle is used to anesthetize the superficial skin with 1% lidocaine. Then, a 21-gauge ultrasound needle is advanced using an in-plane technique from lateral to medial with careful avoidance of neurovascular structures. After negative aspiration, 6-8 mL of 1% mepivacaine is deposited beneath the prevertebral fascia and above the longus coli muscle into the stellate ganglion.

The presence of a transient Horner syndrome (ipsilateral miosis, anhidrosis, and ptosis) 5-15 minutes after the SGB is expected. Post-procedure adverse effects will be documented. If participants develop globus or dysphagia they are asked to remain NPO for an additional 2 hours post-procedure.

All participants will be monitored for adverse effects prior to, during, and immediately following each SGB. A continuous electrocardiogram (ECG) is run from just prior to the start of the procedure until ten minutes following its completion. Vital signs, including pulse oximetry, blood pressure, heart rate, and respiratory rate will be obtained prior to the beginning of the procedure and repeated until ten minutes post-procedure.

Placebo Injection. The placebo sham injection will be performed in an identical fashion as the stellate ganglion block by Dr. Crock with the exception of using 6-8 mL of 0.9% saline injection instead of mepivacaine. A Horner syndrome is not expected after placebo injection, but its presence has been noted in prior studies with sham SGBs.

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 contact database of COVID-19-induced olfactory dysfunction patients based on the inclusion/exclusion criteria. For those meeting the selection criteria, we will access name, telephone number, age, sex, and date/time of any upcoming clinic visits. For interested and potentially eligible individuals, including those contacting the study team, eligibility will be determined based on the inclusion/exclusion criteria and completion of the DisODOR questionnaire. If they have been treated at the medical center for COVID, their medical record will be accessed.

F2 Schedule of Measurements

The first visit will be completed at the Clinical and Translational Research Unit (CTRU). The second and third visits 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, respiratory rate, heart rate, and pulse oximetry within the CTRU for a minimum of 10 minutes after completion of the block to ensure patient stability prior to discharge. Additional monitoring will be provided as needed based on patient response to the procedure. Participants will be discharged once stability is determined and instructed to continue wearing an eye patch for an additional 2 hours. It will be ensured that they have someone to drive them home prior to discharge.

Visit 1

At the initial visit, demographic information, including age, sex, race, and length of time of parosmia will be collected from each enrolled patient. Prior to undergoing the first SGB, participants will complete the Parosmia trigger question, DisODOR, UPSIT, CGI-S for Parosmia, OCS, HADS, and Pre-Intervention Expectations Questionnaire. The assessment of the blind will occur just prior to discharge from the first visit.

Visit 2

The second visit will be virtual and will occur approximately 1 month after the first visit. Participants must have access to email and the internet to receive a link which will

connect them with the questionnaires to complete about their smell ability and how they are feeling.Their answers will be saved in saved in REDCap. Participants will be asked to fill out the Parosmia trigger question and the DisODOR. They will also complete the CGI-I for Olfactory Dysfunction, the LCQ, the Participants Satisfaction with Treatment Questionnaire, OCS, HADS, and Adverse Events Assessment.

Visit 3

The third and final visit will be virtual and will occur approximately 3 months after the injection. Participants must have access to email and the internet to receive a link which will connect them with the questionnaires to complete about their smell ability and how they are feeling.Their answers will be saved in saved in REDCap. At 3-months post-SGB, participants will virtually complete the Parosmia trigger question, DisODOR, CGI-I for Olfactory Dysfunction, LCQ, Participant Satisfaction with Treatment Questionnaire, OCS, HADS, and Adverse Events Questionnaire.

