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ABSTRACT

Vagus nerve stimulation devices are conditionally approved in MRI with stimulation turned off and the requirement to modify the stimulation settings may be a barrier to scanning in some radiology practices. There is increasing interest in studying the effects of stimulation during MRI/fMRI. This study evaluated the safety of standard and investigational microburst vagus nerve stimulation therapies during MRI/fMRI. A prospective, multi-center study was conducted in patients with an investigational vagus nerve stimulation device that delivered either standard or investigational microburst vagus nerve stimulation. Thirty participants underwent sequential MRI and fMRI scans encompassing 188 total hours of scan time (62.7 hours with standard vagus nerve stimulation and 125.3 with investigational microburst vagus nerve stimulation). No adverse events were reported with active stimulation during MRI or during 12 months of follow-up. Our results support the safety and standard and investigational microburst vagus nerve stimulation therapy during MRI and fMRI scans.

ABBREVIATIONS: VNS = vagus nerve stimulation; μVNS = microburst VNS; DRE = drug-resistant epilepsy; U.S. = United States; FOS = focal onset seizures; PGTC = primary generalized tonic-clonic seizures; IDE = investigational device exemption; SD = standard deviation; EEG = electroencephalogram.

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From the Department of Neuroradiology, Mayo Clinic College of Medicine, Jacksonville, FL (E.M), Department of Neurology, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL (J.S;M.B;J.A;), Neuromodulation Division, LivaNova USA, Houston, TXL (J.B;K.H), Department of Neuroradiology, Denver Health; Department of Radiology, University of Colorado School of Medicine, Denver, CO (A.T), Sellers Communications, LLC, Springfield, MO (J.S)

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Please address correspondence to Erik H. Middlebrooks, MD, Department of Neuroradiology, Mayo Clinic College of Medicine and Science, 4500 San Pablo Road, Jacksonville, Florida 32224, USA; Middlebrooks.erik@mayo.edu.

INTRODUCTION

Approximately one-third of epilepsy patients will develop drug-resistance and may be candidates for alternative therapies including neuromodulation.[1] In 1997, the FDA approved the use of vagus nerve stimulation (VNS) as an adjunctive therapy for decreasing the incidence of focal onset seizures (FOS) resistant to antiepileptic medications in adults and adolescents older than 12 years of age.[2]

VNS devices are surgically implanted under the skin in the upper chest area and connected to the left cervical vagus nerve (Figure 1). Standard VNS sends tonic pulse trains of stimulation (e.g., 1, 2, or 5-30 Hz signal frequency in 5 Hz increments) to the brain through the vagus nerve to treat seizures.[3] Pulse delivery to cortical areas is believed to be mediated by nuclei close to the brainstem. There has been increasing interest in investigational microburst VNS (μVNS) consisting of high-frequency bursts (e.g., 100-350 Hz signal frequency in 50 Hz increments in small pulse trains of 4-7 pulses/burst), which has preclinical evidence to suggest that it works by modulating other areas of the brain, including the thalamus.[4,5]

These implants are encountered frequently in patients needing MRI. FDA-approved standard VNS therapy has instructions that recommend turning the stimulation current off to safely scan patients. VNS pulse generators are designed with a magnetic reed switch intended to either inhibit stimulation (presence of a suitable magnetic field) or trigger on-demand stimulation after brief exposure to the magnetic field. fMRI has been performed safely and effectively with previous commercially approved models of the pulse generator with careful orientation of the device (the strong B_0 field does not interact with the reed switch).[6] Current VNS devices carry an MR Conditional rating at 1.5T and 3T by the FDA, and MRI can be safely performed under the specified conditions with a body coil or a local transmit/receive coil (Figures 2 and 3).[7] The approved conditions require modified device programming during MRI to turn the stimulation current off and MRI facilities may lack staff familiar with adjusting the device settings to comply with these conditions.[7] This paper reports

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safety results from a prospective trial of patients undergoing 3T MRI and fMRI during the administration of standard VNS and investigational μVNS therapy. The feasibility protocol is published elsewhere.[3]

METHODS

A prospective, interventional, unblinded multi-center study (NCT03446664) designed to collect data from drug-resistant epilepsy (DRE) patients 12 years of age and older with an implanted investigational VNS (Model 1000C µB SenTiva VNS Therapy System manufactured by LivaNova USA [Model 1000C]) was conducted between February 1, 2018, and October 7, 2021.[8] The study was conducted in accordance with the ethical principles in the Declaration of Helsinki consistent with Good Clinical Practice described in ISO 14155 and the applicable regulatory requirement(s). All study participants provided informed consent and study sites adhered to the Institutional Review Board/Ethics Committee.

