Non-invasive Vagus Nerve Stimulation for Parkinson's Disease

Investigators

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I. Introduction

Although breakthroughs in the management of Parkinson's disease (PD) have emerged in recent decades resulting in better control in symptoms, majority of patients with PD are still living with various disabling motor and non-motor symptoms despite they are already receiving the best contemporary medical or surgical treatments available to them. Moreover, each treatment option has its pros and cons, and a specific treatment option may not suit the needs of an individual patient. For example, although levodopa is a potent symptomatic pharmacological agent, its long-term use is associated with motor complications. Deep brain stimulation (DBS) is an effective option for medication refractory symptoms and motor complications for advanced PD, DBS remains an invasive and expensive procedure. Older patients or those with apparent cognitive impairment may not be eligible for receiving DBS. In addition, certain symptoms are less responsive to medications or to DBS, e.g., freezing gait and postural instability. To date, disease modifying treatments for PD are yet not available. There is obviously a need to develop additional treatment modality to further optimize the control of symptoms and/or slow the disease progression for patients having PD.

Noninvasive brain stimulation (NBS) like transcranial magnetic stimulation (TMS) transcranial direct current stimulation (tDCS) have shown promise as adjunctive therapies for PD symptoms. Vagus nerve stimulation (VNS), another NBS modality has been approved for the treatment of various neurological disorders including epilepsy, migraine, and depression. VNS is believed to modify brain rhythms by modulating the nucleus of the solitary tract and locus coeruleus and other regions known to play a role in gait. Moreover, VNS may modulate inflammatory pathways and reduce oxidative stress, making it a potential disease modifying treatment approach for neurodegenerative diseases linked to neuroinflammation such as PD.[1] Some small case series using VNS among PD patients have shown some positive results, while some have not. While a recent systematic review suggests a potential benefit of non-invasive VNS in improving mainly gait impairment in PD.[2] However, the same review reported a study showing decline in verbal fluency associated with VNS.[2] Moreover, various stimulation electrical signals may yield different clinical effects or risk benefit ratio.[2] Overall, further study is warranted to explore the efficacy of non-invasive VNS for its effects on gait and other symptoms of PD as well as the anti-inflammatory effects.

II. Study Objectives and Hypothesis

The objective of the present study is to investigate the feasibility, safety, and potential efficacy of 2 different non-invasive VNS stimulation protocols (conventional and exploratory) for patients with PD. The immediate effects of VNS as well as the medium-term effects of daily VNS at 2 and 4 weeks poststimulation, and the delayed effects of non-invasive VNS at 8 weeks of both stimulation protocols will be investigated. The effects of non-invasive VNS of the 2 different stimulation protocols will also be compared with sham stimulation. The study will be a randomized single blind study. The tested subjects, not the assessor, will be kept unaware of which treatment protocols they are receiving

We hypothesize the VNS stimulations may provide immediate effects, medium-term effects and delayed effects.

III. Research Plan

1. Inclusion criteria

a. Idiopathic PD as defined by the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria
b. Age 40 – 75 years old
c. Presence of gait impairment as defined by any of the below:
    i. a UPDRS Part 2 Item 15 (Walking) with a score of 2, i.e., moderate difficulty, but requires little or no assistance;
    ii. b. UPDRS Part 3 Item 26 (Leg Agility) with score of 2 or 3, i.e., moderately impaired, with definite and early fatiguing, may have occasional arrests in movement; or severely impaired, with frequent hesitation in initiating movements or arrests in ongoing movement
    iii. UPDRS Part 3 Item 29 (Gait) with score of 1 or 2
d. Availability of a caregiver at home
e. Cantonese speaker

2. Exclusion criteria

a. Patients with atypical parkinsonism (e.g., multiple system atrophy, progressive supranuclear palsy, dementia with Lewy Bodies)
b. PD with dementia
c. PD patients with DBS in-situ
d. Severe PD with a Hoehn and Yahr staging of 4 or above
e. Low blood pressure with systolic of < 110 mmHg or with postural hypotension as defined by a decrease in systolic and diastolic blood pressure by 20 mmHg and 10mmHg upon standing, respectively)
f. Cardiac pacemaker in-situ

