Vagus Nerve Stimulation Paired with Upper Limb Rehabilitation After Chronic Stroke: A Blinded Randomized Pilot Study

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Abstract

Background and Purpose: We assessed safety, feasibility and potential effects of vagus nerve stimulation (VNS) paired with rehabilitation for improving arm function after chronic stroke.

Methods: We performed a randomized, multisite, double-blinded, sham-controlled pilot study. All participants were implanted with a VNS device and received 6-weeks in-clinic rehabilitation followed by a home exercise program. Randomization was to Active VNS (n=8) or Control VNS (n=9) paired with rehabilitation. Outcomes were assessed at day 1, 30 and 90-post completion of in-clinic therapy.

Results: All participants completed the course of therapy. There were 3 serious adverse events related to surgery. Average FMA-UE scores increased 7.6 with Active VNS and 5.3 points with Control at day-1 post in-clinic therapy (difference=2.3 points, CI: -1.8 to 6.4, p=0.20). At day-90, mean scores increased 9.5 points from baseline with Active VNS and the Control scores improved by 3.8 (difference=5.7 points; CI: -1.4 to 11.5, p=0.055). The clinically meaningful response rate of FMA-UE at day-90 was 88% with Active VNS and 33% with Control VNS ($p<0.05$).

Conclusions: VNS paired with rehabilitation was acceptably safe and feasible in participants with upper limb motor deficit after chronic ischemic stroke. A pivotal study of this therapy is justified.

Clinical Trial Registration: ClinicalTrials.gov NCT02243020

Introduction

Impaired use of the upper limb is one of the most common symptoms following stroke and improving upper limb function is a priority for many patients (1). Clinical trials of increased dose of upper extremity task-specific training have been disappointing (2). This suggests new interventions are needed to maximize post stroke motor recovery (3).

Vagus nerve stimulation (VNS) paired with movement has been shown to drive task-specific plasticity in the motor cortex in rodent models and improve forelimb function after experimental stroke (4). In our first-in-human, randomized, controlled, open clinical trial, VNS paired with upper limb rehabilitation was safe and feasible in people with upper limb deficit at least 6 months after ischemic stroke (5).

The purpose of this pilot study was to further assess safety, feasibility and efficacy of VNS paired with upper limb rehabilitation in chronic ischemic stroke, with blinded, sham VNS control.

Methods

This manuscript adheres to the AHA Journals' implementation of the Transparency and Openness Promotion (TOP) Guidelines. Requests for data will be considered by the corresponding author after FDA post market approval.

This was a randomized, sham stimulation controlled and fully blinded study of VNS paired with rehabilitation in people with arm weakness after ischemic stroke. Participants in both groups were implanted with the VNS device. Participants, therapists, and outcome assessors were blinded to group allocation.

The study was approved by an institutional review board at each institution and subject to appropriate regulatory approvals (FDA Investigational Device Exemption (IDE, #130287) and UK MHRA No #CI/2015/0011). It was registered on clinicaltrials.gov (NCT02243020).

Written informed consent was obtained in compliance with the requirements set forth in U.S. FDA, Code of Federal Regulations Title 21. The study was conducted according to the Declaration of Helsinki.

Participants

Enrollment at the four sites is shown in Supplemental Table I. People with a history of unilateral supratentorial ischemic stroke that occurred between 4 months to 5 years prior to randomization, aged ≥30 years and ≤80 years, and with an FMA-UE between 20-50 were eligible for inclusion (Supplemental Table II).

Protocol Summary

A pre-surgery assessment was performed. After VNS implantation and approximately one week of recovery, participants were randomized to either Active VNS (0.8mA) or Control VNS (0.0mA) and baseline assessments were repeated. In-clinic rehabilitation therapy began on the next day and was delivered approximately 3 times a week for 6 weeks (18 visits, Supplemental Figure I). Outcomes assessments were performed on day-1, day-7, day-30 and day-90 following completion of in-clinic therapy.

Following 6 weeks of in-clinic therapy, all participants began daily, therapist-prescribed home exercises. For the first 30 days of at-home therapy, all participants received 0 mA VNS. Thereafter, participants received VNS according to their randomized allocation. After the day-90 assessment, the Control VNS group crossed over to receive 6-weeks of in-clinic rehabilitation paired with Active VNS (0.8mA) followed by outcome assessments at day 1, 7, 30, and 90 thereafter.

Further details on methodology are given in the supplementary appendix.

Main Study Outcome Measures

The main safety outcome measure was the number of serious adverse events related to the device or therapy. The main feasibility measure was number of participants that completed

the minimum number of visits during the randomized portion of the study (at least 12 therapy visits).

Efficacy outcomes included the FMA-UE (6), Wolf Motor Function Test (WMFT Time and Functional), Box and Block, Nine Hole Peg Test (NHPT), Stroke Impact Scale (SIS) and Motor Activity Log (MAL). Since this was a pilot study, no primary or secondary efficacy measures were designated.

Sample Size and Statistical Analysis

No formal sample size calculation was performed for this pilot study. Efficacy analyses were performed on the intention-to-treat (ITT) population and included all randomized participants. Missing data were not imputed. The change in outcome measures at each time point was compared between groups using two-tailed, unpaired t-tests. Fishers exact test was used to calculate the significance for response rates. For all comparisons, alpha was set at 0.05.

