Vagus Nerve Stimulation to Improve Post-operative Outcomes of Degenerative Cervical Myelopathy

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A Introduction

A1 Study Abstract

A2 The objective of this study is to generate preliminary data to establish the feasibility and effectiveness of transauricular Vagus Nerve Stimulation (taVNS) to improve post-operative outcomes of patients with moderate to severe Degenerative Cervical Myelopathy (DCM), The central hypothesis of this study is that taVNS as an adjunct surgical intervention in patients with DCM is feasible and improves post-operative outcomes compared to patients who do not receive taVNS. We will investigate this by evaluating the feasibility and short-term effectiveness of taVNS as an adjunct to surgical intervention for DCM. We will prospectively enroll 36 patients with DCM, in three groups: stimulation before only group, stimulation before and following the surgery group, and sham group. We will also compare long-term outcomes among the three groups to substantiate the hypothesis that a short course of taVNS has long-term effects which remain meaningful.Primary Hypothesis

The primary hypothesis is that taVNS is a feasible adjunct to surgical intervention for DCM. Patients with DCM who receive taVNS therapy will show relatively greater improvements in mJOA at 3 months follow-up.

A3 Purpose of the Study Protocol

The objective of this study is to generate preliminary data to establish the feasibility and effectiveness of transauricular vagus nerve stimulation (taVNS) to improve post-operative outcomes of moderate to severe degenerative cervical myelopathy (DCM).

B Background

B1 Prior Literature and Studies

Degenerative cervical myelopathy is a common and debilitating disease whose prevalence continues to grow with aging population[1]. DCM can manifest as gait imbalance, weakness and impaired dexterity, among others. These signs and symptoms arise due to structural and functional impairment of spinal cord integrity as well as cortico-cortical and cortico-spinal connectivity.[2,3]

Functional recovery following surgery for DCM is often delayed – with patients realizing functional recovery over weeks to months following surgery. Moreover, up-to 20% of patients do not experience functional recovery post-operatively and up to 5% may actually get worse following surgery.[1] There is an unmet need of adjuncts to surgical management of DCM that enhance recovery, improve post operative length of stay and functional outcomes.[2,3]

B2 Rationale for this Study

Delayed functional recovery following surgery for DCM is linked to mechanisms including neuroinflammation and a lack of augmentation of neuroplasticity.[1,4] While elevated serum levels of IL-6 have been associated with DCM severity and worse post-operative DCM outcomes, they remain elevated following surgery indicating continued neuro-degeneration. Similarly, TNF-alpha levels remain elevated even after 3 months following surgery.[5-7] These data point to the need of an adjunct to surgery and therapy for DCM as the ongoing inflammation cannot be modulated without one. Vagus nerve stimulation (VNS) has long been known to modulate inflammation through reduction in cytokine production. Recently transauricular VNS (taVNS) has shown its benefits in sub-arachnoid hemorrhage, where it reduced radiographic vasospasm, lowered TNF-α and IL-6 levels, and led to higher favorable discharge outcomes (38.4% for VNS vs. 21.4% for sham).[8-11]
Neuroplasticity is limited in older age. But, it can still be augmented significantly, a practice critically lacking for patients with DCM.[12] Following damage to neural structures, latent neural circuits can still be recruited to rehabilitate and regain useful function.[13] VNS therapy has been shown to do exactly this – i.e. restore motor function in patients with stroke.[14-17] Given the critical lack of adjuncts for surgical intervention in patients with DCM, it is only imperative to implement VNS and leverage its action to improve outcomes of surgery for DCM.[18]

C Study Objectives

C1 Primary Aim

The primary objective of this research is to gather preliminary data to determine the feasibility of and effectiveness of taVNS to improve post-operative outcomes for patients undergoing surgery to treat moderate to severe DCM, in the short as well as long term.

C2 Secondary Aim

Secondarily, this study will also examine opioid usage for post-operative pain by the patients who receive taVNS and those who do not.

