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Vagus nerve stimulation therapy for treatment-resistant epilepsy: A 15-year experience at a single institution

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ABSTRACT

Objective: Treatment-resistant epilepsy (TRE) occurs in 20–30% of patients. The goal of this study is to assess the efficacy and safety of vagus nerve stimulation (VNS) in this group of patients, including adult and pediatric populations and several off-label indications.
Methods: This is a retrospective review of 59 consecutive patients in whom 60 VNS devices were implanted at a single institution during a 15-year period. Patients were evaluated in the Multidisciplinary Epilepsy Committee and complete presurgical workup was performed. The series included indications not approved by the FDA, such as children under 12 years of age, pregnancy and right-sided VNS. Performing the procedure on an out-patient basis was recently adopted, minimizing hospital length of stay.
Results: There were 42 adults and 17 children (14 under 12 years of age) and the mean age at implantation was 26 years. Duration of VNS therapy ranged from 6 months to 9 years. For the entire cohort, the mean percentage seizure reduction was 31.37%. Twenty patients (34.48%) were considered responders (seizure reduction ≥50%); 7 patients (12.06%) had seizure reduction of ≥75% and 2 patients had seizure control of ≥90% (3.4%). The patient in whom right-sided VNS was implanted achieved the same reduction in seizure burden and the patient who became pregnant could reduce antiepileptic drugs dosage, without complications. Side-effects were mild and there were no permanent nerve injuries. One patient died in the follow-up due to psychiatric disorders previously known.
Conclusions: VNS is a safe and effective palliative treatment for TRE patients. There are an increasing number of indications and further randomized trials would potentially expand the number of patients who may benefit from it. A multidisciplinary team is crucial for a complete preoperative evaluation and selection of the optimal candidates for the treatment.

1. Introduction

Approximately 50 million people worldwide are affected by epilepsy [1] and it represents the second neurological disorder in incidence and prevalence after cerebrovascular disease [2]. It has a significant psychological and social impact on patients and relatives, and its high morbidity and low mortality create increasing and disproportionately high costs of illness compared with other diseases [3,4]. Most of the patients are successfully controlled with antiepileptic drugs (AEDs); however, treatment-resistant epilepsy (TRE) has been reported to occur in 20–30% of patients [1,5–7] and only 20–40% of them meet criteria for surgical treatment [8]. Vagus nerve stimulation (VNS; VNS Therapy System; Cyberonics, Inc., Houston, TX, USA) is the most widely used and studied neurostimulation procedure and it constitutes an alternative of treatment for this group of patients. It was approved by U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) in

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1997 and 1994, respectively, for the treatment of intractable partial epilepsy in adults and children over 12 years of age. Nevertheless, use of VNS therapy has been progressively increasing and many off-label indications of VNS therapy have been reported since its approval [8–14], including right-sided vagus nerve stimulation in complicated cases [15,16]. Surgical technique is not difficult, with low morbidity [17,18], and it can be performed on an out-patient basis in most of the cases [8,19–21], as we have adopted recently. In this paper, we report our series of patients treated with VNS therapy at our institution since the first implant in 1998.

2. Materials and methods

This is a retrospective observational analysis of all patients (adults and children) treated with VNS therapy at Cruces University Hospital since April 1998 until June 2013. Data collected included demographic information, surgical and medical history, etiology, physical and neurological exams, epilepsy characteristics and time to implant, seizure frequency (obtained from logs kept by patients or caretakers) and concomitant pharmacological treatment.

Each patient underwent a presurgical evaluation in the Multidisciplinary Epilepsy Committee that included clinical history, physical and neurological exams, psychological and psychiatric evaluation, video/EEG monitoring, magnetic resonance imaging (MRI) (1.5/3 T) and in some cases, MRI functional studies and PET. Selection criteria for VNS implantation included: (1) multifocal or diffuse seizure onset not amenable to surgical resection; (2) recurrent or persistent seizures following intracranial epilepsy surgery and not candidates to a new surgery; and/or (3) patient or family preference for conservative measures.