Results

Twenty-two people consented to participate in the study. Of these, 17 participants were implanted and randomized [8 to Active VNS and 9 to Control] (Supplemental Figure II). All participants completed the randomized portion of the study. Baseline characteristics of participants are shown in Supplemental Table III. Details on protocol adherence, feasibility and blinding are provided in the supplement.

Safety

There were three serious adverse events related to implantation surgery including one implantation wound infection requiring treatment with intravenous antibiotics but resolved, one case of shortness of breath and dysphagia, likely due to intubation, which recovered, and one case of hoarseness due to vocal cord palsy. There were no serious adverse events

reported as associated with stimulation. Full details of adverse events are shown in the supplemental appendix.

Efficacy

Between group differences in FMA-UE are shown in Figure 1, and Table 1. At day-90, the response rate [defined as FMA-UE change ≥ 6 points (7)], was 88% in the Active group and 33% in Control (p=0.03) (Figure 2). Between group differences in WMFT are shown in Figure 1 and Table 1.

Following crossover to Active VNS in controls, FMA-UE scores increased to 9.8 points above baseline at day-1 after in clinic therapy ($p<0.001$) and by 6.6 points at day-90 (p=0.01) (Figure 1). Response rates were 88% and 57% at these time points respectively (Figure 2). WMFT data are shown in Figure 1. Full details on all outcome measures are shown in Supplemental Tables V and VI.

Discussion

The primary objective of this pilot study was to assess the safety and feasibility of using paired VNS to improve arm function after chronic ischemic stroke. We found this technique to be feasible, including use of home-based VNS, and demonstrated safety in-line with that expected for VNS devices. The study was not powered to assess efficacy, although there were significant differences between groups in some measures at day-90.

There are several important differences between this and our previous clinical study (5). This study was fully blinded, all participants were implanted with a VNS device, Control participants crossed-over to receive the Active VNS therapy, and participants continued rehabilitation exercises at home for several months.

There were no significant differences between groups immediately after in-clinic therapy completion, but there was a significant difference by 90-days due to maintained benefit by

the VNS group with corresponding decline in the Control group, and a higher percentage of responders who achieved a clinically meaningful change for the FMA-UE (change ≥ 6 points) with Active VNS treatment (7). While we cannot definitively conclude these differences are due to paired Active VNS treatment, our findings are consistent with the effect of a neuroplastic treatment where time may be needed for benefit to accrue. It is of note that Control participants experienced a benefit similar to the initial VNS participants when they crossed over to active VNS treatment.

This pilot study showed that rehabilitation paired with VNS is an acceptably safe and feasible intervention for the treatment of upper limb weakness after ischemic stroke. The study demonstrated sufficient safety, feasibility and potential efficacy to support a larger pivotal trial.

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Disclosures

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Figure Legends

Figure 1. Fugl Meyer Assessment - Upper Extremity (FMA-UE) (mean ± SEM) and Wolf Motor Function Test (WMFT) scores (mean ± SEM). A. Change in FMA-UE score during blinded follow-up for Active VNS and Controls from baseline and three post-treatment assessments. **B**. Change in FMA-UE score following cross-over to active VNS. **C**. Change in WMFT Functional score during blinded follow-up for Active VNS and Controls (***=** $p=0.029$ at post-90 and $p<0.001$ at post-30). **D**. Change in WMFT score following cross-over to Active VNS. Shaded area indicates the 6-weeks of in-clinic therapy. Rebase = baseline in controls prior to starting Active VNS. Day-1 to Day-30 (after in-clinic therapy) consisted of at-home therapy with no VNS for both groups. From Day-30 to Day-90, Active VNS group received VNS (0.8 mA) and controls received Control VNS (0 mA) with at-home therapy.

Figure 2. Average Fugl Meyer Assessment - Upper Extremity (FMA-UE) Response Rate. A. Responder rate (defined as FMA-UE change ≥6 from baseline) for the first 90 days in paired VNS (black) and Controls (gray) (*$p<0.05$, Fishers Exact Test). **B.** Responder rates after control group crossed over to receive active VNS therapy. Rebase = baseline in controls prior to starting active VNS therapy.

Table 1. Change in Outcome Measures [ITT analysis, n=17 (Active VNS=8; Control=9)]

Measure	**Day-1 Difference Post In-Clinic Therapy*** (95% CI)	P Value	**Day-90 Difference Post In-Clinic Therapy*** (95% CI)	P Value
FMA-UE	2.29 (-1.9, 6.47)	0.2604	5.72 (-.15, 11.6)	0.055
WMFT Functional	0.12 (-.10, 0.33)	0.2625	0.33 (0.04, 0.61)	0.029
WMFT Time (s)	-3.02 (-11, 5.24)	0.4215	-4.04 (-14, 5.64)	0.362
SIS (Hand)	5.66 (-11, 22.7)	0.4889	2.71 (-14, 19.9)	0.741
Box and Block	-2.93 (-6.3, 0.44)	0.0835	-0.23 (-4.1, 3.66)	0.903
Nine Hole Peg	-2.25 (-58, 53.5)	0.9245	-9.18 (-48, 29.2)	0.580
Motor Activity Log	NA	NA	17.93 (-.37, 36.2)	0.054

FMA-UE = Fugl-Meyer Assessment - Upper Extremity; ITT = intention to treat; NA = not applicable; SIS = Stroke Impact Scale; VNS = vagus nerve stimulation; WMFT = Wolf Motor Function Test. * difference between groups: Active VNS – Control VNS.