C3 Rationale for the Selection of Outcome Measures

The modified Japanese Orthopaedic Association (mJOA) score is an international standard and a validated measure of neurological impairment in degenerative cervical myelopathy, with a defined minimum clinically important difference (MCID) of 2 points. The Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire assesses upper

extremity function with a clinically meaningful change of ~–8 points in patients with cervical spine disease. The Neck Disability Index (NDI) is a measure of activity limitations associated with neck pain; an MCID of 7.5 (on a scale of 0 - 50) has been validated for cervical spine fusion. Although not exclusively validated for DCM, the visual analogue scale (VAS) is the most commonly used tool to describe neck and arm pain in degenerative disease of the cervical spine.

D Study Design

D1 Overview or Design Summary

This prospective, randomized, partially blinded trial will enroll 36 subjects with moderate to severe DCM undergoing surgical intervention at Washington University School of Medicine. Transauricular vagus nerve stimulation (taVNS) will be delivered to the left cymba Conchae with a transcutaneous electrical nerve stimulation (TENS) unit at established parameters given in the table below:

Table 1. Stimulation parameters of VNS for targeted plasticity	
Sessions/Week	5
Sessions/Day	2/day
Session Duration	~30 minutes
Frequency	20 Hz
Pulse Width	250μs
Intensity	0.4-2 mA

There are three subject cohorts:

1. Pre-Post Group (P-P): The P-P Group will undergo taVNS for up to 6 weeks before and for three months following surgery
2. Post Group: The Post Group will undergo sham stimulation (clip will be applied to lobe instead of cymba conchae) for up to 6 weeks before surgery. They will receive taVNS for 3 months after surgery.
3. Sham Group: The Sham Group will undergo sham stimulation to the earlobe for up to 6 weeks before and for 3 months after surgery.

Subjects will not know into which group they will be placed as we do not expect them to understand the difference between the location of the device placement in terms of stimulation.

We will also examine opioid usage in terms of total morphine milligram equivilants (MME) and duration of opiate prescriptions up until 3 months postoperative.

Patients will be given an opportunity to participate in optional tasks that will test dexterity, balance and sensitivity.This will be described in further detail below.

D2 Subject Selection and Withdrawal

All patients who present with DCM will be screened to be included in our study.

2.a Inclusion Criteria

- 18 years of age or older
- Moderate or severe degenerative cervical myelopathy according to the mJOA
- Decompression surgery planned

2.a Exclusion Criteria

- Pregnancy
- Electrically active implants (e.g. pacemaker)
- Known diagnosis of amyotrophic lateral sclerosis, multiple sclerosis, rheumatoid arthritis, concomitant thoracic and/or lumbar stenosis, spine tumor, HIV-related myelopathy
- Ongoing cancer therapy
- Ongoing use of immunomodulating or suppressive medication
- Sustained bradycardia with a heartrate <50 beats per minute for > 5 minutes following admission.
- Prior cervical spine surgery

2.b Ethical Considerations

The use of the stimulation device is in addition to their standard of care medical treatment. Surgery will not be delayed due to the use of the stimulation device.

2.c Subject Recruitment Plans and Consent Process

Patients will be recruited and consented in one of the following ways:

1. Patients may be identified during their clinical visit to the surgeon. A study coordinator or surgeon may introduce the study. The coordinator will review the objectives and activites of the study. The patient will be asked to complete the modified Japanese Orthopedic Assocation (mJOA) questionnaire in order to determine if their myelopathy is categorized as moderate to severe. If so, the consent will be presented for signature.

2. A study coordinator will review the surgical schedule to identify patients who may qualify for this study. The coordinator will will contact the patient by phone and use an IRB-approved phone script to introduce the study. The patient will be asked to complete the mJOA over the phone if it has not been completed as part of SOC. If myelopathy is moderate to severe, and the patient is interested in participating, the coordinator will email the consent to the patient. A time will be set up to review the consent by phone or via Zoom. If the subject agrees, an ICF will be sent via Docusign for signature.