The investigational VNS device, Model 1000C, is physically identical to the conditionally approved Model 1000 (SenTiva VNS Therapy System manufactured by LivaNova USA) except for markings and firmware changes. Testing for the Model 1000 followed the requirements of ISO 14708-3, which points to ISO/TS 10974 as the proper methodology for MR conditional assessments of active implantable medical devices. Modifications to the Model 1000 for the investigational Model 1000C included configuration to deliver either commercially available standard VNS or investigational µVNS. The investigational VNS device is also configured with the ability to disregard the reed switch response under the presence of a magnetic field, removing the necessity for any careful alignment with respect to the B_0 field. Additional testing (clause 17 combined fields) was performed on the Model 1000C, the investigational VNS device, to monitor stimulation output during MRI (normally off) and was submitted as part of the Investigational Device Exemption (IDE) submission. No additional MRI device interaction risk was created by the addition of stimulation output.

Two groups were studied: 1) those with focal onset seizures (FOS) and, 2) those with EEG-verified primary generalized tonic-clonic seizures (PGTC) seizures. Participants were neuromodulation-naive and additional investigational devices and/or investigational drugs were not permitted.

Participants underwent sequential fMRI at 2-weeks and 1-, 3-, and 6-month visits.[3] They were placed into the 3T MRI scanner and had a series of 3 fMRI scans per visit with VNS "on" and a minimum scan time of 30 minutes (6 levels, 5 minutes per level) per day. There was additional time of scanning with VNS "off" that could add 10-15 minutes per session, which included structural MRI and resting state fMRI. Time for patient positioning in the magnet varied with an additional 5-10 minutes per session. Participants were instructed to inform the physician, radiologist, and/or MRI technologist overseeing the procedure if they experienced any adverse effects during their scans. Inquiries were also made by the study investigator to the participant during each visit.

A single-channel transmit/receive (T/R) head coil was utilized for data acquisition. Recent regulatory approval under "Group A" scan conditions permits the use of the body transmit coil, yet those parameters are more stringent than the T/R head coil and using the body coil would have necessitated modifications to the proposed study protocol versus the initial pilot study. Each scan included acquisition of a localizer scan and isotropic 3-dimensional T1-weighted anatomical sequence followed by fMRI during active stimulation of the VNS device (either standard or microburst).[3] Functional data were acquired using gradient-echo EPI with the following parameters: TR/TE=3000/25 ms, flip angle=84 degrees, voxel size=3 mm isotropic, field of view=256 mm, whole-brain coverage, 603 measurements, and partial Fourier factor=6/8. fMRI scans were conducted in a dose-dependent manner leveraging a block design with 30 seconds of stimulation (on-time) followed by 30 seconds of no stimulation (off-time). Each on/off cycle repeated 5 times for a total of 5 minutes before a new parameter was changed for the next 5 minutes. Six 5-minute cycles were utilized for the fMRI scanning time of 30 minutes. During the fMRI study procedures, the parameter sweep feature on the investigational device was used and the reed switch (used to either inhibit or stimulate in Magnet mode) was disregarded.[3] The study design required participants to have the device stimulated during the parameter sweep phase while undergoing the fMRI, so the fMRI results could further guide therapeutic adjustments. Following completion of a parameter sweep, the reed switch response was re-enabled and functioned as intended for normal use of the stimulator. Participants were continuously monitored by the MRI technologist and the LivaNova (device manufacturer) field engineers during and between scans.

Statistical analysis was not conducted to compare the demographics or outcomes of the study groups, therefore no formal sample size calculation was provided.[8] The number of subjects per cohort was deemed sufficient to provide initial information on the safety of the device. The final analysis was conducted when all participants completed the study at month 12.

