Title: Safety and efficacy of non-invasive Vagus Nerve Stimulation (nVNS) in the treatment of headache in Subarachnoid Hemorrhage (SAH)

MAY, 1, 2022

NCT04126408

Overview of study design

This is a single site, randomized, sham-controlled, double-blind study assessing the feasibility, safety, tolerability, and efficacy of non-invasive VNS (nVNS) in the treatment of headache in subarachnoid hemorrhage (SAH).

We hypothesize that two two-minute noninvasive stimulations of the cervical branch of the Vagus nerve, every 5 hours, is efficacious in safely reducing headache intensity and frequency in patients with headache due to SAH, during the patient's intensive care unit (ICU) stay.

After screening and obtaining informed consent, eligible patients diagnosed with SAH on head scans, admitted to the Neurosurgical Intensive Care Unit (NSCU) at Northshore University Hospital will be randomized to either the treatment (stimulation of the cervical branch of the Vagus nerve) or sham (inactive stimulation) group.

Pain intensity will be evaluated every 4 hours. Non-invasive stimulation will be performed every 5 hours.

The treatment arms are the following:

Group 1: Control (patients will receive treatment using an inactive VNS device)

Group 2: Treatment (patients will receive treatment using an active VNS device)

The patients are randomized with equal probability to one of the treatment arms. In total, approximately 40 patients will be recruited

Primary objective
The primary objective of this study is to evaluate the effectiveness of VNS compared to sham device as measured by the mean daily morphine equivalence dosage during the study

Secondary Objectives
The secondary objectives of the study are to compare VNS to sham treatment with respect to effects on the following:

- total overall morphine equivalence dosage
- mean daily headache intensity during the study
- cytokines levels
- blood brain permeability markers in the blood and/or CSF before and after stimulation
- blood brain barrier integrity

Exploratory objectives:

- stroke, vasospasm, DCI, seizure, and central fever
    - The presence of DCI,
    - Transcranial doppler velocity,
    - The number of days with central fever,
    - Incidence of seizures
- severity of cerebral vasospasm during DSA

Safety objectives:

- Opiate related adverse events (such as urinary retention, constipation, sedation, nausea, vomiting and pruritis)
- Occurrence of Adverse Events (AEs)/Serious Adverse Events (SAEs)
- Vital Signs
- Rate of side effects:
    - presence of intolerable pain at the stimulation site,
    - skin irritation,
    - nasopharyngitis,
    - hoarseness,
    - dysgeusia,
    - shortness of breath,

Outcome measures

Primary efficacy variable:

The daily morphine equivalency dosage by visit

Secondary efficacy variables:

- total overall morphine equivalence dosage
- mean daily headache intensity during by visit
- cytokines levels
- blood brain permeability markers in the blood and/or CSF before and after stimulation
- blood brain barrier integrity

Exploratory variables:
(Stroke, vasospasm, DCI, seizure, and central fever)

- The presence of DCI,
- Transcranial doppler velocity,
- The number of days with central fever,
- Incidence of seizures)
- severity of cerebral vasospasm during DSA

Safety variables:
Opiate related adverse events

- urinary retention,
- constipation,
- sedation,
- nausea,
- vomiting and
- pruritis
- Occurrence of Adverse Events (AEs)/Serious Adverse Events (SAEs)

Rate of side effects: presence of intolerable pain at the stimulation site,

- skin irritation,
- nasopharyngitis,
- hoarseness,
- dysgeusia,

- shortness of breath,
- Vital Signs (weight, BMI, SBP, DBP, and pulse rate are collected at each day)

Statistical considerations

Sample size determination
There are no statistical hypotheses in this study, and therefore there is no sample size justification for this study. This is a feasibility pilot study that will allow us to better calculate the sample size for a large, randomized control study comparing VNS to sham device.

General approach:

- Baseline is defined as the value measured at visit 1 (Day 1). Endpoint is defined as last observed value during visit 14 (Day 14).
- Missing efficacy. Two statistical approaches to handling missing data will be performed in this study.
    - The primary analysis will be a repeated measures analysis of the primary efficacy endpoint. Estimates have been shown to be unbiased when the missing data are missing completely at random and when there is ignorable nonrandom missing data.
    - A secondary analysis will utilize an LOCF analysis

- All statistical tests for treatment difference will be 2-sided and conducted at the 0.05 level of significance.

Analysis populations

The following analysis sets will be used for the statistical analysis and presentation of data:

- ITT: All randomized participants will be included in the Intent To Treat (ITT) population.
- Modified ITT (mITT): A modified Intent-to-treat (mITT) population inclusive of all ITT subjects who are treated at least 7 days with at least 3 stimulations of the study device.
- The Per Protocol Set (PPS): Patients who are compliant with the treatment regimen for the duration of the study will be analyzed.
- The safety set will consist of all randomized patients who received at least one stimulation.

The mITT is considered as the primary analysis dataset and will be used for all primary and secondary efficacy analyses. The primary efficacy analyses will be repeated using the PP set. Any discrepancy between the results from the mITT and the PP will be analyzed and discussed.

The secondary variables will be analyzed based on mITT only.

Baseline data and safety analysis will be based on the safety set.

Patient characteristics

In general, data will be summarized by means of summary statistics. Continuous data will be presented with the number of observations, mean value, standard deviation, minimum, median and maximum value. The mean, standard deviation and median will be given with one decimal more than the original values. When applicable, values at each visit, as well as changes from baseline, will be summarized.

