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Noninvasive vagus nerve stimulation in spontaneous subarachnoid hemorrhage (VANQUISH): A randomized safety and feasibility study

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1. Introduction

Spontaneous subarachnoid hemorrhage (SAH) typically presents with severe thunderclap headache, often described as the "worst headache of life". The vast majority of patients (90 %) have persistent severe headache while in the intensive care unit [1] and more than a third continue to have this headache for years following cerebral insult, which adversely affects their quality of life [2]. Currently, there is lack of effective treatments or guidelines, and the data evaluating the efficacy of analgesic medications for these patients is scarce. As a result, clinicians tend to resort to opiates, with a reportable daily mean morphine equivalent dosage of 15.7 mg, with no significant improvement of headache intensity or decrease in opiate usage during the hospital stay [1,2]. Moreover, opiates continue to be used for a long time after discharge as an outpatient medication [3].

Opiates have well-known major side effects. Among them are respiratory drive depression, constipation, nausea and vomiting, pruritus, urinary retention, delirium, and hypotension. There is also a risk of tolerance and addiction, with the over prescription of opiates being recognized as one of the major causes of opiate epidemic in the unites states. In general, clinicians attempt to avoid opiates or use the lowest effective dose possible in patients admitted with spontaneous SAH, as these medications may affect the neurologic status of the patient including altering the level of consciousness. As any change in neurologic examination is alarming in patients with SAH, it can lead to unnecessary measures to rule out other serious complications such as delayed cerebral ischemia and hydrocephalus. Unfortunately, known non-opiate analgesics have been found to be ineffective in patients suffering from headaches associated with SAH [1]. At the same time, insufficiently treated pain can lead to patient discomfort and suffering, worsening delirium and risk of developing chronic pain syndrome [4]. As a result, opiate consumption is high in this patient population even though it has numerous safety concerns. There is a critical need for a multimodal approach with an emphasis on therapies that could decrease opiate usage while providing adequate pain control.

Non-invasive vagus nerve stimulation (nVNS) is approved by the US Food and Drug Administration (FDA) for the treatment of migraine and cluster headaches and has been shown to be safe and well tolerated. Its safety is unknown in SAH. A recent study has shown that nVNS is safe in patients with ischemic stroke but only 8 patients with intracranial hemorrhage were included. It was not noted whether these encompassed SAH [5]. SAH is of particular interest given that it triggers a systemic inflammatory response syndrome, can lead to cortical spreading ischemia, and the breakdown of the blood-brain barrier. These mechanisms are thought to be involved in the pathogenesis of headache and secondary brain injury in SAH. nVNS has the potential to mitigate these pathways [6].

The main objective of our study is to evaluate the safety and feasibility of nVNS application in patients with spontaneous subarachnoid hemorrhage. Our secondary objective is to evaluate the efficacy of nVNS in decreasing pain intensity and opiate consumption in this patient population.

2. Material and methods

2.1. Study design

VANQUISH was a multicenter, randomized, double-blinded study designed to evaluate the safety, feasibility and efficacy of nVNS in the treatment of headache in spontaneous SAH. Patients were recruited

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between October 30, 2019, and June 20, 2022 from 3 hospitals affiliated with Northwell Health in New York. Study protocol was approved by the Institutional Review Board at Northwell Health.

The trial was conducted in accordance with the standards of Good Clinical Practice and the Declaration of Helsinki.

2.2. Participants

Eligible patients were aged 18–75 years, admitted with severe headache, or headache with a visual analog scale (VAS) of 7 or more, diagnosed with aneurysmal or perimesencephalic subarachnoid hemorrhage. nVNS was not initiated until the cerebral aneurysm, if diagnosed, was secured. At the time of enrollment and throughout the study period, patients were able to verbalize their pain score.

Patients were excluded if they had a contraindication for nVNS of the cervical branch of the vagus nerve (implantable devices, history of internal carotid artery atherosclerosis), if they had a history of current alcohol abuse, substance addiction or chronic opiate use present at the time of the enrollment. Patients with a history of heart block or ventricular arrhythmia were also excluded. Written informed consent was obtained from all participants.

