Vagus Nerve Stimulation for Intractable Seizures in Children: the University of Puerto Rico Experience

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Objective: Vagus nerve stimulation (VNS) is considered an alternative treatment for patients with medically refractory epilepsy who are not candidates for resective surgery. It consists of intermittent electrical stimulation of the left vagus nerve in the neck. Such stimulation has been demonstrated to be efficacious, safe, and well tolerated, offering these patients another option for seizure control. The aim of this study was to evaluate the experience of VNS at the University of Puerto Rico, and to examine demographic data, types of seizures, and seizure-control outcomes among treated subjects. This study is the first account of VNS in a pediatric population living in the Caribbean area.

Methods: A retrospective analysis of 13 patients treated at the University Pediatric Hospital in San Juan, Puerto Rico, was undertaken. Different types of seizures were identified and managed.

Results: The mean age at implantation was 12 years; 77% of patients were female. The most common type of seizure treated was generalized tonic-clonic (24%), followed by complex partial (23%). Sixty-nine percent of patients demonstrated a reduction in monthly seizure frequency. Ninety-three percent of caregivers reported improvements in alertness and communication.

Conclusion: Vagus nerve stimulation is a safe and effective way to treat medically refractory epilepsy and should be considered as a non-pharmacological treatment for select patients with medically refractory epilepsy. [*P R Health Sci J 2011;30:128-131*]

Key words: Vagus nerve stimulation, Epilepsy, Pediatrics

Epilepsy is the most prevalent neurological condition and the second most common chronic neurological disorder after stroke, affecting approximately 2% of the population (1). Despite advances in the neuropharmacology and molecular biology of epilepsy, 30% of patients remain with inadequate seizure control or experience undesirable side effects from their medications (2-3).

Children with epilepsy differ from adults not only in the clinical manifestations of their seizures, but also by the presence of unique electroencephalogram (EEG) patterns, etiologies, and responses to antiepileptic drugs. The immature brain differs from the adult brain in terms of the basic mechanisms of epileptogenesis and propagation of seizures. While a child's brain is more prone to seizures than is an adult's, these seizures are apt to disappear with time (4-6). Thus, the long-term prognosis for seizure cessation tends to be better in children, particularly those who are neurologically intact (7). Epidemiological studies have demonstrated that the prognosis for pediatric epilepsy is more favorable than it is for adults, with up to 80% of epileptic children achieving remission (8). Nevertheless, a given patient's prognosis must be examined in the context of the particular etiology of that patient's condition, as remission is less likely in the case of an inherited syndrome (8-9).

The pediatric brain is more susceptible to neurocognitive disabilities that are secondary to refractory epilepsy. Declines in mean intelligence quotient scores secondary to refractory epilepsy are well documented in the literature (8). Refractory epilepsy represents a considerable risk to the intellectual capacity and the quality of life of those children who suffer from it and thus needs to be addressed in a timely manner.

Epilepsy surgery is a therapeutic alternative for medically refractory epilepsy. Procedures including cortical resection, lobectomy, and/or disconnection of structures are an important alternative to drug therapy in carefully selected patients. The incidence of seizure-free outcomes after epilepsy surgery in children and adolescents is reported to be between 59-68% (10-11). However, when an epileptogenic zone cannot be located or is localized in the eloquent brain, epilepsy surgery

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is not acceptable. Patients who are not candidates for resective surgery are left with few options.

In 1997, the United States Food and Drug Administration approved vagus nerve stimulator (VNS) therapy as an adjunct therapy for reducing seizure frequency. VNS is a relatively novel method of treatment for medically intractable epilepsy. Its usefulness in epilepsy extends from the experimental finding that vagus nerve stimulation desynchronizes the electroencephalogram (EEG) in animals (12-15). Vagal nerve afferents pathways relay impulses to multiple regions in the central nervous system that are potential sites for epileptogenesis, such as the hippocampus and the amygdala. Although the mechanism of the antiepileptic efficacy of VNS therapy remains unknown, there is evidence that the modulation of afferent vagal nerve activity increases the seizure threshold (16-17).

