

Vagal Nerve Stimulation in Refractory Epilepsy

The First 100 Patients Receiving Vagal Nerve Stimulation at a Pediatric Epilepsy Center

Jerome V. Murphy, MD; Richard Torkelson, MD; Irene Dowler, RN; Stephen Simon, PhD; Sara Hudson, LPN, CCRC

Objective: To determine the outcome of intermittent left vagal nerve stimulation on the first 100 consecutive patients treated at our pediatric epilepsy center.

Methods: Patients were identified by means of operating room records. Data collected described the patient's epilepsy, previous and subsequent therapies, adverse events, nonepileptic changes, and outcomes.

Results: Average age was 10.4 years; years of epilepsy, 8.5; total number of antiepileptic therapies, 8.4; and median monthly seizure frequency, 120. Data on seizure frequency at follow-up were available for 96 of the 100 patients. Forty-five percent of patients achieved greater than 50% reduction; and 18% had had no seizures for the last 6 months. Response was similar in patients with more than 7 years of refractory epilepsy as compared

with patients with a shorter history. Magnet-generated, on-demand current reduced seizure intensity in almost half of the patients with available data. Generator infections occurred in 3 patients. Twenty-four patients had their generators removed. Subsequently, 2 of these patients died.

Conclusions: Seizure reduction was the same in patients younger than 12 years and 12 years or older and in patients with shorter and longer histories of refractory epilepsy. Adverse effects were few in this population, particularly in those younger than 12 years. Vagal nerve stimulation appears to be a relatively safe and potentially effective treatment for children with severely intractable epilepsy.

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From the Neurology Section (Drs Murphy and Torkelson and Ms Dowler) and Research and Grants Administration (Dr Simon and Ms Hudson), Children's Mercy Hospital, Kansas City, Mo. Dr Murphy has received honoraria from Cyberonics, Inc, Houston, Tex, the manufacturer of the device described in this article, has participated in research funded by the same company, and has been on one of their medical advisory boards. Dr Torkelson has received an honorarium from Cyberonics, Inc.

IN JULY 1997, the Food and Drug Administration approved the use of intermittent stimulation of the left vagal nerve (VNS) "as adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures which are refractory to antiepileptic medications."¹ Since then, 2 multicenter reports have described experience with VNS in 60 and 125 children with medically refractory epilepsy.^{2,3}

Other articles have reported benefit of VNS in hypothalamic hamartomas,⁴ tuberous sclerosis,⁵ generalized seizures,⁶ and Lennox-Gastaut syndrome.⁷⁻¹⁰ The only publication describing limited benefit is an abstract on its use in 10 children 3 years old or older with infantile spasms.¹¹ A recent abstract¹² showed improved response to VNS if patients underwent implantation when their refractory epilepsy had lasted less than 6 years, as compared with the 6 years or more group.

The only previous report of results from a single center, to our knowledge, described 64 patients treated with VNS.⁷ We

recently reviewed our experience with the first 100 patients to undergo implantation at our pediatric hospital. The purposes were to compare the age-related changes in seizures, to report complications, to determine outcome in patients in whom this intervention failed, and to learn any nonepileptic benefits from VNS.

METHODS

A list of all patients who underwent implantation at this hospital was obtained from operating room records. Expedited approval was given by the University of Missouri Pediatric Institutional Review Board, Kansas City, to review the charts and to contact treating physicians and families of patients, when necessary, to learn the outcome of this therapy.

The generator was implanted by either a neurosurgeon or any of several otolaryngologists. Most patients had the generator activated before discharge on the day of surgery. At this time the generator was turned up to the highest tolerated current. At subsequent visits the current was increased to tolerance or to the maximum available current, 3.50 mA. The highest tolerable current was realized by induced coughing, or complaints of discomfort

at higher settings. Duty cycles were either 30 seconds on and 5 minutes off (used before 1997) or 30 seconds on and 3 minutes off. After Food and Drug Administration approval, the off time was reduced from 5 to 3 minutes on the basis of observations in rats.¹³ Pulse width was generally 500 microseconds, and frequency was 30 Hz. Rarely, intolerance of even the lowest currents necessitated reduction of these variables. The magnet-generated current was used as an on-demand therapy to terminate a seizure. This current was set slightly higher than the routine intermittent current and lasted 60 seconds. A more rapid-duty cycle (7 seconds on, 12 seconds off) was used for at least 3 months in patients not benefiting from VNS after 1 year, before the generator was removed.