2.3. Randomization and masking

Patients were randomized using variable block design, assigned as 1:1 to the treatment group and the sham group, with concealment of allocation. Each electroCore provided device was labeled with a serial number. The active and the sham devices were not marked, but the serial number permitted mapping the devices to the respective allocated group. The active and the sham devices had no differences in design, shape, color and were identical in every detail, including the way they operated (visual, auditory signals). The sham device was inactive and did not produce any electrical signal. An unblinded research assistant's role was to randomize the patients and keep a log of the participant randomization numbers and the corresponding device serial number. The device was provided to the medical team with instructions on its use given to the patient and clinicians. To maintain blinding and decrease the risk of bias, once the training was completed, the unblinded research personnel had no further interaction with the participant or clinicians. This re-enforced the blinding process of the study participants, investigators and clinicians who assessed the pain intensity scale, provided analgesic medications, and monitored for adverse events.

2.4. Procedures

GammaCore® (nVNS; electroCore, Inc., Basking Ridge, NJ, USA)is a hand-held neurostimulation device originally FDA cleared for cluster headaches and migraines. It delivers a noninvasive transcutaneous electrical current via two electrodes placed on the skin surface of the neck in the area of cervical branch of the vagus nerve, generating a peak voltage of 24V and peak output current of 60 mA. Its stimulation signal intensity (amplitude) is adjustable and ranges from 0 to 40 a.u. Most of the time, stimulus delivery is unnoticeable, but sometimes it can cause a muscle contraction or tingling sensation around the area of application. The sham device does not produce a stimulation signal but is similar to the active device in every other detail, including the identical display and sounds it produces. Both devices provide a 2-min "stimulation" session and automatically turn off afterwards [7].

The unblinded Research Assistant provided the blinded patient and the medical team with the device. Patients and clinicians were notified of possible discomfort, tingling sensation or muscle contraction during the stimulation session. Patients themselves were to decide on which side of the neck they want to apply the device but were advised to stimulate the side where the headache intensity is the greatest (e.g. left side of neck if headaches are mostly left-sided). The stimulation intensity (0–40 a.u.) was increased to the maximum level that was tolerated by the patients. If the intensity level of stimulation caused an intolerable discomfort, it was lowered to a more comfortable level. The nurse or clinician provided the device assigned to the patient at 6:30 a.m., 11:30 a.m., 4:30 p.m. and 9:30 p.m., monitored and assisted the patient when needed (Fig. 1). Timing of stimulation was chosen as not to coincide with the medical staff shift change.

The nurse recorded the vital signs and headache intensity level before and after each stimulation. All patients were on continuous telemetry. In the event of bradycardia (defined as HR $<$ 60 beats/minute) or hypotension (defined as SBP$<$100 mmHg, or MAP$<$60 mmHg) stimulation was aborted and the device was not provided to the patient. In the absence of contraindications and hemodynamic stability, two 2-min stimulations were delivered. Adverse events including known device related side effects, arrythmias, changes in vital signs, dyspnea, desaturation and change in the neurologic examination were monitored during the stimulation session.

Pain intensity was measured with the Visual Analog Scale (VAS) for pain ranging from 0 to 10, where 0 signifies no pain and 10 represents the most severe pain. It was recorded before and after each stimulation followed by the standard of care pain assessment frequency in the neurosurgical intensive care unit.

Depending on pain intensity, a nurse provided analgesic medication according to the neurosurgical unit pain treatment protocol (Appendix). Morphine Equivalent dose was calculated using conversion factors to measure the dose of morphine equivalent to the ordered opiate. The following formula was applied: (mg/day of ordered opioid) x (conversion factor) = oral Morphine equivalent (Appendix).

Of note, opiates used in the operating room for any types of procedures were not included in the analysis.

Several other measures were collected.

- Modified Fisher Scale (mFS) and Hunt Hess grade (HHS)
- Change in the neurologic examination determined to be attributed to cerebral vasospasm
- Incidence of cerebral infarction was measured by comparing the last available neuroimaging with the first one done after aneurysm treatment procedure,
- Hospital length of stay was recorded,
- Modified Rankin Scale (mRS) was measured on admission and discharge from the hospital.

2.5. Outcomes

The main safety end point of the study was the number of serious adverse effects related to nVNS, including hemodynamically unstable hypotension, symptomatic bradycardia, and other types of arrythmias, rate of neurologic deterioration during stimulation and during the delayed cerebral ischemia surveillance period. We evaluated changes in heart rate and blood pressure in the peri-stimulation period and compared these parameters between the active and sham groups. In addition, we evaluated the incidence of expected non-serious device related adverse events.