The experience of VNS in pediatric populations is limited. No controlled studies regarding this therapy are available, but recent studies have demonstrated there to be a seizure frequency reduction of between 50% and 60% with its use (18-19). A reduction in seizure frequency is not immediate but tends to increase over weeks, and continues to increase over months until a plateau is reached within 18-24 months. In this context, VNS is an option for children with drug-resistant epilepsy. VNS is traditionally reserved for those children without lateralized or localized epilepsy or for those children for whom primary epilepsy surgery has failed. In this study we retrospectively analyzed and now describe the experience with VNS in a pediatric population in Puerto Rico.

Methods

A retrospective study running from July 2005 to September 2008 was conducted. Thirteen patients underwent VNS placement at the University Pediatric Hospital in San Juan, Puerto Rico, as an adjunctive treatment for medically refractory epilepsy. All patients were treated by one neurosurgeon. A minimum of nine months of follow-up was conducted. All patients were being treated with 2-4 anti-epileptic medications, all at their maximum dosages. For the purposes of this study, patients who were candidates for VNS did not show any definitive surgical lesions; the disorders of these individuals were classified as idiopathic epilepsy. Records were reviewed for age, gender, age of seizure onset, post-implantation frequency, and side effects. Each patient's monthly seizure frequency was determined using a seizure diary. Caregivers were interviewed regarding the effects of VNS on daily activities and on overall quality of life.

Surgical technique

All patients underwent the same standardized implantation procedure; this is performed under general anesthesia and employs a left-side approach. An incision over the anterior border of the sternocleidomastoid muscle is made and the vagus nerve identified in the carotid sheath and mobilized; next, the nerve is carefully freed and bipolar helical electrodes are placed around it. A horizontal incision is then made below the mid-clavicle, and a subcutaneous pouch is prepared to receive the pulse generator. Connectors are then tunneled from the neck incision to the chest incision and fitted into the generator. VNS stimulation is started 2-4 weeks after the implantation procedure (15).

Results

The mean age at implantation was 12 years (range 6-18, standard deviation [SD] = 5). Seventy-seven percent (77%) were female and 23% were male. The mean age at the presentation of epilepsy was 24 months (range 1-60, SD = 19). The mean duration of epilepsy before implantation was 9.7 years (range 5-16, SD = 5) (Table 1).

Table 1. Demographic features, types of seizures, and outcome of 13 patients treated with vagus nerve stimulation

Sex, n (%) female	10 (77)
Female:male ratio	3.3:1
Age at implantation, mean years	12.0
Duration of epilepsy, mean years	9.7
Types of seizure, n (%)	
Generalized tonic–clonic	9 (24)
Complex partial	8 (22)
Tonic	4 (10)
Absence	4 (10)
Atonic	4 (10)
Complex partial with secondary generalization	3 (8)
Myoclonic	3 (8)
Drop	2 (5)
Gelastic	1 (3)
Reduction of monthly seizure frequency, %	
50-100%	54
25-50%	15
0-25%	31

The most common type of seizure was generalized tonic–clonic (24%), followed by complex partial (23%) (Table 1). Sixty-nine percent (69%) of the patients demonstrated a reduction in monthly seizure frequency. Fifty-four percent (54%) of the patients had a fifty percent or greater reduction in seizure frequency. In this subgroup, 2 patients experienced a 75% reduction, and 1 patient achieved seizure freedom. Fifteen percent (15%) of the patients had a 30-40% reduction in the frequency of their seizures, and 30% of the patients had no improvement of symptoms. Ninety-three percent (93%) of caregivers reported increased alertness and improved abilities to communicate in

their patients following VNS implantation, a finding that, though based on subjective observation, remains noteworthy.

Procedure-related complications were minimal: only one complication occurred, which was seen in a patient who experienced partial wound dehiscence; this was successfully treated with cleansing and debridement and intravenous antibiotics. Stimulation-related complications were not encountered.

Discussion

Medically refractory epilepsy remains one of the most complex medical scenarios for physicians to manage. VNS offers a non-pharmacological treatment for patients who are not candidates for resective surgery. Level I evidence has demonstrated that VNS is an effective therapeutic intervention for patients with partial onset seizures, and new open-label studies have been demonstrated to be efficacious in the treatment of most seizure types (20-21). However, the experience of VNS in pediatric populations remains limited. Recent studies have reported seizure-frequency reductions of greater than 60% in children, with minimal complications and side effects (22-23).