The data collected included age at onset of epilepsy, cause of seizures, seizure types, presence or absence of mental retardation, years of epilepsy, age of patient when they underwent implantation, previous epilepsy surgeries, average monthly frequency of seizures for the 3 months before implantation and monthly frequency preceding the last evaluation, total number of antiepileptic drugs (AEDs) used before VNS, number of AEDs being taken at the time of the implant, number of AEDs being taken at the latest follow-up, surgical complications, adverse effects of VNS, changes in the patients' general well-being, present status of VNS, and outcome of patients in whom this intervention failed. Seizure frequency was recorded at each follow-up visit from seizure calendars or from family recall, if the former was not available. Not all data were available for every patient.

Where appropriate, confidence intervals for the difference in proportions were used to compare specific groups of patients, by means of StatXact software, version 3 (Cytel Software Corporation, Cambridge, Mass).

RESULTS

POPULATION

A profile of the 100 patients is given in **Table 1**. The first 28 patients were part of one of the preapproval trials in this country, and, as such, their implantation and initial follow-up were funded by the manufacturer of the device (Cyberonics, Inc, Houston, Tex) when insurance was not available. Some of these patients have been included in previous reports.^{2,4-6,14,22} The first patient underwent implantation in November 1992 and the 100th in July 2000. Patient follow-up was 1 to 9 years (mean, 2.7 years). Twelve patients had only a 1-year follow-up. Another 12 patients were older than 18 years at implantation; 4 of these had been followed up at this hospital since their youth, and 8 were adults referred specifically for VNS. One of our patients was receiving no antiepileptic therapy, as her family claimed nothing helped. In 13 patients, previous epilepsy surgery, either corpuscallosotomies (8 patients) or resections (5 patients), had failed. Twenty-one had normal intelligence as determined by developmental skills and scholastic performance.

OUTCOME

Follow-up data on seizure frequency was available in 96 patients. Of the remaining 4, 1 family refused to discuss their child's status, 2 physicians never forwarded data on seizure frequency for patients living elsewhere, and 1 family could not be located. **Table 2** gives the percentage reduction in seizures, comparing the frequency during

Table 1. Profile of the First 100 Patients to Receive Implants

	Range	Mean	Median
Age at implant, y	2-40	10.4	11.5
Years of epilepsy	2-32	8.5	8.5
Total No. of previous antiepileptic therapies	3-29	8.4	7
No. of antiepileptic therapies at implant	0-5	2.2	2
Monthly seizure frequency	1-4500	556.3	120
No. with previous epilepsy surgery	13		
No. with normal development/intellect	21		

Table 2. Reduction in Seizure Frequency by Age Groups

Age, y	No. of Patients	Reduction in Frequency, No. (%) of Patients		
		100%	>90%	>50%
All	96	17 (18)	25 (26)	43 (45)
12-18	34	7 (21)	10 (29)	16 (47)
6-11	37	7 (19)	11 (30)	17 (46)
≤5	13	3 (23)	3 (23)	6 (46)

Table 3. Response to Vagal Nerve Stimulation by Age of Patients

Response	No. (%)		Confidence Interval, %
	Younger (<12 y) (n = 50)	Older (12-18 y) (n = 34)	
No seizures	10 (20)	7 (21)	-17 to 20
>90% Reduction	14 (28)	10 (29)	-18 to 22
>50% Reduction	23 (46)	16 (47)	-21 to 22

the month before the most recent visit with the monthly average for the 3 months before implantation, by age group for these 96 patients. Eighteen percent of patients had no seizure during the 6 months preceding the last evaluation. The percentages of patients with no seizures, more than 90% reduction, and more than 50% reduction were similar in the patients 6 to 11 years old at implantation and the patients 12 to 18 years old.