Patient compliance was used to assess the feasibility of the study. Compliance rate was measured by evaluating the number of stimulations that participants received when deemed appropriate for the procedure. The number of sessions defered due to hemodynamic instability or arrythmias and the number of sessions declined by the patients were recorded.

The main efficacy assessment was the change in morphine equivalent dose (MED) from baseline to each treatment day. In addition, the cumulative average MED at Day 7 and Day 14 were calculated. Mean post-stimulation headache intensity and the difference in headache intensity before and after stimulation were also evaluated.

Our exploratory outcomes were modified Rankin Scale (mRS) at discharge, hospital length of stay, and rate of cerebral infraction on neuroimaging.

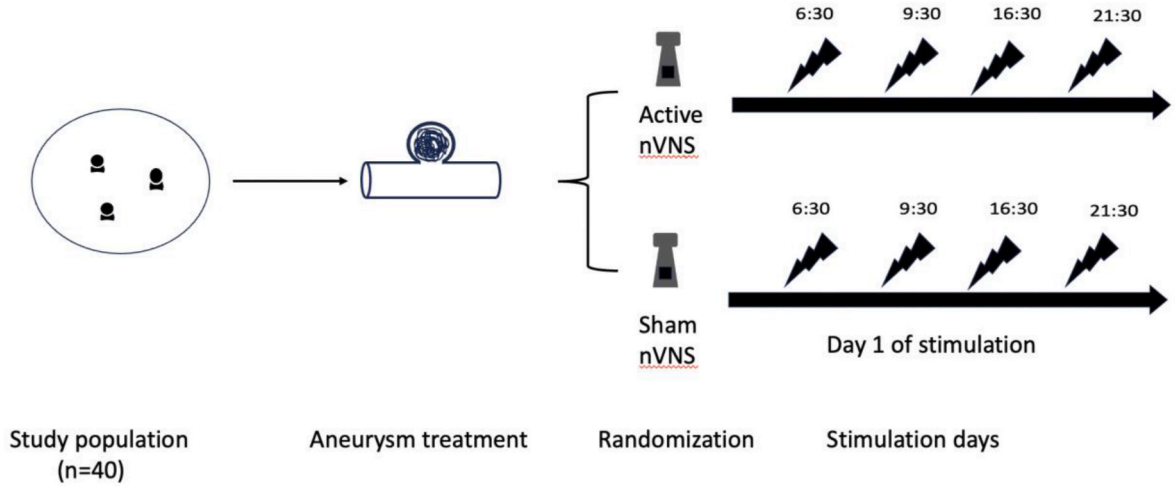

Fig. 1. Study design. Patients were enrolled after aneurysm treatment, if they were alert and able to verbalize their pain score. Stimulation was provided at around 6:30, 9:30, 16:30 and 21:30 if hemodynamically stable (Heart rate ≥60 beats per minute, Systolic Blood Pressure ≥100 mm Hg and MAP ≥60).

3. Statistics

Descriptive statistics (frequency distribution for categorical variables and mean, median, standard deviation, interquartile range, minimum and maximum for continuous variables) were calculated.

The primary analysis was based on the modified intention to treat (mITT) population set. For the safety outcomes and the pain outcome, Mixed Model Repeated Measures (MMRM) was used. For each of the exploratory outcomes, the difference between groups was examined using a Student T-test or Wilcoxon Rank Sum test, as appropriate, for continuous variables, and Fisher's exact test for categorical variables at each visit. Side effects and adverse effects were compared by the treatment group. Differences between treatment groups were compared using Fisher's exact test.

The efficacy outcome, change in morphine equivalent dose (MED) from baseline to each treatment day, was analyzed using a restricted maximum likelihood (REML)-based repeated measures approach (Mixed Model Repeated Measures (MMRM)). The model included fixed, categorical effects of treatment, visit, and treatment by visit interaction, and the continuous, fixed covariates of baseline MED value. An unstructured (co)variance structure was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The primary treatment comparison was the difference between the active and sham group with respect to change in MED. Comparisons between treatments on Day 7 and on Day 14 were also performed. Treatment group differences contrasts were computed for each analysis visit (i.e., Day 1, Day 2, Day 3, …, Day 14). Significance tests were based on least-squares means and Type III sum-of-squares, using two-sided tests at the 0.05 level. No imputed values were used for the MMRM analysis. Log-transformation was applied to daily morphine equivalent dose to meet the model assumptions.