Categorical data will be presented as counts and percentages. The data will be presented for each treatment group by visit.

Patient demographics and vital signs will be summarized for all randomized patients. For each of the variables, the treatment group difference will be examined using T-test for continuous variables, and Fisher's exact test for categorical variables.

Efficacy Analysis

The primary analysis of the primary efficacy variable will be based on the mITT population set.

The primary efficacy variable, the daily morphine equivalency dose by visit, will be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach (Mixed Model Repeated Measures (MMRM)). The model for analysis will include fixed, categorical effects of treatment, visit, and treatment by visit interaction, as well as the continuous, fixed covariates of baseline value. An unstructured (co)variance structure will be used to model the within-patient errors. If this analysis fails to converge, compound symmetry will be tested. The (co)variance structure converging to the best fit, as determined by Akaike's information criterion will be used as the primary analysis. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The primary treatment comparison will be the contrast between treatments at Day 14 for active treatment versus sham treatment. Treatment group differences contrasts will be computed overall and for each analysis visit (i.e., Day 1, Day 2, Day 3, …, Day 14) and displayed with the respective 95% CIs. Significance tests will be based on least-squares means and Type III sum-of-squares, using two-sided tests at the 0.05 level (two-sided 95% confidence intervals). No imputed values will be used for the MMRM analysis.

Sensitivity analysis

All analyses on the primary efficacy endpoint will be repeated on the PPS

Additionally, the missing data for the mean daily morphine equivalency dose will be computed using an LOCF algorithm and analyzed using the MMREM model.

Analysis of Secondary and Exploratory Variables

For each of the variables mentioned above, the randomization group difference will be examined using a T-test for continuous variables, and Fisher's exact test for categorical variables at each visit.

Analysis of safety variables

Treatment group differences in the occurrence of serious adverse events will be evaluated using Fisher's exact test.

Adverse events:
The primary safety endpoint of this study is the overall incidence of device related serious AEs. AEs and SAEs will be summarized and presented as proportions and respective 95% exact binomial confidence intervals (CIs).
Frequency and percentage of subjects experiencing a specific adverse event will be tabulated by system organ class, preferred term, and treatment group.
Summary tables and subject data listings will be provided.

- Rate of Symptomatic bradycardia defined as a drop in HR to less than 60 beats per minutes with symptoms, not due to nimodipine. The timing of nimodipine relative to the VNS will be recorded. All patients are on telemetry during the stimulation.
- Rate of drop in blood pressure, defined as a drop in blood pressure requiring fluid resuscitation or vasopressor support thought to be due to the device.
- Rate of side effects:
    - presence of intolerable pain at the stimulation site,
    - skin irritation,
    - nasopharyngitis,
    - hoarseness,
    - dysgeusia,
    - shortness of breath,
    - chest pain,
    - nausea and vomiting.

Vital signs and weight over time:

Weight, BMI, pulse rate, systolic and diastolic blood pressure will be summarized together with the respective changes from baseline to all study visits.

Laboratory tests over time:

Hematology and biochemistry values will be summarized by treatment group and by visit together with the respective changes from baseline to all study visits.

Procedure	Screening and randomization	enrollment/Baseline Days 2-5 till discharge from NSCU	Step down unit Neurosurgical floor	Final Study discharge
Demographics	x			
Medical history	x			
Physical exam (including height and weight)	x	x	x	x
Vital signs (temperature, BP, HR, Oxygen saturation	x	hourly or as needed	x	x
Performance status	x	x	x	x
Hematology, serum chemistry	x	x	x	
Daily narcotic use	x	x	x	
Adverse events	x	x	x	x
Radiologic/Imaging assessment (CT, MRI, CTA/CTP, angiogram)	x	x	x	x
Patient satisfaction assessment				x
EKG (as indicated)	x	x	As needed	
Concomitant medication review	x	x	x	x

During the ICU length of stay, the following will be assessed and recorded per standard of care:

• Transcranial dopplers (TCD)
• Neuroimaging (CT head, MRI brain, angiograms, CT perfusion with permeability study)
• EVD weaning and day of start of weaning
• Presence of vasospasm delayed cerebral ischemia, Central fever, Cerebral salt wasting.

These are usually recorded in the medical record.

• Urinary retention documented as frequent straight catheterization for more than 3 days
• Constipation evaluated by the need for enema, suppository, lactulose or magnesium

oxide administered
• Blood tests, CSF studies
• EEG results
• Neurologic examination including Glasgow coma score, and NIHSS
• Delirium score

Table 2: Hunt-Hess Score in aneurysmal SAH: (26, 27)
1. Asymptomatic, mild headache, slight nuchal rigidity
2. Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
3. Drowsiness, confusion, mild focal neurologic deficit
4. Stupor, moderate-severe hemiparesis
5. Coma, decerebrate posturing

Table 3: Modified Fisher Scale:(28)
grade 0: no subarachnoid hemorrhage (SAH), no intraventricular hemorrhage (IVH)
grade 1 focal or diffuse, thin SAH, no IVH
grade 2 thin focal or diffuse SAH, IVH present
grade 3 thick focal or diffuse SAH, no IVH
grade 4: thick focal or diffuse SAH, IVH present