3. Subject Identification

Subjects will be identified at specialist clinics at Prince of Wales Hospital

4. Sample Size Estimation

60 subjects subject with PD will be recruited and divided into 3 groups. The sample size of 20 per group is based on a previous pilot study showing the potential positive efficacy of VNS with a sample size of 17-19 subjects per treatment arm.[1]

IV Methodology

1. Group Distribution

We plan to recruit 60 subjects with PD for this study. All subjects will be randomized in 1:1:1 ratio to one of the following 3 groups: conventional VNS (cVNS), exploratory VNS (eVNS),

and sham VNS (sVNS). Each group will consist 20 subjects.

2. Visit Schedule

a. Screening Visit

i. Confirm eligibility
ii. Informed consent

b. Baseline

i. Baseline visit can be combined with screening visit
ii. Cognitive and motor assessments (will be performed at the "off" medication state.)
iii. Collect vital signs and demographic information
iv. ECG
v. Randomization
vi. Study blood drawing

c. Initiation stimulation Visit

i. Should be scheduled within 2 weeks from baseline visit
ii. Pre-stimulation BP
iii. Initial stimulations at study site (3 cycles, see figure 1: Acute Treatment)
iv. Post-stimulation assessments (will be performed about 10 minutes after the 3rd cycle; perform at the "off" medication state.)
v. Record AE/SAE

d. 2-week home-stimulation phone follow up

i. Record and AE/SAE

e. 4-week home-stimulation follow up

i. Collect vital signs
ii. Cognitive and motor assessments (will be performed at the "off" medication state.)
iii. Study blood drawing
iv. ECG
v. Record AE/SAE

f. 8-week post stimulation follow up

i. Collect vital signs
ii. Cognitive and motor assessments (will be performed at the "off" medication state.)
iii. ECG
iv. Study blood drawing
v. Record AE/SAE

3. Stimulation protocols of each treatment group

a. *Stimulation Site and frequency*

The stimulation protocol for the cVNS, eVNS, and sVNS treatment group is similar. On the day of initiating the stimulation, 3 cycles of stimulation will be applied at "off" mediction. (figure 1) Each cycle of VNS treatment consists of 4 sets of 2 minutes' stimulation (i.e., total 8 minutes/cycle). First set of stimulation targets one side of the neck first (e.g., right side), followed by second set of stimulation targeting the other side of the neck (e.g., left side). The third and fourth set of stimulation will repeat the stimulation on the right and left side, respectively again. For the 1st set of stimulation in the first cycle, stimulation current will start with 5 miniampere (mA).

b. Initial Stimulation

Stimulation current will be increased by 1mA for the 2nd to 4th set of stimulation, i.e., 6mA, 7mA, and 8mA for 2nd, 3rd, and 4th set of stimulation, respectively. If the subject tolerates 8 mA, the 1st set of stimulation current of the second cycle will start from 9mA, and it will be increased by 1mA for the subsequent sets of stimulation, i.e., 10mA, 11mA, and 12mA for 2nd, 3rd, and 4th set of stimulation, respectively. If the subject tolerates 12mA, the 1st set of stimulation current of the third cycle will start from 13mA, and again, the stimulation current will be increased by 1mA for the subsequent sets of stimulation, i.e., 14mA, 15mA, and 16mA for 2nd, 3rd, and 4th set of stimulation, respectively. In case the subject has difficulty in applying the stimulation, a caregiver should be available to provide assistance. In case the subject cannot tolerate the next level of stimulation current, the current will be kept at the level that the subject is able to tolerate.

c. 4-week Home Stimulation

After this initiation phase, the subject/caregiver will be advised to apply the stimulation treatment at home for 4 weeks that consists of 3 cycles of treatment per day e.g.in the morning, afternoon, and evening, on or off medication. The minimum time between 2 cycles should be 3 to 6 hours. For the morning cycle of stimulation on the first day after the initiation phase, stimulation current from the 1st to 4th set of stimulation should be increased from 17mA to 20mA (if tolerable). Stimulation current will be increased by 1mA each time until a current of 30mA is reached or until intolerable side effects occur.

d. Mechanism of the devices

The cVNS emits a low-voltage 5.56 KHz sinusoidal wave electrical signal bursts lasting 0.9 ms via two flat stimulation contact surfaces. (Figure 2) These bursts repeat once every 38 millisecond (ms). Each set of stimulation will be applied for 2 minutes. Stimulation current can be self-adjusted by the subject. This conventional stimulation waveform was approved by the US FDA for the treatment of migraines.