The level of significance was set at 5 % unless stated otherwise. All aims were analyzed using SAS software Version 9.4 (Cary, NC).

Sample size determination.

There are no statistical hypotheses in this study, and therefore there was no sample size calculation performed 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.

Role of the funding source.

The trial was funded by ElectroCore, Inc. The company provided active and sham devices, and the funds were used to support our research staff for the conduct of the clinical trial. ElectroCore, Inc. had no responsibility for collecting or analyzing the data, nor did it participate in the writing of the manuscript. The authors have no personal relationships with the company.

4. Results

4.1. Participants

One hundred and twenty participants were screened between October 30, 2019, and June 20, 2022, of which 40 patients were enrolled and randomly assigned to the treatment (19 patients) or sham group (21 patients). One patient refused all stimulation after signing the informed consent and was excluded from the intention-to-treat analysis (Fig. 2).

Baseline characteristics were similar between the active and sham groups. Almost all patients were diagnosed with aneurysmal SAH, except for 4 patients (2 in each group) who had peri-mesencephalic SAH. Most hemorrhages were classified as high modified Fisher scale (mFS 3–4) but low Hunt & Hess grade (HH 1–2). (Table 1).

The median (IQR) time from admission to aneurysm treatment was 1 (0–1) day. The median (IQR) time from aneurysm treatment to first stimulation was 2 (1–3) days.

4.2. Safety and feasibility results

There was a significant decreased in the Systolic Blood pressure (SBP) ($p = 0.02$) within the nVNS group. However, when compared to the sham group, there was no significant difference in pre-to post-stimulation SBP ($p = 0.68$). SBP trend evolved differently over time in the two treatment groups ($p = 0.06$). There was no significant difference in the change in Heart Rate (HR), or Diastolic Blood Pressure (DBP) during stimulation between the active and sham groups or within each group ($p > 0.05$) (Fig. 3).

None of the patients had a neurologic deterioration during stimulation. There was no statistically significant difference in the rate of neurologic deterioration thought to be due to cerebral vasospasm. 3 (19 %) patients in the active group compared to 6 (31 %) in the sham group developed neurologic deterioration and were treated with hemodynamic augmentation, in some cases requiring therapeutic cerebral angiography.

There were no device-related serious adverse events such as hemodynamic instability with hypotension, symptomatic bradycardia or other arrythmia. One patient in the sham group died from cerebral infraction with malignant brain edema that led to brain death. 44.4 % ($n = 8$) of the patients that received stimulation had muscle twitching

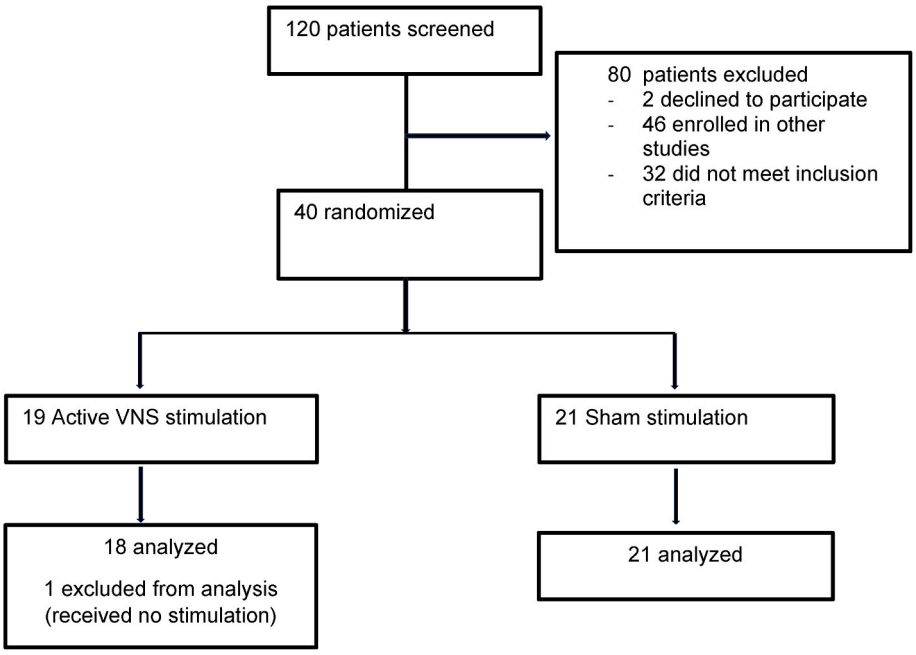

Fig. 2. Flow diagram.