RESULTS

A total of 33 participants (N=21 FOS and N=12 PGTC seizures) were enrolled of which 32 (N=20 FOS and N=12 PGTC seizures) were implanted with the investigational µVNS device. One participant was lost to follow-up prior to implantation of the device. Within the group of participants with implanted devices, 30 participants (N=19 FOS and N=11 PGTC seizures) completed the study (Figure 4). Within the implanted study population, half were men (N=16; 50%) and half were women (N=16; 50%) and the sexes were also equally represented in both cohorts. Most of the subjects were White (N=29; 90.6%) and not Hispanic or Latino (N=30; 93.8%). The mean age was 31.2 years (SD=13.7; range=14-61).

Following implantation and a two-week recovery, participants reported to the research site and MRI scanning facility to have their VNS device turned on and titrated following an fMRI assessment. Three additional titrations without fMRIs were completed between the 1- and 3-month fMRI visits to help the participants acclimate to the increases in the output current for microburst stimulation. The participants also underwent a VNS tolerability paradigm test in which maximum tolerable output current was determined for standard VNS and µVNS. The VNS parameter settings at the start of each follow-up visit are listed in Table 1 of the supplemental material. Upon completion of the third fMRI scan at each visit, the VNS device was programmed to the microburst settings which resulted in the greatest thalamic activation (i.e., spatial extent and peak intensity). Participants continued to report to the site for safety follow-up visits at 9- and 12-months.

There were no reported adverse events from the participants during active fMRI with the investigational VNS device in 188 hours of active scan time (62.7 hours with standard VNS stimulation and 125.3 with investigational microburst VNS stimulation). There were also no issues with image quality.

DISCUSSION

VNS therapy is a less invasive, peripheral approach to alter epileptic networks that has been proven safe and effective for a variety of seizure types. Commercially approved standard VNS and investigational µVNS devices are MR Conditional. The investigational µVNS device used in this study was designed and approved to be capable of delivering standard and investigational µVNS therapy while inside the MRI and are subject to scanning requirements of commercial devices.

Knowledge of the commercial and investigational VNS devices, the current conditional guidelines for standard VNS (low frequency, ≤ 30 Hz) therapy with MRI, and the investigational µVNS (high frequency, 250-350 Hz) therapy can help assuage the concerns of radiologists and MRI technologists. A thorough understanding of the three available modes of therapy (e.g., Normal, Magnet, and AutoStim) with the investigational µVNS and its MRI-compatible design for 1.5T and 3T is essential. The investigational µVNS devices used in participants scanned for 188 hours (62.7 hours with standard VNS stimulation and 125.3 with investigational microburst VNS stimulation) with no adverse effects. The study demonstrated that standard VNS and investigational µVNS therapy can be safely administered and is clinically compatible for patients undergoing fMRI and 3T MRI scans with no adverse events when protocols and guidelines are followed.[8,9] Modest sample size, lack of a control group, unblinded status, and use of a single VNS model limits generalizations to other devices.

Additionally, significant deviations from the equipment and protocols utilized in this study may pose additional risks. Further investigation with larger randomized controlled trials is needed to confirm the findings of this study.

CONCLUSION

Standard VNS and investigational µVNS devices are safe during fMRI without device removal, provided certain restrictions are followed. Active VNS stimulation during MRI and fMRI is also safe without risk of adverse events. The ability to perform fMRI during active standard and microburst stimulation is an important tool to understanding the mechanism of VNS and may be a valuable biomarker for stimulation optimization.

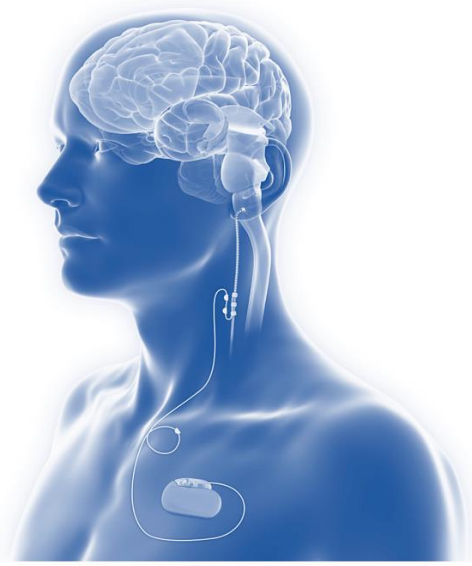

FIG 1. Implanted VNS device. The pulse generator is implanted in the left chest and the lead connected to the left vagus nerve in the neck. VNS pulses are delivered to the brain via the vagus nerve. Adapted with permission from reference 3.

