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Long-term seizure and psychosocial outcomes of vagus nerve stimulation for intractable epilepsy

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ABSTRACT

Vagus nerve stimulation (VNS) is a widely used adjunctive treatment option for intractable epilepsy. Most studies have demonstrated short-term seizure outcomes, usually for up to 5 years, and thus far, none have reported psychosocial outcomes in adults. We aimed to assess long-term seizure and psychosocial outcomes in patients with intractable epilepsy on VNS therapy for more than 15 years. We identified patients who had VNS implantation for treatment of intractable epilepsy from 1997 to 2013 at our Comprehensive Epilepsy Program and gathered demographics including age at epilepsy onset and VNS implantation, epilepsy type, number of antiepilepsy drugs (AEDs) and seizure frequency before VNS implantation and at the last clinic visit, and the most recent stimulation parameters from electronic medical records (EMR). Phone surveys were conducted by research assistants from May to November 2014 to determine patients' current seizure frequency and psychosocial metrics, including driving, employment status, and use of antidepressants. Seizure outcomes were based on modified Engel classification (I: seizure-free/rare simple partial seizures; II: >90% seizure reduction (SR), III: 50–90% SR, IV: <50% SR; classes I to III (>50% SR) = favorable outcome). A total of 207 patients underwent VNS implantation, 15 of whom were deceased at the time of the phone survey, and 40 had incomplete data for medical abstraction. Of the remaining 152, 90 (59%) were contacted and completed the survey. Of these, 51% were male, with the mean age at epilepsy onset of 9.4 years (range: birth to 60 years). There were 35 (39%) patients with extratemporal epilepsy, 19 (21%) with temporal, 18 (20%) with symptomatic generalized, 5 (6%) with idiopathic generalized, and 13 (14%) with multiple types. Final VNS settings showed 16 (18%) patients with an output current >2 mA and 14 (16%) with rapid cycling. Of the 80 patients with seizure frequency information, 16 (20%) had a modified Engel class I outcome, 14 (18%) had class II, 24 (30%) had class III, and 26 (33%) had class IV. Eighty percent said having VNS was worthwhile. Among the 90 patients, 43 patients were ≥18 years old without developmental delay in whom psychosocial outcomes were further analyzed. There was a decrease in the number of patients driving (31% vs 14%, $p = 0.052$) and working (44% vs 35%, $p = 0.285$) and an increase in the number of patients using antidepressant medication (14% vs 28%, $p = 0.057$) at the time of survey compared to before VNS. In this subset, patients with >50% SR (60%) were taking significantly fewer AEDs at the time of survey compared to patients with unfavorable outcomes (median: 3 vs 4, $p = 0.045$). The associations of >50% SR with the psychosocial outcomes of driving, employment, and antidepressant use were not significant, although 77% of this subset said VNS was worthwhile.

This is the first study that assesses both seizure and psychosocial outcomes, and demonstrates favorable seizure outcomes of >50% SR in 68% of patients and seizure freedom in 20% of patients. A large majority of patients (80%) considered VNS therapy worthwhile regardless of epilepsy type and psychosocial outcomes.

1. Introduction

Almost 30% of all epilepsies remain intractable to antiepilepsy drugs (AEDs) [1], and adjunct nonpharmacologic therapies that include surgical treatment options, stimulation therapies, and ketogenic or alternative medical therapies are often explored in those cases. Since 1997, VNS (by VNS Therapy Systems, Cyberonics, Inc., Houston, TX, USA) has been approved by the U.S. Food and Drug Administration (FDA) as an

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adjunctive therapy for treatment of intractable epilepsy, and short-term efficacy has been established through a randomized controlled trial [2]. Subsequent studies have reported seizure outcomes for up to 5 years [3–7] and rarely to 10–11 years [8,9]. A few studies have assessed behavioral and cognitive outcomes after VNS therapy in children [10] and the effect on mood in adults [11]. However, thus far, no data assessing common psychosocial outcomes are available in adults. The aim of our study was to assess long-term seizure and psychosocial outcomes for more than 15 years in all patients with intractable epilepsy who had VNS implantation at our tertiary epilepsy center by conducting follow-up phone surveys. This study was, to some extent, a continuation of the assessment of long-term outcomes of surgical therapies for intractable epilepsy at our center [12].

2. Materials and methods

2.1. Study description, approvals and consents

This was a retrospective study on patients with intractable epilepsy to gather pre-VNS implantation information and a cross-sectional study to assess postimplantation seizure and psychosocial outcomes. Patients who had VNS implantation for intractable epilepsy from 1997 to 2013 were retrospectively identified. Data were collected using medical record chart reviews and phone surveys. Low-risk, retrospective methodologies of the chart review led to waiving of written consents. Prior to starting every phone survey, verbal consents were obtained. This study was approved by the Henry Ford Health System Institutional Review Board (IRB # 8835).