Our results showed that the most common indications for VNS among our population were the presence of generalized tonic-clonic (24%) and complex partial seizures (23%). A seizure-frequency reduction of 50% or more was achieved in 53% of the patients, with one patient being seizure free. This is concordant with most studies, which report 50% or greater reduction in seizure frequency in 40-50% of patients and infrequent complete seizure freedom (24-25). Acute-phase clinical studies investigating the efficacy of VNS have demonstrated a mean reduction of seizure episodes of 46% (19). While long-term efficacy was not evaluated, recent studies have demonstrated that, over time, VNS reduces seizure frequency and stabilizes epilepsy. Although changes and variations occur in seizure frequency, these are readily controlled with modifications to a given patient's existing antiepileptic drug regimen (26). There was a patient who became seizure-free following implantation of a VNS; while this is rare in VNS implantation, it is possible that stimulation and drug therapy worked synergistically to eliminate all seizure-related activity. Female gender predominance was noted among studied subjects (77%), which correlates with population studies showing that idiopathic epilepsy tends to affect females more than it does males (27). Although results were analyzed by age as a group, there were no variations in the findings among age subgroups. In anecdotal reports, VNS has been reported to improve cognitive function, particularly in patients with learning disabilities, improving their quality of life and their ability for social integration (28-30). These findings were observed in our study, with 93% of caregivers perceiving improvements in alertness and communication and perceiving as well an overall improvement in patient quality of life.

Complications after VNS placement include wound infection, vocal cord palsy, facial palsy, and, rarely, bradycardia, and asystole (31-35). The most common complication reported is wound infection, with an incidence of 3-6 % (21-23). In our study, one patient developed a wound infection that was successfully treated with intravenous antibiotics and cleansing and debridement. The most severe complication after VNS implantation is severe bradycardia which can lead to asystole. The reported incidence of this latter is 0.1% (24). This complication can be avoided by the restricted use of VNS of the left vagus nerve, as the right vagus nerve is involved in the innervation of the sinoatrial node (25).

In conclusion, VNS is an effective non-pharmacologic treatment for seizure control in medically refractory seizures, offering a significant chance of seizure control for patients. VNS should be strongly considered in patients with epilepsy that has demonstrated a refractory course to appropriate medication and who are not candidates for resective surgery. Although controlled trials have focused primarily on partial seizures, it appears from uncontrolled reports and post-marketing experience that VNS exhibits the same efficacy in a wide range of epilepsies and seizure types, including partial and generalized (36-38). It should be emphasized that VNS should be considered only after all other surgical options have been exhausted. VNS offers a valuable treatment alternative for patients with poor tolerance to antiepileptic medications, and it does not have the cognitive and systematic side effects that are often seen when such drugs are used (39).

Resumen

Objetivo: La estimulación del nervio vago es considerada como una vía alterna de tratamiento para pacientes con epilepsia refractaria que no son candidatos a cirugía. Este método consiste en estimular intermitentemente el nervio vago en su curso por el cuello. Se ha demostrado que este método es eficaz, seguro y tolerable. El objetivo de este estudio fue evaluar la experiencia clínica de la estimulación del nervio vago en la Universidad de Puerto Rico y examinar los datos demográficos, los tipos de convulsiones y su control en los pacientes tratados. Este estudio representa la primera recopilación acerca de la estimulación del nervio vago en pacientes que residen en el área del Caribe. Métodos: Se realizó un análisis retrospectivo de 13 pacientes tratados en el Hospital Pediátrico Universitario en San Juan, Puerto Rico. Los distintos tipos de ataques epilépticos fueron identificados y manejados. Resultados: La edad promedio de implantación fue de 12 años; 77% de los pacientes fueron del género femenino. El tipo de convulsión más comúnmente tratada fue tónico-clónica generalizada (24%), seguida de parcial compleja (23%). Sesenta y nueve por ciento tuvieron una reducción en la frecuencia mensual de ataques epilépticos. En un 93% se reportó una mejoría en el nivel de comunicación

y atención de los pacientes. Conclusión: La estimulación del nervio vago es una forma segura y efectiva para el tratamiento de la epilepsia refractaria y debe ser considerada como un método alterno para una población selecta de pacientes con epilepsia refractaria.

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