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Efficacy of Vagus Nerve Stimulation in Brain-Tumor Associated Intractable Epilepsy and the Importance of Tumor Stability

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Abstract

Object—Vagus nerve stimulation (VNS) is a viable option for patients with medically intractable epilepsy. However, there are no studies examining its effect on individuals with brain tumor associated intractable epilepsy. This study aims to evaluate the efficacy of VNS in patients with brain tumor associated medically intractable epilepsy.

Methods—Epilepsy surgery databases at two separate epilepsy centers were reviewed to identify patients in whom a VNS was placed for tumor-related intractable epilepsy between January 1999 and December 2011. Pre-operative and post-operative seizure frequency and type as well as antiepileptic drug (AED) regimens and degree of tumor progression were evaluated. Statistical analysis was performed using odds ratio and T tests to examine efficacy.

Results—Sixteen patients were included in the study. Eight patients (50%) had an improved outcome (Engel I, II, or III) with an average follow-up of 39.6 months. The mean reduction in seizure frequency was 41.7% ($p = .002$). There was no significant change in AED regimens. Seizure frequency decreased by 10.9% in patients with progressing tumors and 65.6% in patients with stable tumors ($p = .008$).

Conclusion—VNS therapy in individuals with brain tumor associated medically intractable epilepsy was shown to be comparably effective in regards to seizure reduction and response rates to the general population of VNS therapy patients. Outcomes were better in patients with stable as opposed to progressing tumors. Our findings support the recommendation of VNS therapy in

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patients with brain tumor associated intractable epilepsy, especially in cases where imminent tumor progression is not expected. VNS may not be indicated in more malignant tumors.

Keywords

Brain Tumors; Medically Intractable Epilepsy; Seizures; Vagus Nerve Stimulation

INTRODUCTION

Medication refractory seizures occur in 20–30% of epilepsy patients.^{9,10} For patients who are not candidates for brain surgery, VNS (NeuroCyberonic Prosthesis System; Cyberonics Inc., Houston, TX, USA) therapy is a viable therapeutic option.^{7,8,17,26,36} VNS was FDA approved in 1997 for control of partial onset seizures in patients older than 12 years of age who are refractory to AEDs. The NeuroCyberonic Prosthesis (NCP) System delivers intermittent stimulation to afferent fibers of the vagus nerve under adjustable parameters, including: output current, frequency, pulse width, and stimulation on/off time. However, the mechanism by which this stimulation exerts its antiseizure effects is unknown.^{35,44,53}

One population of patients in whom the VNS has not been specifically studied is patients in whom partial seizures are associated with a brain tumor. Approximately 30–50% of brain tumor patients will have a seizure at some point and approximately 30% of these will become intractable.^{39,54} Both benign and malignant tumors can cause seizures, which can be exacerbated by tumor growth as well as neo- adjuvant therapy.⁴³ Tumor resection is often indicated in this situation, and is capable of significantly reducing seizures in 30–60% of cases.^{6,11,12,25} However, there exists a subset of tumor patients in whom removal of the tumor does not control seizures, either due to incomplete tumor resection or establishment of an independent seizure focus on the tumor margin.^{15,23,28,54} While some of these patients may be candidates for epilepsy surgery, others are not suitable due to the proximate location of eloquent cortex, seizure multifocality, limited life expectancy, or patient preference.^{15,22} In this group, frequent seizures can impair quality of life and may even interfere with adjuvant therapy, resulting in decreased life expectancy.^{13,14,18,23}

There is currently no literature on the efficacy of VNS for tumor-associated epilepsy. The aim of this study is to evaluate the efficacy of VNS therapy for seizure control in patients with brain tumor induced intractable epilepsy.

METHODS

The authors retrospectively analyzed epilepsy surgery databases at Weill-Cornell Medical College and New York University Langone Medical Center. Patients in whom a VNS was placed for tumor related epilepsy between January 1999 and December 2011 were identified. Institutional review board approval was obtained for this study at both institutions.

There was no single set of guidelines used to choose patients suitable for VNS implantation. All but one patient had undergone prior surgery for their brain tumor, each had histologically confirmed tumors with intractable focal epilepsy arising from the same lobe as

the tumor, and each had failed trials of multiple AEDs. All patients were evaluated by an epileptologist with patient interview, scalp electroencephalography (EEG) and patient/eyewitness accounts.

The NCP system was implanted according to methodology that has been previously described.^{4,32,35,41} Stimulation was initiated when the patient had fully recovered, usually 1 ± 4 weeks after surgery. The stimulation settings were modified at the discretion of the treating epileptologist during follow-up visits. The patients were also provided a magnet allowing additional stimulation to be carried out by the patient or caretaker in case of an aura or seizure.