2.1. Surgical technique and follow-up

Surgical procedure for VNS device implantation has been previously reported elsewhere [1,3,20]. Briefly, the surgery is performed with the patient supine, neck slightly extended, under general anesthesia and endotracheal intubation. Two small skin incisions of about 4 cm are performed on the left side. The first one is on a horizontal fold of skin on the anterolateral surface of the neck and the second one is located on the chest below the left clavicle. We have used the subaxillary placement in two cases (two women) for cosmetic reasons. After neck incision, section of the platysma is performed, followed by muscle dissection and opening of cervical fascia to expose the left vagus nerve in between the common carotid artery and internal jugular vein. Under the operating microscope, the electrode is wrapped around the vagus nerve with the aid of usual forceps. On the chest, a subcutaneous pocket is made, large enough to harbor the pulse generator, which is connected subcutaneously to the electrode already placed around the vagus nerve. The system is tested through telemetry with 1 mA impulse to verify the correct impedance. Finally, the incisions are closed after assessing hemostasis, and dry dressings are placed over the surgical wounds. Patients usually stay at hospital for one night; however, we have recently started performing the procedure on an out-patient basis (same day discharge) in some cases, without complications.

One patient had VNS implanted on the right side. During follow-up, telemetry showed high impedance throughout the system and significant fibrosis around left vagus nerve was observed in surgical revision. Complete cardiac evaluation was performed prior to surgery (24 h Holter-monitoring, echocardiography) and new VNS was implanted on the right side, using the same surgical technique. VNS was turned on during 24 h after surgery and no cardiorespiratory events were reported during continuous Holter-monitoring. Patient was discharged home and controlled with periodic electrocardiograms in the out-patient clinic.

Follow-up is conducted by the Epilepsy Unit epileptologist and by the neuropediatrician in pediatric patients. VNS is turned on approximately 2 weeks after surgery and adjustments of VNS parameters or AEDs are performed at the discretion of the epileptologist, on a variable schedule. Seizure control is reported as responder rate (% of patients in whom seizure burden is reduced ≥50%) and/or percentage seizure reduction. Seizure frequency, use of the magnet and side effects are obtained from the logs kept by patients, information given by relatives or phone enquiries. Therefore, systematic data recording and quantitative assessment of seizure reduction are often difficult and inherently subject to error. For patients who underwent device removal or had their devices turned off, follow-up was censored at time of VNS therapy termination.

We acknowledge that VNS therapy in patients with generalized epilepsy and children ≤12 years of age, as well as right-sided VNS, are off-label usages not approved by the US FDA or EMA.

3. Results

During a 15-year period, 60 VNS have been implanted in 59 patients in our Epilepsy Unit. One patient had the VNS implanted on the right side two years after left-sided VNS surgery. All surgeries were primary implantations. Patient demographics and clinical data are summarized in Table 1.

Seizure origin was frontal in 42.37% of the patients, and temporal or parieto-occipital in 5% of the cases each. Multifocal origin was diagnosed in 28.81% of the patients, being the ictal focus not well defined in 18% of the cases. According to seizure type, most of the patients had complex partial seizures (CPS, 44.06%), followed by secondarily generalized CPS and CPS + drop-attack (30.50% and 11.86%, respectively). Epilepsy etiology was unknown in 28.81% of cases and among patients with underlying conditions, the most common causes included neuronal migration disorders (12/59), perinatal encephalopathy (12/59), tuberous sclerosis complex (4/59), traumatic brain injury (4/59) and Lennaux-Gastaut (3/58). History of previous surgeries was present in 8/59 patients (13.55%).

The mean duration of VNS therapy was 38.91 months (6 months–9 years). One patient committed suicide during the follow-up (she had been previously treated for psychiatric disorder with a suicide attempt prior to device implantation). Excluding 1 child who had the device removed in the immediate post-operative period because of infection (1.7%), 58 patients were available for the analysis (follow-up > 3 months). For the entire cohort, the mean percentage seizure reduction was 30.05%, 31.81%, 31.98% and 31.64% at 3, 6, 12 months and at last follow-up, respectively. Twenty patients (34.48%) were considered responders (percentage seizure reduction ≥50%); 7 patients (12.06%) had seizure reduction of ≥75% and ≥90% seizure control was achieved in two patients (3.4%). The patient in whom right-sided VNS was implanted experienced the same reduction in seizure burden as with left-sided

Table 1
Demographic and clinical data for 59 patients who underwent VNS insertion.

Variable	No. or mean ± (range)
Sex	
Male	36
Female	23
Age at seizure onset	7.45y (3 days–24 years)
Duration of epilepsy prior to VNS	18.91y (2–42 years)
Age at VNS insertion	26y (2–52 years)
Adults (≥18 years)	42
Children <18 years	17
Children ≤12 years	14
Median seizure frequency (per month)	17.64 (1–140)
Mean number of AEDs	3.07 (1–5)