Table 1
Baseline characteristics.

Characteristics	No. (%) Active (n = 19)	Sham (n = 21)
Age, mean (SD), years	54 (13)	51 (11)
Gender		
Female	14 (74)	13 (62)
Male	5 (26)	8 (38)
Hunt-Hess Classification		
1	5 (26)	7 (33)
2	10 (53)	11 (52)
3	2 (10)	2 (10)
4	2 (11)	1 (5)
Modified Fisher Classification		
1	4 (21)	2 (10)
2	1 (5)	2 (9)
3	8 (42)	9 (43)
4	6 (32)	8 (38)
Treatment Modality		
Clip	7 (41)	8 (42)
Coil	10 (59)	11(58)
Etiology of SAH		
Aneurysmal	17 (88)	19 (89)
Peri-mesencephalic	2 (12)	2 (11)

during stimulation compared to 9.5 % (n = 2) in the sham group (p = 0.03). 33.3 % (n = 6) had lip pulling and 22.2 % (n = 4) had nausea/vomiting during stimulation with the active device (p = 0.006 and p = 0.04 respectively) (see Table 2). Upon further review of the latter group, it was established that 7 out of 433 (1.6 %) stimulations performed with the active device led to nausea/vomiting.

Median (IQR) days of stimulation was 9 (6–12) days with 2 (1–3) stimulation sessions per day. Out of the total 1260 nVNS attempts, 950 (75 %) stimulations were completed. 133 (12 %) were missed due to sinus bradycardia and 40 (3 %) were not delivered because the patient was either not physically present or available at the scheduled time of stimulation. Out of the 1087 attempted stimulations, 172 (19 %) were declined by the patients due to the following reasons: participant was too tired and wanted to postpone stimulation till the next scheduled procedure time, or feeling that the device was not helping with the pain, or patient was not experiencing pain and did not want the stimulation at the particular scheduled time.

4.3. MED and pain results

At baseline, before the intervention, the mean MED was 14.69 (SD = 13.28) mg in the active group and 14.50 mg (SD = 12.60) mg in the sham group. When compared to the sham group, patients who received active stimulation had a 10 % reduction in mean MED at 7 days (21.99 [SD = 21.4] mg vs 24.29 [SD = 20.11] mg, p = 0.93) and 15 % reduction at 14 days (19.91 [SD = 19.13] mg vs 23.21 [SD = 18.06] mg, p = 0.79). There was no group by treatment day interaction (p = 0.57). There was no significant difference in change in MED from baseline between treatment groups ((F (1,47 .4) = −0.19 mg, p = 0.66) (Fig. 4).

There was a significant decrease in headache intensity post-stimulation within the active nVNS group (P < 0.001) but not in the sham group (p = 0.21). When comparing pre-to post-stimulation pain scores between the two groups, there was a significant reduction in post-stimulation pain score in the active group compared to the sham group (p = 0.005) with no significant trend over the hospital days (Fig. 5).

4.4. Exploratory endpoint

All patients had no baseline disability (mRS = 0). At hospital discharge, 94.4 % (n = 17) of patients who received nVNS had an excellent modified Rankin scale of 0–2, compared to 80.0 % (n = 16) in the sham group (p = 0.34). One patient in the sham group died due to severe cerebral vasospasm and cerebral edema progressing to brain death.

Median (IQR) length of stay in the hospital was 16 (15–17) days for the active group and 18 (13–22) days for the sham group (p = 0.14).

The incidence of new cerebral infraction on neuroimaging was 5.6 % (n = 1) in the nVNS group compared to 23.8 % (n = 5) in the sham group (p = 0.19).