Patient demographics including: sex, age, age at epilepsy onset, age of insertion of VNS, location of epileptic focus, surgical complications, seizure frequency before and after surgery, AED use before and after surgery, tumor histology, tumor progression and duration of follow-up were retrospectively obtained from patient charts and telephone calls. The change in seizure frequency after placement of VNS was based on patient diaries and epilepsy clinic chart review. Tumor progression was evaluated via follow-up MRI reports and neurosurgery clinic chart review.

Outcome of VNS was also assessed on the basis of the Engel classification – class I: free of disabling seizures; class II: rare disabling seizures (almost seizure-free); class III: worthwhile improvement; and class IV: no worthwhile improvement.²⁰ Since VNS therapy is not a “curative” therapy, patients were divided into two groups, either: “improved” (Engel I, II, and III) or “not improved” (Engel IV) for the purpose of statistical analysis. Statistically significant response was determined using paired T-tests and difference in responses between patients with stable or progressing brain tumors was determined using odds ratio and two sample T-tests.

RESULTS

Demographics

Sixteen patients were included in the study. Demographic characteristics of these patients are presented in Table 1. The average age was 41.7 years and 56.3% were male. All patients were referred for VNS once their tumor care was stable, in other words, any surgery and adjuvant therapy was completed. Four patients had undergone epilepsy surgery before VNS implant. Two patients had a previous partial lobectomy/subdural electrode array implantation, one had a partial corpus callostomy, one had a left temporal lobectomy and hippocampectomy, and one had a frontal lobe resection, all of which were not successful at curing their epilepsy. VNS was turned off in seven patients (38.9%) due to lack of efficacy. Follow-up imaging of tumors was performed by turning the VNS “off” before the MRI and then back “on” after the MRI. There were three patients who had stimulator replacements due to end of service, and one of these patients had two replacements. Battery life of all devices in this study averaged 92.3 months.

Efficacy

Baseline, postoperative, and final follow up seizure frequencies are presented in Table 2. After a mean (SD) follow-up of 43.3 (34.7) months, eight patients (50%) improved with > 50% seizure reduction after VNS initiation. Evaluation of overall change in seizure frequency via paired T-tests using pre-implant and final follow-up data showed a significant decrease of 41.7% ($p = .002$). Of the 8 patients with > 50% seizure reduction, 3 (18.8%) were Engel class II and 5 (31.3%) were class III. None of these patients were free of seizures (Engel class I). Eight patients (50%) were Engel class IV. Four patients had resective surgeries for recurrent/residual tumor after VNS implant but without VNS removal. The surgery improved one patient's seizure frequency (from 16–19 to 1–3 seizures/month) after which the VNS was disabled. Another patient who had been responsive to VNS (1–3 seizures/month) experienced an increase in seizure frequency after resective surgery. When patients who had repeat surgery for progressive tumor without VNS removal were eliminated from the series, the paired T-test comparing pre-implant with last follow-up seizure frequency yielded a statistically significant decrease of 55.6% ($p = .001$).

Concomitant Treatment

VNS therapy was not associated with changes in AED regimens. Table 2 shows the difference in AEDs before and after VNS implantation. Mean number of AEDs did not change (2.50 to 2.56, $p = .598$). Six patients had been changed to completely different AED regimens. There was no significant change in number of AEDs used after VNS therapy.

Complications

There were no intraoperative complications. Adverse events related to VNS treatment (presented during one or more visits) were: stimulus-related hoarseness in three patients (18.8%), coughing in two patients (12.5%), and jaw pain (6.3%), difficulty swallowing (6.3%), nausea (6.3%), and emesis (6.3%) each in one patient. All complications were transient and generally responded to stimulation parameter adjustment. One patient had reoperation to move the generator to a different location due to irritation/cosmetic reasons. No explants for infection were performed and adverse events did not lead to discontinuation of VNS therapy for any patients.

Discontinuation

Seven patients discontinued VNS therapy after an average of 2.8 years. Discontinuation was most common at time of subsequent tumor resection for magnetic resonance imaging/operation and was mainly removed because of inefficacy. One patient discontinued due to resolution of seizures after recurrent tumor resection.

Stimulation Duration and Seizure Outcome

Patients under VNS therapy for a longer duration did not exhibit a higher percent reduction in seizure frequency. In fact, patients with VNS treatment for 41.5 months or longer (median-split) ($n = 8$) had only a 27.3% decrease in seizure frequency, while patients with shorter treatment ($n = 8$) periods had a 56.0% decrease.

