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ORIGINAL ARTICLE

Short-term Results of Vagus Nerve Stimulation in Pediatric Patients with Refractory Epilepsy

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Background: Vagus nerve stimulation (VNS), an alternative method to manage patients with medically intractable epilepsy, has shown favorable results in reducing seizure relapse and improvements in quality of life. In 1997, the U.S. Food and Drug Administration approved the use of this device as an adjunctive therapy for intractable seizure in adults and adolescents older than 12 years of age.
Methods: We present a preliminary study of pediatric patients, who suffered from medically intractable seizure and underwent VNS implantation after observation of the baseline seizure frequency. Classification of epileptic syndrome, seizure patterns, age of onset, seizure frequency reduction and adverse effects were recorded.
Results: Patients who underwent VNS implantation included four adolescents and four children. The follow-up duration ranged from 9–33 months. All the patients were responders after the beginning of the stimulation. Five of the eight patients responded to VNS with a seizure frequency reduction rate $>$ 50%, and four of the eight patients experienced a $\geq$ 90% seizure reduction. No significant adverse effects were noted in all patients during the observation period.

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Conclusion: The effective management of medically intractable seizure remains challenging to most clinical physicians. In addition to ketogenic diet and epilepsy surgery, VNS provides an alternative way to manage this issue. Our results suggest that VNS is well tolerated in pediatric patients, and is a favorable and safe method of treating intractable seizure in common clinical practice.

1. Introduction

Despite the number of different antiepileptic drugs (AED) currently available in the management of epilepsy with optimal drug administration, about one fourth of patients cannot achieve seizure-free status. Of course, some of these patients can benefit from epileptic surgery, which is generally considered as a safe and effective treatment for medically refractory epilepsies.[1] However, physiologic and anatomic limitations have been linked to surgical failure.[2] For those who are not candidates for epileptic focus resection or do not benefit from surgery, vagus nerve stimulation (VNS) provides an alternative and effective choice for seizure control.[3,4] In 1997, the U.S. Food and Drug Administration approved VNS to be indicated for use as an adjunctive therapy in reducing the frequency of medically intractable seizures in adults and adolescents older than 12 years of age.[5] The efficacy of VNS in the treatment of variable types of medically refractory epilepsy has been demonstrated.[6] Several studies have shown the efficacy of VNS in seizure reduction. The mean percentage of seizure reduction for adult patients with a >50% reduction rate has been estimated at approximately 50%—60% of all patients.[3,4] The responder rate has been reported as being in concordance with a decrease in overall seizure frequency. Although it was approved for use with adults and adolescents, VNS is also effective and safe in cases of childhood epilepsy.[7] In addition to its indication for focal epilepsy, VNS is suggested to be effective in epileptic syndrome.[8]

In this preliminary study, we examine the efficacy and outcome of using this method in pediatric patients, including adolescents and children younger than 12 years old with medically refractory epilepsy.

2. Methods

This study was retrospective, multi-centered and open-labeled. The patients with medically intractable seizures were defined as refractory epilepsy on two or more AEDs. All patients had been previously followed up for at least 2 years, and had undergone detailed clinical-history taking, several types of medication, brain magnetic resonance imaging and electroencephalogram. After observation of the baseline seizure frequency and seizure types, the VNS devices were implanted. The follow-up periods for all participants were at least 12 months.

The devices used for VNS were purchased from Cyberonics (Houston, TX, USA). The VNS generators were implanted in subcutaneous pockets on the pectoralis fascia through a 1-2 cm incision in the left-side anterior axillary fold. Each stimulation lasted for 30 seconds, at 30 Hz frequency and 500 usec pulse width, with 5 minutes between stimulations and 0.25 mA output current initially for each patient. Adjusted output current was set at maximum of 1.5 mA in accordance with the manufacturer's guidelines.