5. Discussion

This study assessed the safety and feasibility of transcutaneous stimulation of the cervical branch of the vagus nerve in spontaneous subarachnoid hemorrhage. It evaluated nVNS as a therapeutic adjunct to

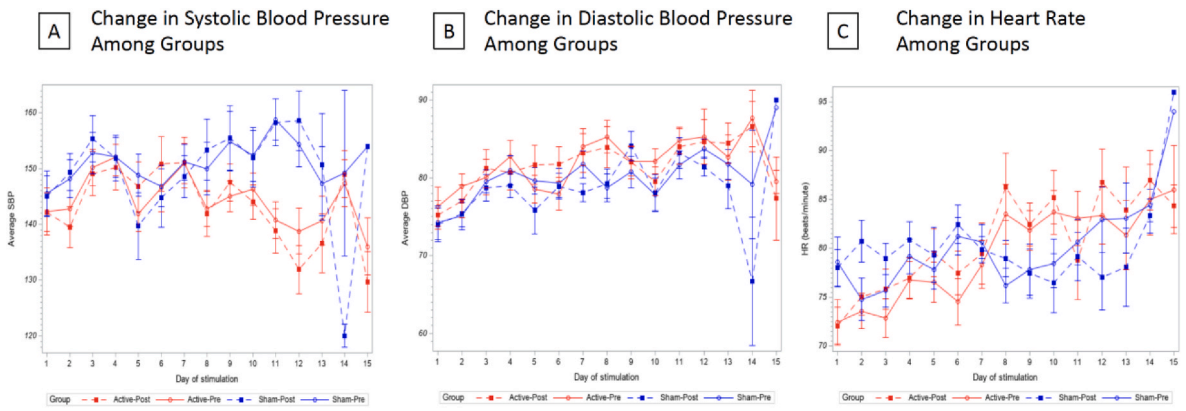

Fig. 3. Peri-stimulation vital signs. There was no significant change in peri-stimulation Systolic Blood Pressure (SBP) (a), Diastolic Blood Pressure (DBP) (b), or Heart Rate (HR) (c) between the active and sham group.

Table 2
Safety outcomes.

Safety endpoint	nVNS (n = 18)	sham (n = 21)	p value
Tingling at Stimulation Site	9	5	0.15
Pain at Stimulation Site	6	2	0.1
Muscle Twitching	8	2	0.02
Lip Pull	6	0	0.005
Facial Droop	0	0	N/A
Dizziness	0	2	0.4
Nausea/Vomiting	4	0	0.03
Shortness of Breath	1	0	0.46
Arrythmia	0	0	N/A
Hemodynamically unstable hypotension	0	0	N/A
Symptomatic Bradycardia	0	0	N/A

standard analgesics, in reducing opiate consumption as well as headache intensity due to subarachnoid hemorrhage in the intensive care unit. We found that two-two-minute stimulations of the cervical branch of the vagus nerve, up to four times a day, was feasible and not associated with increased adverse events. It was associated with a significant reduction in headache intensity when compared to sham stimulation. Moreover, even though before stimulation patients in the active group required more MED compared to the sham group, there was a trend towards a reduction in opiate consumption in patients who received stimulation with the active device.

To our knowledge, this is the first study evaluating the safety and feasibility of nVNS in critical patients with subarachnoid hemorrhage. Most patients were compliant and received their stimulations. This suggests that the patients were willing to try a novel treatment option given that the headache intensity in SAH is severe, disabling and often unresponsive to high doses of opiates. Twelve percent of the stimulations were skipped due to sinus bradycardia, which is common in this patient population, especially while receiving nimodipine per standard of care treatment of SAH. Most patients received their first stimulation within 3 days of aneurysm treatment. This is important for future studies aimed to evaluate the potential neuroprotective effects of VNS in SAH.

Overall, nVNS was not associated with serious adverse events. Although it decreased SBP during stimulation, when compared to the sham group, the decrease was not significant. Moreover, there was no clinically significant hypotension seen with nVNS. This decrease in SBP could be due to the improvement in pain intensity post-stimulation. NVNS did not affect the HR or DBP. Our results are similar to a recent