The participant will receive a signed copy of the consent document.

2.d Randomization Method and Blinding

Patients will be randomized into one of the three study cohorts. They will have an equal chance to be included in each group. The study is single-blinded, so the patients will not know to which group they are randomized. .

2.e Risks and Benefits

There may or may not be a benefit for participation in this study depending if the stimulation therapy improves the outcomes after surgery. There may be a benefit to society as new knowledge gained by this study may offer new options and improvements of treatments for DCM

Patients may feel discomfort during stimulation.

2.f Early Withdrawal of Subjects

Participants will be in the study until their one-year follow-up visit is completed. If the subject does not return for the study visits, the coordinator will contact the subject by telephone up to 3 times. If there is no response, the coordinator will send a letter to the subject. If no response is received after one month following the letter, the subject will be withdrawn and considered lost to follow-up.
Subjects may decided to withdraw from the study at any time for any reason.
Data that has already been collected will remain in the study and may be used for research purposes.

2.g When and How to Withdraw Subjects

Patients who wish to withdraw from the study may inform the PI or the coordinator that they no longer wish to participate in the study. A letter is available on the WashU HRPO website that may be sent to the study team.

2.h Data Collection and Follow-up for Withdrawn Subjects

Data that has been collected prior to the subject's withdrawal will be kept and used for research purposes. No further data will be collected.

E Study Procedures

E1 Screening for Eligibility

Surgeons may identify potential candidates for the study. A study coordinator will also review the schedule of the surgeons and identify potential candidates. Potential candidates may be approached in person or over the phone as described in the *Subject Recruitment Plans and Consent Process.*

E2 Schedule of Measurements

The following procedures will take place as follows:

E3 ***Baseline:*** The following questionnaires will be collected prior to surgery:

1. Modified Japanese Orthopedic Association (mJOA) – used to determine the level of myelopathy the patient is experiencing
2. Disabilities of the Arm, Shoulder and Hand (DASH) – self-reported measure to assess how musculoskeletal conditions of the upper limbs affect function and symptoms.

3. Neck Disability Index (NDI) – designed to provide information as to how neck pain affects ability to manage everyday life
4. Visual Analog Scale (VAS) – assesses subjective characteristics such as pain and fatigue

The taVNS stimulation is performed by placing an ear clip to the cymba conchae of the left ear. The earpiece will be connected to the TENS unit. The parameters will be set by the study coordinator.
The Sham stimulation is performed by placing an ear clip to the lobe of the left ear. The earpiece will be connected to the TENS unit. The parameters will be set by the study coordinator.

Patients will be randomized into one of the three groups. The patients will be trained on how to perform the stimulation at home. The stimulation (sham and taVNS) will be performed 5 days per week, twice per day up until the surgery date or for 6 weeks, whichever comes first. The surgery date will not be delayed due to the patient's participation in this study.

Patients will be provided the TENS unit free of charge to use for this study. They will return the TENS unit when post-op stimulation is complete. They may bring the until to their 3-month post-op visit or a label will be sent to them to return via FedEx or UPS.

Patients will be asked to download an app called MyCap in order to record start times, end times and comments for each therapy session. The data in MyCap is automatically synchronized with our study database in REDCap. If data is collected while device is offline, it will automatically be sent once internet is restored and app is open.

Participants will be offered the opportunity to participate in optional study activities. They will be asked to download a free app called SynapTrack and asked to perform simple tasks while holding the phone. Activities include tasks such as a tapping test – touching buttons on the screen to test dexterity. They may be asked to walk with the phone in hand to test gait and functional activities. A coordinator will assist with downloading the app and training the participant on study tasks. The participant may choose one of the following options:

1. Perform optional activities for 4 consecutive days prior to starting the taVNS or Sham stimulation prior to surgery. They will also perform the tasks every Monday and Thursday after surgery for 3 months.
2. Perform the optional activities once prior to taVNS or Sham stimulation pre-operatively, once after pre-op stimulation is completed prior to surgery, once at 6 weeks post-op and once at 3 months post-op.
3. The participant may choose to NOT participate in any optional activities.