Table 3 compares the benefit in seizure control between patients 12 to 18 years old and those younger than 12 years. The confidence intervals for the differences in proportion show no difference in response to VNS by these age groups.

In **Table 4**, a similar analysis was performed on the change in patients with refractory epilepsy present for 7 years or less at the time of implantation, as opposed to those who had had epilepsy for more than 7 years when implanted. The numbers are similar, with the responder rate (>50% seizure reduction) being higher, but not statistically significantly so, for patients with more than 7 years of refractory epilepsy.

Four of the 7 patients with previous corpuscallosotomies who were available for follow-up had greater

Table 4. Response to Vagal Nerve Stimulation by Years of Epilepsy

Response	No. (%)		Confidence Interval, %
	Refractory ≤7 y (n = 46)	Refractory >7 y (n = 50)	
No seizures	9 (20)	8 (16)	-20 to 13
>90% Reduction	14 (30)	10 (20)	-28 to 7
>50% Reduction	20 (43)	23 (46)	-18 to 23

than 50% reduction in seizure frequency. Four of the 5 patients in whom resective seizure surgery had failed were also responders.

Five patients had increased seizure frequency (increases of 11% to 150%). The patient with a 150% increase in the number of seizures was nevertheless remarkably improved in well-being, as the seizures were very brief and not associated with injury or postictal lethargy. The other 4 had no improvement in well-being. The causes of epilepsy and seizure types in this group were variable.

We also compared changes in seizure frequency between patients with normal development and those with mental retardation; between patients with 100 or more seizures per month and those with fewer than 100 per month at implantation; and between patients with previous seizure surgery and those without such surgery. In these 3 comparisons, there were no statistically significant differences. The average number of antiepileptic therapies at the time of implantation of the VNS, including the ketogenic diet as a therapy, was 2.23. At the time of this review the number was 2.00.

As with AEDs, there were patients counted among the VNS failures who responded initially, for up to 3 months, and then had recurrences at the former frequency and severity. Any patient who achieved significant improvement in seizure frequency for the first 6 months never experienced deterioration of their condition except at the end of the life of the generator.

The general well-being of the patients was rated by the family at the last available evaluation as much better, better, no change, worse, or much worse relative to pretreatment. This information was available for 68 patients. Two were worse, 24 were the same, 10 were better, and 32 were much better. This did not correlate with seizure control.

Information on using the magnet-generated current to immediately control a seizure was available for 70 patients. One family claimed that use of the magnet made seizures worse, 34 claimed they could abort the seizure and reduce or eliminate postictal lethargy, and 35 noted no benefit from magnet use.

ADVERSE EVENTS

Three patients developed abscesses around the generator requiring device removal, antibiotic therapy, and reimplantation. One patient complained of the voice changes

with stimulation when she was using the telephone at work. We taught her how to hold a magnet on the generator when she was using the telephone, temporarily preventing device discharge.

FOLLOW-UP

In 24 patients, the device was turned off and removed, giving a retention rate, for the 96 patients with follow-up data, of 75%. In 1 patient the removal after 3 months was for cosmetic reasons, and in the remaining patients it was removed after at least 18 months of stimulation because of lack of perceived benefit. Of these 24 patients, 1 had subsequent resolution of his epilepsy after a temporal lobectomy. Two patients died: one was found dead in bed, and the other died of head trauma during a seizure. (No deaths occurred in the patients continuing to receive VNS.) Three patients experienced improvement with the ketogenic diet. In one it was used concurrently with VNS, and the other 2 were nonresponders to VNS. Three other patients responded favorably to the more recently available AEDs. The rest of these nonresponders demonstrated persistence of their refractory epilepsy. In none of the 24 patients who failed to respond to the standard cycle was benefit recognized from changing to 3 months of a rapid-duty cycle, in contrast to findings in a previous report.²²

There was no way to accurately predict the end of the life of the generator in the original generators (model 100). If seizure control deteriorated and the generator was near the end of its life, as predicted by the manufacturer, it was replaced. The newer generators (models 101 and 102) have a longer life and an indication of end of battery life.