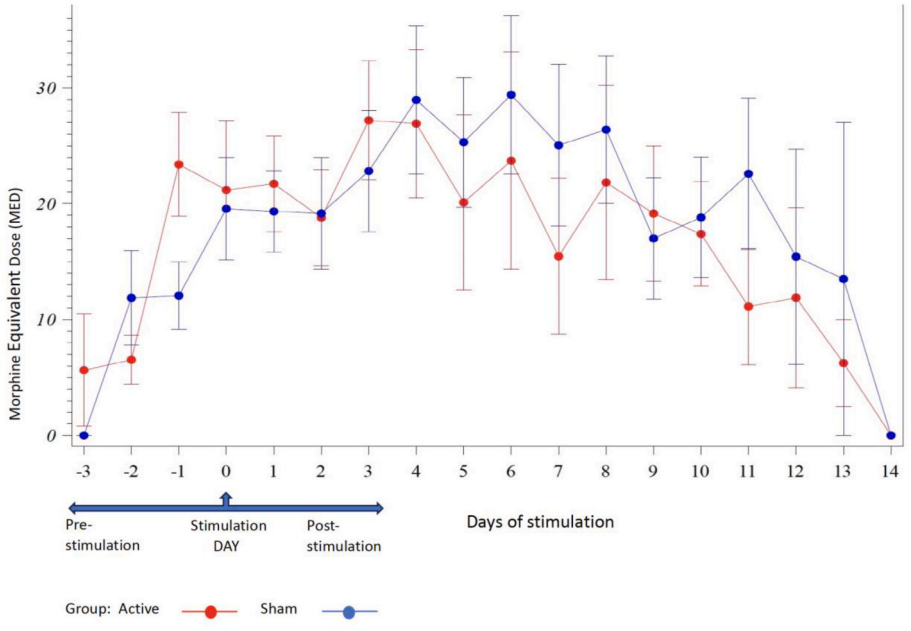

Fig. 4. Average morphine equivalent dose (MED) per day in the nVNS and sham groups.

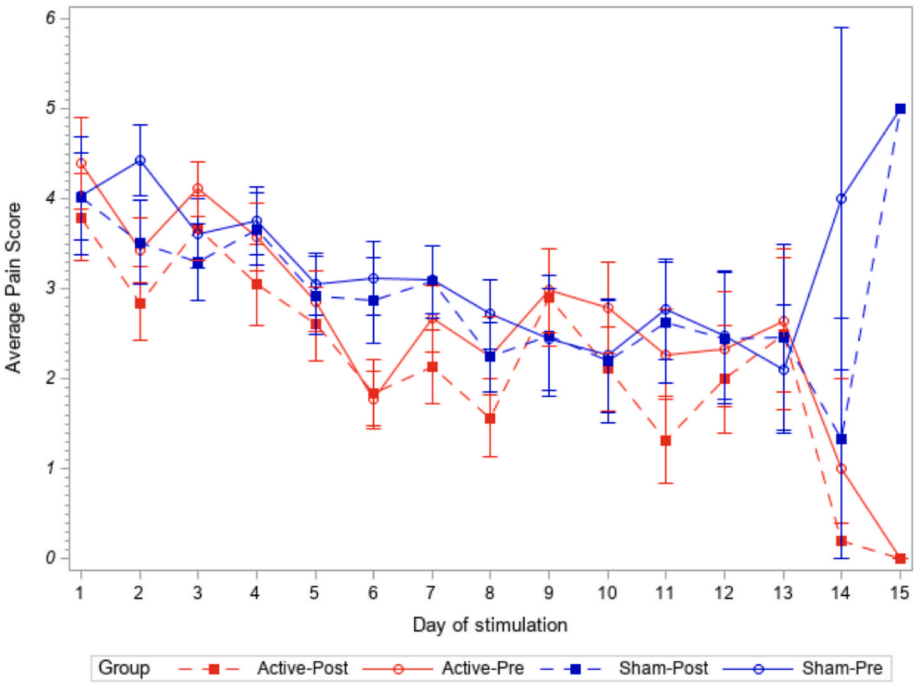

Fig. 5. Average change in pain intensity per day after stimulation in the active and sham groups.

published study evaluating the safety and tolerability of nVNS in acute stroke patients, which found that the device may be safe with no clinically significant hemodynamic instability [5]. Even though nausea/vomiting was significantly higher in the active device group, it was only present in 1.6 % of the active stimulation.

Moreover, this is the first randomized study showing that nVNS is associated with a reduction in headache intensity in patients with subarachnoid hemorrhage. Headache management in this patient population is complex as the pathophysiology remains unknown and seems to be multifactorial. The breakdown of the blood-brain barrier, inflammation, oxidative stress, cortical spreading depression, upregulation of the N-methy-D-aspartate (NMDA) glutamate receptors, the activation of the trigeminovascular system and mood disturbances are among the considered factors [3]. Targeting these pathways could be a potential therapeutic objective for headache management in SAH [3]. Inflammation is thought to trigger the vagus nerve which, through the hypothalamic-pituitary- adrenal axis, regulates the inflammatory response of the spleen and leads to a decrease in cytokine production [8]. Because of its immunomodulatory effect, VNS has been studied in patients with inflammatory diseases such as Crohn's disease, systemic lupus erythematosus, sepsis and more recently Covid-19 patients [9]. Noninvasive VNS is also believed to improve the integrity of the blood-brain barrier, potentially decreasing inflammation [10]. In addition, VNS is thought to modulate the central and peripheral pain centers [8]. The anti-inflammatory and antinociceptive properties could be the potential mechanisms by which pain intensity is decreased after stimulation of the vagus nerve.