E4 Surgery: Participants will undergo the surgery as determined by their surgeon. The study does not change or determine any medical treatment

E5 ***Post-op Stimulation:*** The P-P group and the Post will perform taVNS therapy twice per day/ 5 days per week for three months starting on the day after

surgery**.** The Sham Group will perform Sham stimulation twice per day/ 5 days per week for three months.

Patients participating in the first optional activity will perform their tasks every Monday and Thursday for 3 months.

E6 Post-op Visits:

Patients will return for their standard of care post-op visits. These visits will take place whether or not the the patients are in the study.

- **6 Weeks Post-op:**
  - Patients will complete the study questionnaires (mJOA, DASH, NDI, VAS)
  - If patient is participating the the second optional activity tasks, the coordinator will ask the patient to complete the activity at the appointment if they did not complete the activity prior to the appointment.
  - The study coordinator will ask the patient about their pain medication.

- **3 Months Post-op**
  - Patients will complete the study questionnaires (mJOA, DASH, NDI, VAS)
  - If patient is participating the the second optional activity tasks, the coordinator will ask the patient to complete the activity at the appointment if they did not complete the activity prior to the appointment.
  - The study coordinator will ask the patient about their pain medication.
  - Subjects will bring the TENS unit to their appointment and return it to the research or clinical team.
  - If subject participated in the first optional activity, they will discontinue their optional tasks.
  - If subject participated in the second optional activity, they will complete the activities either at the 3 month visit or prior to their arrival for the appointment.

- **6 Months Post-op**
  - Patients will complete the study questionnaires (mJOA, DASH, NDI, VAS)
  - If patient is participating the the second optional activity tasks, the coordinator will ask the patient to complete the activity at the appointment if they did not complete the activity prior to the appointment.
  - The study coordinator will ask the patient about their pain medication.

- **12 Months Post-op**
  - Patients will complete the study questionnaires (mJOA, DASH, NDI, VAS)
  - If patient is participating the the second optional activity tasks, the coordinator will ask the patient to complete the activity at the appointment if they did not complete the activity prior to the appointment.
  - The study coordinator will ask the patient about their pain medication.

Study participation will be complete after the 12-month visit occurs.

E7 Safety and Adverse Events

7.a Safety and Compliance Monitoring

The medical risks of the surgery are the same whether or not the patient participates in the study. Patients will be trained on operating the TENS unit prior to stimulation. Patients may feel some minor discomfort, slight pain and/or a headache from using the TENS unit.
A risk of study participation is that confidential information may be accidentally disclosed. The study team will take appropriate measures to ensure the safety of the participants' personal information and will not share any PHI with anyone outside the research team.

7.b Adverse Events

Adverse events related to the TENS unit and the stimulation will be collected from the participant. As the surgery and medical treatment is standard of care, we will not collect adverse events related to the surgery only.

E8 Study Outcome Measurements and Ascertainment

Feasibility of taVNS will be assessed through patient compliance and tolerability. Validated outcome measures will include mJoA, disabilities of the arm, shoulder and hand (DASH), neck disability index (NDI), and VAS arm/neck scales (collected at six-weeks, three-months and one-year following surgery). We will also examine opioid usage in terms of total morphine milligram equivalents (MME) and duration of opiate prescription up until 6-months following surgery.

F Statistical Plan

Statistical analysis: Descriptive statistics will assess baseline characteristics of the patients in the three groups. Continuous variables will be reported as means ± standard deviations or medians with interquartile ranges, as appropriate, and categorical variables as counts and percentages. Balance among groups will be assessed using standardized mean differences (for variables e.g., age, sex, baseline mJOA, comorbidities, and surgical characteristics).