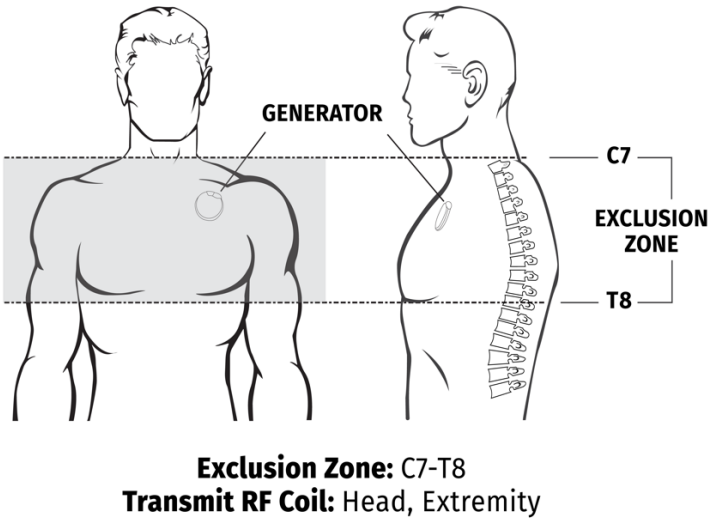

FIG 2. Exclusion zone and permissible area during MRI for head and extremity using local transmit/receive head or extremity coils.

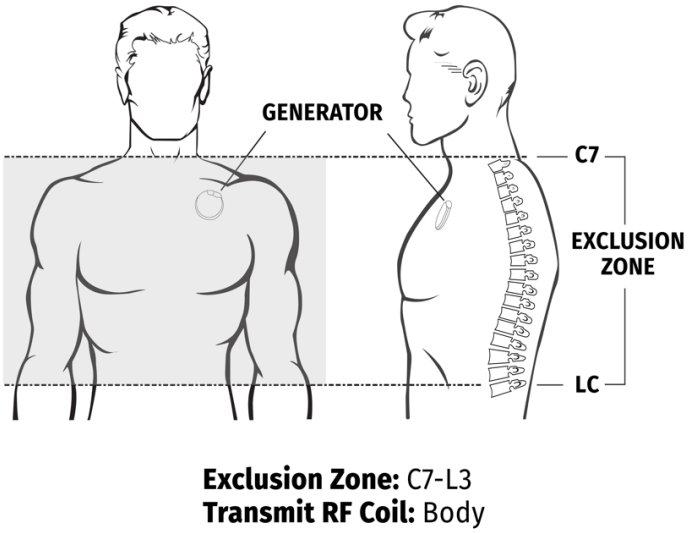

FIG 3. Exclusion zone and permissible area during MRI for body using the body transmit coil and local receive-only coil.

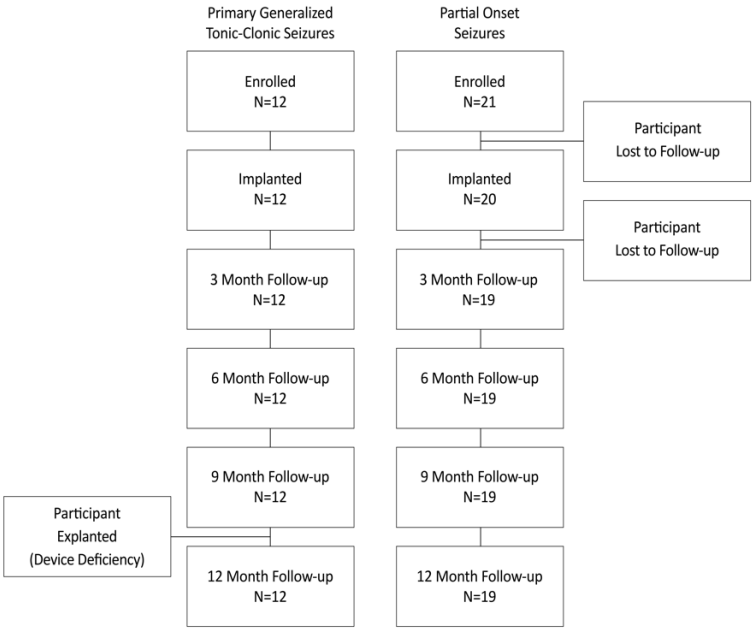

FIG 4. Microburst participant accountability showing the initial enrollment through study completion plus study attrition.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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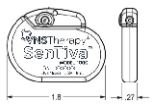
SUPPLEMENTAL FILES