Pathology & Progression

There were 7 patients with tumors that significantly progressed, as noted in MRI and neurosurgery clinic reports, during VNS therapy and 9 patients with stable tumors. The mean reduction in seizure frequency was 10.9% in patients in whom tumor progressed (including 2 anaplastic tumors) and 65.6% in patients with a stable tumor ($p = .008$). The odds ratio for patients with progressive tumors to have a clinical response to VNS therapy as compared to patients with stable tumors was 21 ($p = .024$). Table 3 shows Engel score by pathology and tumor progression. While there was no significant result based on pathology of tumor, there was a statistically significant ($p = .01$) difference in average Engel score between patients with progressing and non-progressing tumor. VNS therapy was not associated with significant changes in AED regimens in either of these groups. Patients with a progressed tumor had an increase in average AED usage from 2.43 to 2.57 while patients with stable tumors had an increase in AED usage from 2.57 to 2.71, neither of which was significant (Table 4).

DISCUSSION

VNS has been used as an alternative treatment in medically intractable epilepsy for more than 15 years. Clinical efficacy and safety of VNS has been demonstrated in several controlled studies.^{1,2,5,8,16,26,27,30–32,34,42,48} These studies show moderate efficacy via a reduction of seizure frequency of at least 50% in around one third of patients. Another third of these patients had no significant response to VNS treatment. Our study, the first in patients with intractable seizures associated with brain tumors, shows similar efficacy in seizure reduction as has been shown with non-tumor etiologies, particularly for patients whose tumors are stable during VNS use. Previous studies have demonstrated an increase in VNS efficacy over time.^{3,8,36,51} Our data did not yield the same results as these earlier reports, potentially a result of tumor growth offsetting the increasing effect of VNS.

Nevertheless, the lack of prior publications on the subject and the small numbers in this series indicate that VNS is likely an underutilized therapy in brain tumor patients afflicted with frequent seizures. There may be multiple reasons for this underutilization. First, neuro-oncologists managing tumor-related epilepsy may be poorly informed of VNS therapy as a treatment option. Second, providers may feel that obtaining periodic MRI scans to monitor for tumor progression may not be safe. However, as long as the safety advice provided by the company is followed, MRI scans do not cause undue risk. For example, if the output settings are set to 0mA before the MRI scan and there is no lead fracture the transmit body coil is avoided, the procedure is generally safe.³⁸ Alternatively, providers may feel that tumor resection is the only way to control seizures and the inevitability of tumor progression makes VNS therapy futile. Finally, providers may want to save patients with potentially limited life expectancy an additional surgical procedure. These latter rationales are reasonable for higher grade tumors, where tumor progression is likely and life expectancy limited, but less applicable to patients with low grade tumors.

Our data indicate that patients with tumors who are not at immediate risk of tumor progression may obtain substantial benefit from VNS therapy for their seizures, which may result in an improvement in quality of life. Because patients with low grade tumors often

survive for many years,^{37,40,45} quality of life is of high importance.^{19,29} Without control of tumor associated epilepsy, there is a significant detriment to quality of life through cognitive deficits and other morbidities.^{47,50,52}

Clearly, patients with tumor-related epilepsy will obtain the greatest benefit from maximal cytoreductive surgery.^{21,23} However, tumors that encroach on functional cortex may not be removable without significant neurological deficits, which can then strongly influence survival. Likewise, tumors may be inadequately removed at the first operation. Thus, VNS therapy should not be considered a first line therapy, but instead reserved for patients who cannot safely undergo further tumor removal. Similarly, patients with focal intractable epilepsy and reasonable life-expectancy may benefit from subdural implantation of electrodes to identify a seizure focus that may lead to a cure once removed. Indeed, certain tumors that cause intractable epilepsy are best treated with an “epilepsy operation”, with additional removal of adjacent epileptogenic cortex, in addition to tumor resection to maximize the therapeutic benefit of surgery.²⁴ However, once resective surgical options have been pursued and seizures remain, VNS should be considered as additional therapy.

The primary caveat to the applicability of VNS is lack of imminent tumor progression. Hence, patients with aggressive tumors may have less of a response as tumor progression will increase epileptogenicity and decrease VNS efficacy. These same patients may have more limited life expectancy and also may want to avoid additional surgery. However, this aspect of the study is limited. Because the criteria for stratification of patients as having stable or progressing tumors is based on physician notes, it is susceptible to bias. In addition, individuals without response to VNS may be subject to more MRIs and clinic visits, making this group more likely to have a progressing tumor identified. This would also lead to bias in the study. More data is needed on larger groups of patients with more stringent stratification criteria to determine if and what role VNS has in this patient population.