Eight pediatric patients (seven males and one female) with medically refractory epilepsies, who had undergone VNS device implantation between Feb 2008 and Mar 2010, were enrolled in the study. Patients were aged from 4 years to 17 years of age, and durations of seizure disorder ranged from 2—14 years. Specific epileptic syndromes were diagnosed by clinical physicians if possible. Etiologies included two cryptogenic etiologies, three encephalitis, and three epileptic syndromes (one severe myoclonic epilepsy of infancy, one West syndrome, and one Lennox-Gastaut syndrome). None of the patients had an underlying metabolic disorder. Before implantation of VNS, all patients had received three to four antiepileptic drugs at therapeutic levels. None of the patients had ever been put on a ketogenic diet or received epilepsy surgery before implantation (Table 1). Based on the effectiveness of VNS, patients were classified into seizure reduction levels, including > 90% seizure reduction, > 50% seizure reduction, and < 50% seizure reduction. Patients with seizure reduction of more than 50% were considered as a VNS responder.

All patients had a psychologic evaluation before VNS initiation, and all of these children were cognitively impaired. They were classified as severe mental retardation, moderate mental retardation, or mild mental retardation as assessed with the Bayley Scales of Infant Development or the Wechsler's Pre-school and Primary Scale of Intelligence.

3. Results

Prior to VNS, patients had a seizure frequency ranging from one to two episodes per month to 10 episodes per week. After implantation of VNS, four of the eight patients had a > 90% seizure frequency reduction, one (1/8) had a 50% to 90% seizure reduction, and three (3/8) had a < 50% seizure reduction; no child became seizure-free. In cryptogenic epilepsies and epileptic syndromes, three patients showed a > 90% seizure frequency reduction and two had a < 50% seizure frequency reduction. In cases of encephalitis-related seizure, three patients showed a mild response, including one patient with a > 90% seizure frequency reduction, one with a 50%—90% seizure frequency reduction

Table 1 Clinical manifestations of patients with refractory epilepsy.

Patient no.	Age (y)	Sex	Seizure duration (y)	Seizure type	EEG finding	Etiology/Epileptic syndrome	MR
1	17	M	14	CPS and 2G	Background slowing	Encephalitis	Borderline
2	17	M	7	CPS and 2G	Focal slowing in the left temporal area	Encephalitis	Borderline
3	7	M	7	Myoclonic, and 2G	Synchronous spikes in the bilateral frontotemporal areas	SMEI	Moderate
4	17	F	10	CPS and 2G	Multifocal spikes with continuous slowing in the right hemisphere.	Cryptogenic	Mild
5	15	M	7	CPS and 2G	Independent spikes in the right and left frontal areas with rapid generalization multifocal spikes and waves over bilateral frontal regions, and generalization	Cryptogenic	Below average
6	4	M	4	Myoclonic, tonic	Hypsarrhythmia	West syndrome	Severe
7	7	M	2	SPS and CPS	Independent spikes and sharp waves with focal slowing in the left temporal and right frontal areas	Encephalitis	Normal
8	7	M	6	CPS and 2G, tonic, clonic	Generalized slow spike-and-wave complexes	LGS	Severe

2G = secondary generation; AED = antiepileptic drug; CPS = complex partial seizure; EEG = electroencephalogram; F = female; LGS = Lennox-Gastaut syndrome; M = male; MR = mental retardation; SMEI = severe myoclonic epilepsy in infancy.

and one with a $< 50\%$ seizure reduction. By age, patients included four adolescents (12—18 years old) and four children (younger than 12 years of age). Three of the adolescents had a $< 50\%$ seizure frequency reduction, and only one had a $> 90\%$ seizure frequency reduction. In patients younger than 12 years, three showed a $> 90\%$ reduction in seizure frequency and one of the patients showed a 50%—90% seizure frequency reduction (Table 2).

Half of the patients remained on the same medications during follow-up, and only two patients were able to have their therapeutic regimens decreased. For the remaining two patients, one AED was tapered but later replaced by a new medication. With regard to adverse effects, only two patients complained of hoarseness, and there were no other significant adverse effects for the remainder of the patients.

All patients had a neuropsychological evaluation before VNS initiation, and all of these patients were affected with regards to cognition status. They were classified as severe mental retardation in two patients, moderate mental retardation in one, and mild mental retardation in one as assessed using the Wechsler's Pre-school and Primary Scale of Intelligence. After implantation of VNS, all but two patients showed improvement with respect to emotion control, verbal ability and school performance.