Table 1. VNS Parameter Settings (Normal Mode) at the Beginning of each Follow-up Visit

		1 Month	3 Months	6 Months	9 Months	12 Months
VNS Parameter	**Statistic**					
Off-Time (min)	N	32	31	31	30	26
	Mode	5.0	5.0	5.0	5.0	5.0
	Median (Q1, Q3)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)	5 (5, 5)
On-Time (sec)	N	32	31	31	30	26
	Mode	30.0	30.0	30.0	30.0	30.0
	Median (Q1, Q3)	30 (30, 30)	30 (30, 30)	30 (30, 30)	30 (30, 30)	30 (30, 30)
Output Current (mA)	N	32	31	31	30	26
	Mode	0.3	0.5	1.0	1.5	1.8
	Median (Q1, Q3)	0.3 (0.3, 0.6)	1.1 (0.5, 1.8)	1 (0.5, 1.8)	1.1 (0.6, 1.5)	1.6 (0.8, 1.8)
Pulse Width (usec)	N	32	31	31	30	26
	Mode	250.0	250.0	250.0	250.0	250.0
	Median (Q1, Q3)	250 (250, 250)	250 (250, 250)	250 (250, 250)	250 (250, 250)	250 (250, 250)
Signal Frequency (Hz)	N	32	31	31	30	26
	Mode	300.0	300.0	300.0	300.0	300.0
	Median (Q1, Q3)	300 (300, 300)	300 (300, 300)	300 (300, 300)	300 (300, 300)	300 (300, 300)
Inter-Burst Intervals (sec)	N	32	31	31	30	26
	Mode	0.5	0.5	0.5	0.5	0.5
	Median (Q1, Q3)	1.5 (0.5, 2.5)	0.5 (0.5, 1.5)	1.5 (0.5, 2.5)	0.5 (0.5, 1.5)	0.5 (0.5, 1.5)
Number of Pulses	N	32	31	31	30	26
	Mode	7.0	4.0	7.0	4.0	4.0
	Median (Q1, Q3)	7 (4, 7)	4 (4, 7)	7 (4, 7)	4 (4, 7)	4 (4, 7)

Table 2. Standard versus Microburst VNS Device Comparison

Attribute	Model 1000	Model 1000C
Stimulation Modes		
Normal	Standard	Standard or Microburst
Magnet	Standard	Standard or Microburst
AutoStim	Standard	Standard or Microburst
Technology		
Software	Compatible with Programmer Model 3000 SW Version 1.0	Compatible with Programmer Model 3000C SW Version 1.1
Wand	Model 2000 Programming Wand	Model 2000 Programming Wand
Firmware	Generator Code is written in language, C.	Same as M1000
Hardware	----	Same as M1000
Communication Speed	----	Same as M1000
Features		
Magnet Activation	Provided by Magnet application (output current, pulse width, and signal ON time may be independently programmed for this purpose)	Same as M1000 Magnet Response disabled during "Parameter Sweep"
Tachycardia Detection Algorithm	Yes	Same as M1000
AutoStim Mode	Yes	Same as M1000
Day-Night Mode	Yes	No
Low Heart Rate Detection	Yes	Same as M1000
Prone Position Detection	Yes	Same as M1000
Scheduled Programming	Yes	No
Parameter Sweep	No	Yes
IPG Form Factor		Same as M1000
Parameters		
Output Current	Applicable to Normal/ Magnet/AutoStim Mode 0-1.875 in 0.125 mA steps, 2.0 - 3.5 mA in 0.25 mA steps (±0.1 mA or ±10%; whichever is greater)	Same as M1000
Signal Frequency	1, 2, 5, 10, 15, 20, 25, 30 Hz ±6%	Existing range of signal frequencies in M1000 but also 100-350Hz in 50 Hz increments ±6% for Microburst stimulation

1