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Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: Long-term outcomes and predictors of response

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ABSTRACT

Objective: The goal of this study was to assess the efficacy and safety of vagus nerve stimulation in a consecutive series of adults and children with treatment-resistant epilepsy (TRE).

Methods: In this retrospective review of a prospectively created database of 436 consecutive patients who underwent vagus nerve stimulator implantation for TRE between November 1997 and April 2008, there were 220 (50.5%) females and 216 (49.5%) males ranging in age from 1 to 76 years at the time of implantation (mean: 29.0 ± 16.5). Thirty-three patients (7.6%) in the primary implantation group had inadequate follow-up (<3 months from implantation) and three patients had early device removal because of infection and were excluded from seizure control outcome analyses.

Results: Duration of vagus nerve stimulation treatment varied from 10 days to 11 years (mean: 4.94 years). Mean seizure frequency significantly improved following implantation (mean reduction: 55.8%, $P<0.0001$). Seizure control ≥90% was achieved in 90 patients (22.5%), ≥75% seizure control in 162 patients (40.5%), ≥50% improvement in 255 patients (63.75%), and <50% improvement in 145 patients (36.25%). Permanent injury to the vagus nerve occurred in 2.8% of patients.

Conclusion: Vagus nerve stimulation is a safe and effective palliative treatment option for focal and generalized TRE in adults and children. When used in conjunction with a multidisciplinary and multimodality treatment regimen including aggressive antiepileptic drug regimens and epilepsy surgery when appropriate, more than 60% of patients with TRE experienced at least a 50% reduction in seizure burden. Good results were seen in patients with non-U.S. Food and Drug Administration-approved indications. Prospective, randomized trials are needed for patients with generalized epilepsies and for younger children to potentially expand the number of patients who may benefit from this palliative treatment.

1. Introduction

An estimated 50 million people worldwide are affected by epilepsy, most of whom are successfully treated with single or multidrug regimens [1]. Treatment-resistant epilepsy (TRE) has been reported to occur in 20 to 30% of patients with epilepsy and can be devastating to patients and their families [1]. These effects can be especially profound in children owing to disruption of critical developmental epochs essential to proper intellectual and social maturation.

Nonsurgical treatment options for TRE include the ketogenic diet, complementary or alternative medical therapies, and biofeedback. Surgical treatment options include resective surgery, disconnection procedures, and stimulation procedures. The most widely used and studied neurostimulation procedure is vagus nerve stimulation (VNS; VNS Therapy System; Cyberonics, Inc., Houston, TX, USA), which has been in use since U.S. Food and Drug Administration (USFDA) approval in 1997 for the treatment of intractable partial epilepsy in adults and children over 12 years of age.

Most of the studies reporting on the efficacy of VNS, however, involve a limited number of patients and often have rather short follow-up durations. We report a consecutive series of more than 400 patients with TRE who underwent long-term VNS therapy for refractory epilepsy, analyze the efficacy and safety of VNS therapy, and examine predictors of VNS treatment success.

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2. Methods

2.1. Subjects

Between November of 1997 and April of 2008, 507 patients underwent vagus nerve stimulator operations at the NYU Comprehensive Epilepsy Center or Saint Barnabas Medical Center by a single surgeon (W.K.D.). Seventy-one patients were referred for removal or revision of a device placed at an outside center; 436 consecutive patients with TRE underwent primary insertion of a VNS device at our center and are the subjects of this report. At the initial office visit, all patients were prospectively entered into a database that was created for clinical data storage. Data collected included demographic information, surgical history, physical and neurological exams, epilepsy characteristics, mean weekly seizure frequency (obtained from seizure logs kept by caretakers or patient or caretaker report averaged between the last two office visits), treatment history, and imaging findings. This report is a retrospective analysis of this database.

Each patient underwent a presurgical evaluation that included history and physical, electroencephalography (EEG), magnetic resonance imaging (MRI), and, in most cases, video/EEG monitoring and functional imaging studies. The majority of patients were reviewed at a presurgical multidisciplinary conference (MDC) and deemed to be surgical candidates. Selection criteria for the patients who had VNS device insertion included: multifocal or diffuse seizure onset not amenable to surgical resection (250 [57.3%]); persistent or recurrent seizures following intracranial epilepsy surgery (IES; 127 [29.1%]); antiepileptic drug (AED) toxicity or intolerable side effects (5 [1.1%]); medical unfitness for IES (6 [1.4%]); and patient or family preference for conservative measures prior to or in lieu of possible IES (48 [11.0%]). Focal seizure onsets were deemed to be in eloquent areas if they were in primary sensory or motor gyri, calcarine cortex, or frontal and temporal speech areas.