The need for frequent MRI scans to follow tumors for progression may also make clinicians less inclined to place a VNS. However, as stated above the VNS is not a contraindication to MRI scan as long as the company safety guidelines are followed.^{46,49} In fact, based on the position of the VNS, MRI scanning may be safe with the VNS turned “on”.³³

Unlike in forms of non-lesional epilepsy, we did not find that VNS led to a decrease in the number of AEDs despite a decrease in seizure frequency. This may be due to the small sample size of this study or the patients with progressive tumor or unwillingness of clinicians to lower medications in patients with lesional epilepsy due to fear of tumor progression and subsequent exacerbation of epilepsy.

CONCLUSIONS

In this small retrospective study, we show that the VNS may lead to substantial improvement in seizure frequency in patients with medically intractable tumor-related epilepsy. VNS appears to be particularly effective in patients in whom tumors do not progress. VNS therapy should be considered for patients with stable tumors and medically

intractable epilepsy once all resective surgical options have been exhausted. VNS may not be indicated in more malignant tumors.

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Table 1**Patient Characteristics**

	Total n = 16
Age, mean (SD), y	41.7 (13.8)
Age < 17 y, No. (%)	2 (12.5)
Age at seizure onset, mean (SD), y	21.1 (17.1)
Age at first VNS implant, mean (SD), y	34 (13.3)
Male Sex, No. (%)	9 (56.3)
Duration of epilepsy, median (IQR), y	9 (56.3)
Left side of seizure onset, No. (%)	7 (43.8)
Pre-VNS Antiepileptic drugs used, mean (SD)	2.5 (0.63)
Types of Seizure, No. (%)	
Simple Partial	3 (18.8)
Complex Partial	12 (75.0)
Secondary Generalized	2 (12.5)
Generalized Tonic Clonic	2 (12.5)
Atonic Head Drop	1 (6.3)
Cognitively impaired (%)	6 (37.5)
Tumor Pathology, No. (%)	
Astrocytoma	8 (50.0)
Anaplastic astrocytoma	1 (6.3)
Oligodendroglioma	4 (25.0)
Anaplastic oligodendroglioma	1 (6.3)
Ganglioneurocytoma	2 (12.5)
Meningioma	1 (6.3)
Brain stem glioma	1 (6.3)

Table 2

Seizure Frequency Pre- and Post- VNS Implantation

Participants	Seizures per mo. at Follow Up				Events, mo.			Engel Class
	Baseline	First VNS fu	Last VNS fu	Baseline AED	Final AED	Surgery	Last fu	
1	1-3	16-19	16-19	2	1	44*	41	IV
2	16-19	16-19	1-3	2	2	-	105	III
3	1-3	4-7	1-3	2	3	35**	42	IV
4	>50	>50	12	3	4	-	49	III
5	4-8	4-8	1	3	3	-	16	II
6	30	30	1	4	4	-	11	II
7	12	12	12	3	3	-	16	IV
8	30-60	4-12	4-12	3	4	-	4	III
9	8	8	16	2	2	64	64	IV
10	12-16	12-16	12-16	2	2	-	20	IV
11	12-16	0	0	2	1	-	1	II
12	12	1	5-6	2	3	-	118	III
13	>50	>50	>50	3	2	-	42	IV
14	30	30	30	3	4	12	48	IV
15	8-20	4	2	2	1	-	10	III
16	30	30	30	2	2	-	46	IV
Mean (SD)					2.5 (0.63)	2.6 (1.09)		

* Seizures resolved after resective surgery

** Case complicated by increase in seizure frequency after surgery

fu = follow-up, AED = antiepileptic drug

Table 3

Outcome By Type & Progression of Tumor

Type of Tumor	Engel Class				Total, n (%)	Mean Change In Seizure Frequency (%)
	Group A		Group B			
	I	II	III	IV		
Astrocytoma	0	1	3	4	8 (50.0)	-39.8
Oligodendroglioma	0	1	1	2	4 (25.0)	-44.7
Ganglioneurocytoma	0	0	1	1	2 (12.5)	-42.9
Meningioma	0	0	0	1	1 (6.3)	0
Brain stem glioma	0	1	0	0	1 (6.3)	-83.3
Total	0	3	5	9	16 (100)	-41.7
Progression of Tumor						
Stable	0	3	4	2	9 (56.3)	-65.6
Progressed	0	0	1	6	7 (43.8)	10.9

Table 4

Differences in Stable/Progressing Tumors

Type of Tumor	Stable	Progressing
Mean seizure change (%)	−65.6%	−10.9%
Mean Engel Score	2.89	3.86
Mean AED change	4.76%	4.76%