4. Discussion

In longitudinal follow-up studies, more than 60% of adult and adolescent patients were responders to VNS treatment at the 5-year follow-up, and 5%—10% were seizure-free.[3,4] VNS therapy is also effective and safe in pediatric patients with refractory seizures. It was reported that VNS achieved for children with refractory epilepsy reduction in seizure frequency, severity and improvement in their quality of life.[9] Seizure severity and frequency, as well as quality of life, improved with VNS therapy without significant adverse events in patients who were younger than 18 years of age.[10] The overall seizure reduction rate varies between 45% and 70% by follow-up ranging from 6 to 12 months.[7,11,12] In comparison, we report half of all patients had a $> 90\%$ seizure reduction, one had a $> 50\%$ seizure reduction and three had a $< 50\%$ seizure reduction, and no child became seizure-free.

Despite VNS being approved for focal epilepsies, it has been suggested that VNS is useful in cases involving most epileptic syndromes.[8] The efficacy of VNS in treating focal epilepsies and various types of generalized epilepsies, including idiopathic generalized epilepsy and Lennox-Gastaut syndrome, have been adequately demonstrated.[3] Similar to previous studies, we observed the efficacy of VNS therapy was effective in cases of cryptogenic epilepsies or epileptic syndromes and those with organic lesions.[11] We propose seizure reduction in our patients was related to the etiologies despite the limited number of patients in our study.

In addition to reducing seizure frequency, VNS was associated with improvements in quality of life, including verbal ability and school performance. This effect may not relate to the antiepileptic effect.[13] The nonpharmacologic aspect of VNS therapy makes it particularly attractive for use, due to its minimal side effects and cognition

Table 2 Seizure reduction, adverse effects, and quality of life improvement after VNS implantation.

Pt No	Seizure frequency		Follow-up duration (m)	Medication		Adverse effect
	Baseline	Reduction (%)		Before VNS	After VNS	
1	1—2/mo	< 50%	33	CBZ-XR,CZP TPM	CBZ-XR,CZP TPM	No
2	6—8/mo	> 90%	29	VPA, LMT, LEV	CZP, LMT, LEV	No
3	1—3/mo	> 90%	24	CZP, TPM, LMT	CZP, TPM, LMT	Hoarseness
4	5—10/mo	< 50%	24	CBZ-XR, TPM,CLB	CBZ-XR, TPM,CLB	Hoarseness
5	1—2/wk	< 50%	20	VPA,CBZ-XR, TPM,	CBZ-XR, TPM,	No
6	10/mo	> 90%	13	VGB,VPA, CZP, TPM	VGB,VPA, CZP, TPM	No
7	3—4/wk	> 50%	9	VPA, LTG, PHT	VPA, CZP, PHT	No
8	20—30/d	> 90%	9	VPA, CZP, TPM	VPA, CZP	No

CBZ-XR = oxcarbazepine; CLB = clobazam; CZP = clonazepam; LEV = levetiracetam; LMT = lamotrigine; PHT = phenobarbital; TPM = Topamax; VGB = vigabatrin; VNS = vagus nerve stimulation; VPA = valproate.

impairment with AEDs in pediatric patients.[10] A review of pediatric patients from VNS outcome showed alertness was improved in more than 70% of children studied.[14]

Not only patients with refractory epilepsy can benefit from VNS, but also patients with austic spectrum have been shown to demonstrate improved alertness.[15] Most of the adverse effects were mild and transient with improvement of seizure frequency, and could be controlled by adjusting the current output.[7] As previous study, common adverse effects included cough, hoarseness, mild dysphasia, throat pain, chest discomfort and dyspnea.[16] A large series study reported adverse effects occurred in 68% of pediatric patients, but most were mild or transient.[11] A 5-year longitudinal follow-up study suggested only intolerable symptoms, implantation complication or device failure would be considered as adverse effects, which resulted in only 13.3% of patients experiencing subsequent adverse effect.[3] By comparison, only hoarseness occurred in two (2/8) of our patients, and no device failure or surgical complication occurred in the remaining patients. We supposed most of our pediatric patients were cognition-impaired and consequently unable to actively describe their discomforts.

In conclusion, our study indicates that VNS is effective and safe in pediatric refractory epilepsy, especially with regard to epileptic syndrome and in children. It also possesses several advantages including minimal adverse effects and reducing AED burden. Based on these observations, we suggest that VNS should be considered as an alternative therapy when a patient is determined to be medically refractory, especially for children younger than 12 years of age.

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