The eVNS stimulation parameters, name as "Koala" were designed by Advanced Micro Integration Limited, Hong Kong. The devices have been developed under IAO 13485 Quality Management System QMS. The main components of the VNS devices are manufactured by GMP manufacturers.

The eVNS emits the company-proprietary low-voltage of 3~8 KHz sine-variant smooth-transition wave electrical signal bursts lasting near 0.9 ms via two flat stimulation contact surfaces. These bursts repeat once in intervals of approximately 40 ms. A potential benefit of this waveform is that it can produce less unpleasant skin sensations at a given current intensity and this may enhance the subject to tolerate higher current intensity than that of the conventional stimulation.

The sVNS delivers mechanical motor vibrations to provide a similar perceptible stimulation feeling to the skin. No electrical stimulations are delivered. The device that delivers the sham stimulation is identical in appearance, weight, and user interface. A button to adjust "stimulation current" is also available in the sham device so as to allow the subject/caregiver to adjust the "stimulation current". The protocol of titrating the stimulation current for eVNS and sVNS is identical to that for cVNS.

e. Available safety data of the non-invasive device

1) Electrical safety
   - The case is made of PLA[3] material(s) which is a decent electrical insulator, which helps prevent direct conduction.
   - The rechargeable Li-ion battery has a protection circuit that protects against overcharging, overdischarging, and short-circuiting.
2) Biocompatibility
   - PLA is biocompatible for external, non-invasive applications.
   - PLA is widely used in medical-grade applications such as sutures, implants, and scaffolds.
   - PLA can be non-toxic and well-tolerated by skin when used externally. (Castro et al., 2022)
3) Usability
   - The device is used repeatedly by users who have no prior knowledge of operation. Users can follow the user manual to perform a complete treatment.
   - Users are interviewed regarding the ease of setup and operation, clarity of instructions, user confidence and comfort.
   - All usability tests are performed in a home-like setting without clinical supervision.

4. Withdrawal

If the subject cannot tolerate a minimum simulation current of 10mA or below, the subject will be withdrew and discontinued from further assessment on clinical effects. Post-stimulation cognitive and motion assessment will not be performed if subject cannot tolerate any current below 5mA. AE and/or SAE should be record for any intolerance occur at initial stimulation visit.