Schedule of Events	**Visit 1**		**Visit 2** 1 Month post SGB (=+/- 7 days)	**Visit 3** 3 Months post SGB (+/- 7 days)
	Screening*	**Baseline**		
Informed Consent	X			
Demographics Questionnaire**	X			
Inclusion/Exclusion Criteria	X			
Parosmia trigger question		X	X	X
CGI-S for Parosmia		X		
University of Pennsylvania Smell Identification Test (UPSIT)		X		
Pre-Intervention Expectations Questionnaire		X		
Parosmia Olfactory Dysfunction Outcomes Rating (DisODOR)	X	X	X	X
Olfaction Catastrophizing Scale (OCS)		X	X	X
Hospital Anxiety and Depression Scale (HADS)		X	X	X
Long-COVID Questionnaire		X	X	X
SGB or Placebo Injection		X		

Assessment of the Blind		X		
CGI-I for Parosmia			X	X
Participant Satisfaction with Treatment Questionnaire			X	X
Adverse Events Assessment		X	X	X

*Screening and Visit 1 may occur at the same visit
**Demographic variables include date of birth, sex, race, ethnicity, home address, date of (+) COVID-19 test
***The assessment of the blind will occur just prior to discharge from the first visit.

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 20 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 on our team's previous pilot study with 50% of participants reporting slightly improved olfactory dysfunction at 1 month.

A power analysis was performed using Fisher's exact test in G-Power 3.1.2. Our recently completed SGB trial showed that 1 month after injection, 35% of the participants had an improvement of 15 points of more in ODOR total score. Using a clinically important difference of 25% in proportions of responders between active treatment and control group, we estimated using an exact test that a sample size of 114 subjects (38 controls

and 76 cases) will be needed to detect with 80% power at the 2-sided alpha level of 0.05.

Considering a 20% drop-out rate the total sample size to enroll is up to 140 participants.

G2 Interim Monitoring and Early Stopping

We plan to perform an interim futility analysis. The recruitment will be halted and we will perform interim analysis when the first 40 subjects randomized and who have successfully completed treatment will have completed their 1-month post treatment assessment. Comparison of the primary endpoint between the 2 study groups will be evaluated for the interim futility analysis. Fisher's exact test will be used for the analysis given the small sample size. Conditional power (CP) with is the probability of finding statically significant results at the end of the trial, given the information obtained at interim analysis will be calculated using Mehta & Pocock CP equation. If CP<20% the result will be considered as suggestive of futility and it will serve only as a guideline that initiates more comprehensive discussion as to whether the course of the study should be modified. The data will be frozen for analysis and will be saved, so that additional analyses may be performed, or the analyses recreated, if necessary. Interim comparative data will be considered confidential and the results will be provided in a blinded fashion to research team members.

G3 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 between-subject change in DisODOR.

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. The DisODOR has an MCID of 15 points. A difference of at least 25% from the saline group is considered clinically meaningful. **If a greater than 25% proportion difference in responder rate is achieved in favor of the SGB group, we will offer the SGB to the placebo group at the conclusion of the study.** This will be submitted as a modification to the study.

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 regulatory coordinator with the assistance of the study team will:

- Review of credentials, training records, and delegation of responsibility logs.
- Review of Consent Forms:
    - 100% reviewed for studies with < 100 subjects.
- Review reports on missed events, missing data, and protocol deviations for a determined sample of subjects.
- Compare source documentation and CRFs (REDCap database) to ensure data are accurate and complete.
- Regulatory review of IRB approvals in the Investigator Site File.

Monitoring Schedule:

- The first monitoring activities will occur within 1 month after first subject is enrolled.
- Interim monitoring activities will occur after 20 participants are enrolled and again when enrollment is met and all visits for all participants are completed.
- Ad hoc or for-cause monitoring as needed or requested.

J Attachments

J1 Questionnaires or surveys

- Assessment of the Blind
- Parosmia trigger question
- Parosmia Olfactory Dysfunction Outcomes Rating (DisODOR)
- CGI-S for Parosmia
- CGI-I for Parosmia
- Long-COVID Questionnaire
- Olfactory Catastrophizing Scale (OCS)
- Hospital Anxiety and Depression Scale (HADS)
- Pre-Intervention Expectations Questionnaire
- Participants Satisfaction with Treatment Questionnaire
- University of Pennsylvania Smell Identification Test (UPSIT)

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