2.2. Data collection

Demographic information consisting of gender, age and race, age at epilepsy onset and VNS implantation, epilepsy type, number of AEDs used, and seizure frequency before VNS implantation were collected by retrospective chart reviews using the EMR. Clinical notes from the last visit in EMR were reviewed to obtain information on the most recent seizure frequency and stimulation parameters. The Department of Public Health Sciences obtained patient contact information from EMR or through a public search database. The research assistants (KM, AG) attempted follow-up phone surveys for all the patients from May to November 2014. A script that included confidentiality statements along with questions about the patients' current seizure frequency, the current number of AEDs being taken, and queries on psychosocial metrics was followed by the research assistants during the phone survey. In our experience, phone surveys had a potential for a better response rate, especially given that a number of the patients may have moved out of the area and/or were not receiving their care at our institution, and hence were chosen over mailed or in-person surveys. The selection of the psychosocial metrics of driving, employment, and antidepressant use were chosen as by Dupont et al. [13] and was also based on our experience with patients with epilepsy demonstrated in postsurgical outcomes [12]. Patients who were deceased at the time of survey and those who refused to participate or could not be contacted despite at least three phone attempts were not included in the final outcome assessment.

We aimed to assess the effect of some VNS stimulation parameters on the therapeutic response [14] by assessing seizure outcomes. We considered current stimulation of more than 2 mA as a cutoff for higher intensities as a lower current was safer and better tolerated [15], as in our clinical experience. Duty cycle was calculated (ON time + 4/ON time + OFF time) for each of the VNS settings and the ratio of more than 25% was considered as rapid cycling in our study, as duty cycles of 50% or less are typically known to be safe and effective [14].

2.3. Outcome assessment

Seizure outcomes after VNS implantation were based on modified Engel classification [16], and classes I to III were considered as favorable outcomes with SR of >50% (Table 1). This classification was based on the patients' responses to questioning about seizure frequency at the time of survey compared to before VNS implantation. Psychosocial metrics assessed on the phone survey included driving status, employment status (full-time, part-time, or unemployed) and the use of antidepressant medications before VNS and at the time of survey. Patients' satisfaction was assessed by asking them if it was worthwhile having VNS as an adjunctive treatment for intractable epilepsy.

2.4. Statistical analysis

To assess the associations of survey response, epilepsy type, and favorable outcomes with demographics, VNS stimulation parameters, and psychosocial measures, chi-square tests were used for the binary or categorical variables, two-sample t-tests were used for the continuous measures of age at onset and age at VNS implantation, and Wilcoxon two-sample tests were used for number of years between epilepsy onset and VNS implantation, number of seizures per month before VNS, number of AEDs before VNS, and duration of VNS therapy. McNemar's tests were done to compare preoperative to postoperative responses for driving, employment, and use of antidepressants. Statistical significance was set at the 0.05 level. Statistical analyses were performed using SAS version 9.2.

3. Results

3.1. Description of identified patients

A total of 207 patients with epilepsy were identified as having VNS implantation between 1997 and 2013. Fifteen patients were confirmed to be deceased, and 40 had incomplete data for medical abstraction. Of the remaining 152 patients, 90 (59%) were contacted and agreed to complete the phone survey, 14 (9%) refused to participate, and 48 (32%) of the patients could not be contacted (21 with wrong or no phone numbers, 22 with no answer, and 5 repeatedly postponed answering the survey) after at least three attempts on different days and different times. Ten patients could not have modified Engel classifications because of missing information for frequency of seizures prior to VNS or at the time of the survey. Of the 152 eligible patients, 53% (n = 80) were male, 100 (66%) were Caucasian, and 15 (10%) were African American. The mean age at epilepsy onset was 9.7 years (range: birth to 60 years). The mean duration of epilepsy before VNS was 20.5 years (range: 3 to 54 years).

3.2. Medical record and survey

Comparisons of demographic, medical, and surgical variables between patients with and without completed surveys were performed in order to assess any potential responder bias (Table 2). No differences were detected for gender, race, age at epilepsy onset, age at VNS implantation, duration between epilepsy onset and VNS implantation, presence

Table 1
Seizure outcomes by modified Engel classification for 80 patients with intractable epilepsy on VNS therapy.

Class	Modified Engel description	Number (%)
I	Seizure-free Rare, nondisabling simple partial seizures	16 (20%)
II	>90% reduction in seizure frequency Rare complex partial seizures	14 (18%)
III	50–90% reduction in seizure frequency	24 (30%)
IV	<50% reduction in seizure frequency	26 (33%)