Figure 1. Noninvasive Vagus Nerve Stimulation Protocols

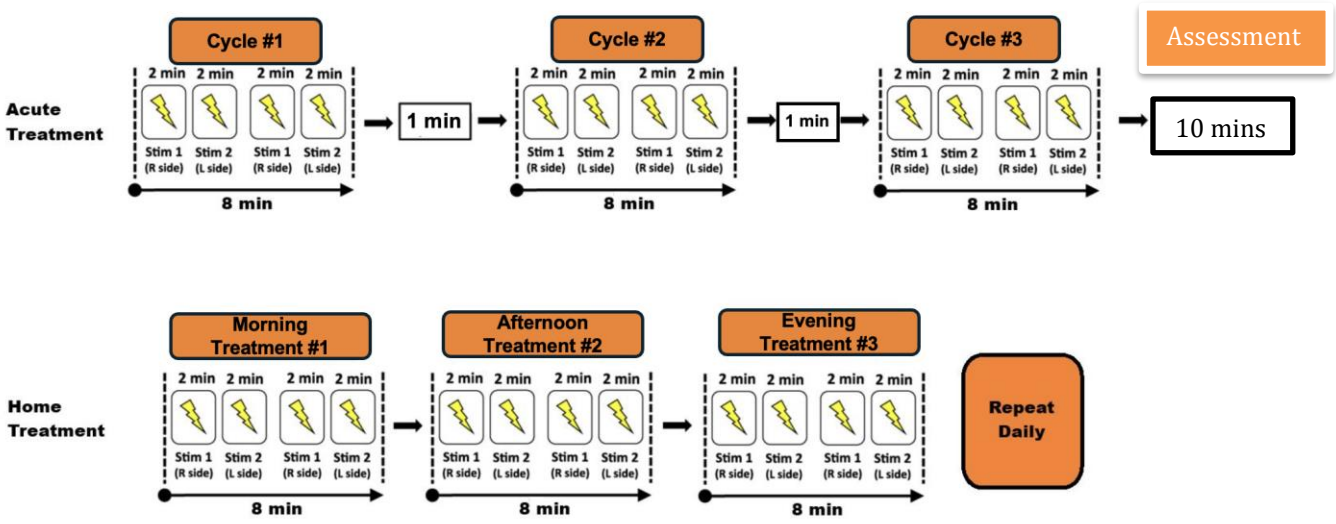


Figure 2. noninvasive Vagus Nerve Stimulator



Landmark of stimulation is at the upper portion around the sternocleidomastoid muscle where the carotid pulsation is felt of each side of the neck

V. Study Measures

Primary outcome measures will be the comparative results of the following assessments. The secondary outcome will the vital sign and AE and/or SAE during the study period from baseline and up to 8-week follow up visit.

1. Baseline, 4-week follow up and 8-week follow up
   a) UPDRS Part 2 and 3.
   b) Timed Up & Go test (TUG) for assessing functional mobility

c) Quantitative Gait Assessment
d) Hong Kong-Montreal Cognitive Assessment (HK-MoCA) (Standard version or alternative version)
e) Geriatric depression scale
f) Blood pressure (supine and standing) and body weight (kg)
g) Blood-based biomarkers: tumour necrosis factor (TNF)- alpha, interleukin (IL)-6, IL-10, and Brain Derived Neurotrophic Factor (BDNF) (2 tubes of EDTA tube, 3ml/tube). Total 18ml of blood will be collected for this study
h) ECG

2. Post initial stimulation (after 3rd cycle):
   a) UPDRS Part 2 and 3.
   b) Timed Up & Go test (TUG) for assessing functional mobility
   c) Quantitative Gait Assessment

VI. Risk and Safety monitoring

Potential risks may include but not limited to: irritation or pain at the stimulation site; dizziness, syncope, hoarse voice, swallowing difficulty during or after the stimulation. Condition of subject will be closely monitored by study team during initial stimulation visit at site.

During the 4-week at home stimulation, subject and caregiver should record any discomfort on the subject diary and report to research team when necessary. A 2-week phone FU will be performed for safety monitoring. Subject should stop if discomfort/side effect persist or worsen and report to study team. Unscheduled visit may be arranged for AE and/or SAE when necessary.

Insurance

Insurance will be purchased for this study

VII. Data Analysis

Analysis will compare the differences of clinical measures and biochemical measures of each subject at all the visit time points in order to measure the efficacy. Adverse events will be record to evaluation safely of VNS. SPSS software version 2 or above will be used for statistical calculation.

VII. Compliance

The study conforms to the Declaration of Helsinki

VIII. Handling and Storage of Personal Data and Study Data

The electronic personal and study data will be stored in encrypted excel file and password protected computer. Hard copy of data will be stored in locked cabinet in locked file room. Only principle investigator, co-investigators and research assistants will be responsible for safekeeping of the person and study data during and after the study. Electronic data will be kept for 10 years after completion of study and will be destroyed after 10 years of study completion. Hard copy of data will be destroyed 5 years after study completion

References

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3. Castro JI, Valencia Llano CH, Tenorio DL, Saavedra M, Zapata P, Navia-Porras DP, Delgado-Ospina J, Chaur MN, Hernández JHM, Grande-Tovar CD. Biocompatibility Assessment of Polylactic Acid (PLA) and Nanobioglass (n-BG) Nanocomposites for Biomedical Applications. Molecules. 2022; 27(11):3640. https://doi.org/10.3390/molecules27113640