This study redemonstrates that opiate consumption for headache due to SAH is elevated with a mean MED of 23 mg at 7 days. Noninvasive vagus nerve stimulation led to a lower mean MED at 7- and 14-day marks when compared to the sham group (by 10 % and 15 %, respectively). There is an association between opiate related adverse events and hospital length of stay [11] and the reduction in opiate consumption seen in our study, along with the neuroprotective properties of nVNS, could have contributed to the trend towards a decrease in hospital length of stay (by 2 days) in the active device group. It would be beneficial to further evaluate the observed decrease in opiate consumption and its effect on various parameters in a larger study.

In addition to the anti-inflammatory properties, nVNS can reduce cortical spreading depression. Animal studies have shown that nVNS can decrease the frequency and propagation speed of cortical spreading depression in the occipital cortex of rats [12]. Inflammation and CSD are thought to be involved in the pathogenesis of delayed cerebral ischemia (DCI) and cerebral infarction in patients with subarachnoid hemorrhage. The decreased incidence of cerebral infarction on neuroimaging in the active group compared to the sham group could be attributed to this neuro-protective effect of nVNS. However, this study was not powered to study the effect of nVNS on DCI and these results should be interpreted with caution.

Our study has limitations. Our sample size limits the generalizability of our findings and a larger randomized clinical trial is needed to evaluate the safety and efficacy of nVNS in spontaneous subarachnoid hemorrhage. We attempted to control for bias by using a sham device that looks the same and produces the same sound as the active device, however, given that active stimulation could lead to muscle twitching, lip pulling and a tingling sensation, this could have led to bias. However, many patients who received sham stimulation complained of tingling/pain at the stimulation site. We did not perform a long term follow up of which more studies will be required to evaluate the long-term effects of nVNS on headache and functional outcome. However, given the safety profile of the nVNS device, and that it is approved for the treatment of migraine as well as cluster headaches in an outpatient setting, we do not expect a development of long-term adverse events with its use.

The fact that some patients declined the device use because they were tired or had no pain at the time of a scheduled stimulation, we suggest that for future headache studies involving nVNS, the use of the device on an "as needed" basis may be implemented. At the same time, nVNS potential of preventing headache occurrence would be interesting to investigate further, and it may be considered by research groups while creating a study design. In this case it may prompt more efforts to encourage participants to use nVNS device more often.

6. Conclusion

This randomized sham-controlled pilot study showed that non-invasive vagus nerve stimulation is potentially safe and feasible in

critical patients with subarachnoid hemorrhage. It might decrease pain intensity and has the potential to decrease opiate consumption. Given its safety profile, a larger sham-controlled randomized clinical study is needed to further investigate these effects and its neuroprotective properties in patients with spontaneous subarachnoid hemorrhage.

CRediT authorship contribution statement

Tania Rebeiz: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tagir Sabirov:** Writing – review & editing, Supervision. **Timothy G. White:** Writing – review & editing, Investigation. **David Ledoux:** Supervision. **Jung-min Kim:** Supervision. **Donna Kerner:** Project administration, Supervision. **Betsy Moclair:** Supervision. **Amanda Lin:** Resources. **Shahab Khazanehdari:** Supervision. **Aashish Patel:** Supervision. **Heustein Sy:** Supervision, Writing – review & editing. **Marc S. Ayoub:** Project administration. **Bensam Benziger:** Project administration. **Kenia Samuel:** Supervision. **Krista Lim-hing:** Supervision. **Celine Rahman DeMatteo:** Supervision. **Richard E. Temes:** Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The trial was funded by ElectroCore, Inc. The company provided the active and sham devices and funds were used to support our research staff for the conduct of the clinical trial and journal submission fees. The company was not involved in the study design, analysis of the data, or writing of the manuscript. The authors declare no personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.04.004.

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