Following institutional review board approval, subjects undergoing VNS procedures were identified from within the database. Missing data were obtained from office and inpatient charts, operative reports, imaging, and electrophysiological studies. Informed consent was waived by the review board.

2.2. Surgical procedure and outcome assessment

The surgical techniques for subcutaneous and subpectoral implantation of the VNS device have been previously described [2]. The majority of patients who underwent implantation were discharged the same day. A small minority of patients had planned inpatient epilepsy monitoring unit admissions for medication adjustment coinciding with their implantation. Since 1999, the stimulator has been turned on at the time of surgery. Surgical follow-up typically occurred 2 weeks postoperatively and, subsequently, on a variable schedule as indicated. Long-term follow-up and adjustments of VNS parameters were conducted by the primary epileptologist. The adjustments in device parameters were performed solely at the discretion of the primary epileptologist with a formal protocol guiding changes.

Retrospective chart review was performed to collect follow-up and outcome data. All patients had the opportunity for at least 1 year of VNS therapy duration unless the device was turned off or removed prior to that time. At the time of last available clinical follow-up, the following data were collected: mean weekly seizure frequency (from seizure logs kept by caretakers or patient or caretaker report, calculated as an average of the last 3 months prior to final follow-up or the last two office visits if a longer follow-up visit ensued), complications of VNS therapy, duration of VNS therapy, timing and reason for revisions and removals of VNS devices and all subsequent surgical procedures. A standardized questionnaire that addresses complications and side effects was completed at each follow-up visit at our centers. Although caretakers were queried about the use of the magnet for seizure prevention or termination, its use was at the discretion of the caretaker or patient, usually dependent on the presence of an aura and not systematically reported.

To limit the bias created by nonresponder attrition, we computed follow-up duration using a last visit carried forward (LVCF) analysis in lieu of a declining-n analysis [3]. Telephone interviews were conducted with patients, families, or caretakers to determine most recent seizure frequency and current AED regimen. For patients who could not be reached by phone, follow-up was censored at time of last office visit or inpatient admission. For patients who underwent device removal or had their devices turned off, follow-up was censored at time of VNS therapy termination. Given the demonstration of VNS effect by 3 months from the randomized trials, we considered patients who had VNS therapy for at least 3 months with clinical follow-up data to have adequate follow-up. Patients who did not have follow-up of at least 3 months were deemed to have inadequate follow-up and were excluded from outcome analyses.

Two hundred forty-five patients were included in a study describing our experience with subpectoral and subcutaneous VNS generator placement [2] and another report on the efficacy of VNS in 17 patients with tuberous sclerosis complex [4].

We acknowledge that VNS therapy in patients with generalized epilepsies and children $\leq$12 years of age is an off-label usage not approved by the US FDA.

2.3. Statistical analyses

Averages are expressed as means $\pm$ SD and medians. The numbers of pre- and post-VNS AEDs used were not normally distributed (nonparametric), and pre- and postoperative usage was compared via paired-sample Wilcoxon signed ranks testing. Seizure frequency before and after VNS lacked normal distributions when $n<30$ per group (as noted in corresponding tables); therefore, the paired-sample Wilcoxon signed ranks test was employed to compare pre- and postoperative values in those cases. For groups with $n\geq30$ with normal distributions, the paired-sample t test was employed to compare pre- and postoperative seizure frequency within subgroups. Percentage seizure reduction was normally distributed when $n>20$ and is reported as both median values and mean values with 95% confidence intervals. Uni- and multivariate linear regression analyses were performed to determine the impact of the following independent variables (continuous, dichotomous, or multinomial) on mean percentage seizure reduction (dependent variable): age at epilepsy onset, age $\leq$5 years at onset of epilepsy, age at implantation, age >12 years at implantation, age >18 years at implantation, duration of epilepsy prior to VNS, duration of epilepsy >10 years prior to VNS therapy, prior IES, number of prior IESs, preimplantation seizure frequency, number of reported seizure types, focal seizures only, epilepsy classification and etiology, underlying diagnosis if applicable, EEG findings, number of preimplantation AEDs, number of failed AEDs and history of infantile spasms, febrile seizures, developmental delay, or status epilepticus. Demographic and clinical data comparing patients with and those without adequate follow-up were evaluated with Fisher's exact test for proportions, The Mann–Whitney U test for nonparametric data, and Student's t test for parametric data. All variables with a P value of <0.10 on univariate analyses were entered stepwise into the multivariate linear regression model. All statistics were performed using SPSS Version 17.0 for Mac (SPSS Inc., Chicago, IL, USA). A two-tailed P value <0.05 was considered statistically significant.

3. Results

3.1. Patient demographics and clinical data of the primary implant group

Patient demographics and clinical data for the 436 patients (220 females/216 males) who had primary implantations are summarized in Table 1.