We expect the patients to have a compliance rate of 80% or more (defined as percentage of VNS sessions received relative to the total required sessions) and a tolerability of 70% or more (defined as the percentage of duration of VNS sessions completed relative to the total duration required). The comparisons from baseline to post-operative, in mJoA, DASH, NDI, and VAS-arm/neck score will be estimated using a mixed model for repeated measures (95% CI and a 2-sided P value of <0.05). Opioid MME and duration of opiate-use until 3 months post-operatively, among the three groups will be compared using Wilcoxon rank-sum test ($\alpha = 0.05$).
Sample size: Given the pilot nature of the study, a sample size estimation is not possible. However, we will enroll 12 patients in each group.

F1 Interim Monitoring and Early Stopping

Interim monitoring will be conducted weekly for each patient for safety and tracking of adverse events related to taVNS. Patients will also be informed to report immediately to

the study team if an adverse event occurs, or if they believe their session was abnormal in any way. The study will be paused or terminated early if unexpected serious adverse events occur or if mJoA of the patients worsens by more than 2 points.

G Data Handling and Record Keeping

Data will be stored electronically in REDCap. Daily diaries from the stimulation sessions will be collected via MyCap and synchronized with REDCap immediately if there is an internet connection. If data is collected offline, data will be sent once internet is restored and app is open. Data on the patient's device will be erased once it is transmitted.

A study visit tracker and master list containing patients' names and study IDs,birthdays, and surgery/visit dates will be stored on the network drive of Washington University. A username and password is required to access the network. The visit tracker/master list will be protected by a password that is known only to the research team.

G1 Confidentiality and Security

Every effort will be made to ensure our study participants' data is protected and will not be shared with anyone other than the research team.

G2 Case Report Forms and Source Documents

Case Report Forms will be used if data is collected on paper before being entered into Redcap. If paper forms are used, they will be scanned and uploaded into Redcap, and the paper copies will be shredded.

G3 Records Retention

Study records will be kept until 7 years after the study closure.

H Study Administration

H1 Organization and Participating Centers

This is a single-site trial. Washington University is the only participating site.

H2 Funding Source and Conflicts of Interest

This study is not funded by an outside source.

H3 Subject Stipends or Payments

Participants will not be paid for their participation.

H4 Study Timetable

We expect enrollment will be completed in one year. Participants will be in the studies for one year. Total time for study is 2 years after enrollment begins.

I Publication Plan

Results of this study will be submitted for publication in a peer-reviewed scientific journal relevant to spine surgery, neuromodulation, or neurorehabilitation. Findings may also be presented at national or international academic conferences. All publications and presentations will report only de-identified, aggregate data to protect participant confidentiality.

J Attachments

J1 Tables

J2 Informed consent documents

Patients will sign a consent document after it has been reviewed with the study coordinator. A signed copy will be provided to the participant. If patient is contacted by phone, a phone screen will be utilized to introduce the study and assess eligibility. If patient is agreeable, the consent form will be reviewed. The consent will be sent to the participant via Part 11 Compliant Docusign. After all signatures have been collected, the participant will receive a signed copy of the consent.

J3 Questionnaires or surveys

The following questionnaires will be collected at Baseline/Screening, 6 weeks, 3 months, 6 months and one year post-surgery.

- mJOA – Modified Japanese Orthopedic Association determines the severity of the participant's myelopathy.
- *DASH:* Disabilities of the Arm, Shoulder and Hand is a self-report measure to assess how musculoskeletal conditions of the upper limb affect physical function and symptoms.
- *NDI:* The Neck Disability Index is a questionnaire designed to give us information as to how your neck pain has affected your ability to manage everyday life.
- *VAS:* The Visual Analog Scale assesses subjective characteristics such as pain and fatigue.

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