In our first patient, seizure control unexpectedly deteriorated, from 1 seizure every 5 months to several seizures a week, several months after she had a new model 100 implanted. A representative from the manufacturer studied the generator in vivo and told us it was working as expected. Nevertheless, replacement was associated with the return of the previous degree of control. Such device malfunction was rare.

COMMENT

Follow-up data on seizure frequency are presented in 96 of the first 100 patients treated with VNS at this institution. These are uncontrolled observations. The responder rate (>50% reduction in seizure frequency) was 45%. This rate compares favorably with the long-term responder rate of 42.7% in the preapproval studies.¹⁹

Five patients had increases in seizure frequency, but in 1 patient who had a 150% increase in seizure frequency, there was remarkable improvement in performance due to a reduction in seizure severity and injuries, and absence of postictal lethargy. The remaining 4 had no improvement.

Comparison of response rates between the group of patients 12 to 18 years old and those 11 years old or younger by confidence intervals demonstrates that the

What This Study Adds

Vagal nerve stimulation is presently approved for patients 12 years and older with medically refractory partial seizures. This article, along with others in the literature, supports the opinion that it is as effective in younger patients with other medically refractory seizures. This is the first article (1) to show a failure to significantly reduce other AEDs in patients receiving VNS; (2) to describe outcome in patients in whom this therapy failed and who had the device removed; (3) to describe outcome in a large pediatric population at one center; (4) to indicate the frequency of benefit from the magnet-activated rescue current in children; and (5) to address the signs of the end of the life of the older generator, the model 100 series, as compared with the 101 and 102 series, which have an indicator of approaching end of life.

response was the same in both age groups (Table 3). The wide confidence intervals indicate that the sample size was adequate to rule out a very large difference, but not moderate or small differences.

Patients with more than 7 years of refractory epilepsy were compared with those with a duration of 7 years or less; we did not find a significant benefit in earlier treatment with VNS. This stands in contrast to a recently published abstract.¹² The reason for this difference in findings is unclear; the abstract used a registry of data maintained by Cyberonics, Inc, and used 6 years of refractory epilepsy as a cutoff, rather than 7 years.

Infection occurred in 3 patients who required device removal and antibiotic treatment before surgical reimplantation. Three different surgeons implanted the devices that became infected. This infection rate compares favorably with that seen in implanted cardioverter defibrillators, 2.2% to 7.2%,²³ but it is higher than the VNS preapproval clinical study rate of 1.1%.^{24,25}

In almost half of the 70 patients for whom data were available, there was benefit from using the magnet-generated, on-demand current. This would reduce the duration and intensity of the seizure with a corresponding reduction or elimination of the postictal state.

The number of patients with improvement in general well-being, 42 of 68, is of interest. This did not always correspond to a reduction in seizure frequency, and it preceded any change in AEDs. In this group the most common observation by the family and the school was that the patient was "so much brighter." The improvement in function, independent of seizure control, has been observed by others.¹⁰ This benefit is supported by reports of enhanced recognition memory and reduced daytime sleepiness in adult patients with epilepsy treated with VNS.²⁶

Despite the responder rate of 45%, 75% of the patients continued treatment with VNS. The reasons for this high retention rate, in addition to improved seizure control, could be the availability of on-demand rescue treatment with the magnet, increased alertness, or a

preference not to undergo another surgery for removal. This retention rate of 75% is lower than the 88% reported earlier in an extension study of patients in the preapproval trials.¹⁹

One major issue with VNS is the inability to predict who will benefit. Save for Lennox-Gastaut syndrome⁶⁻⁹ and tuberous sclerosis,⁵ we cannot predict which patients will respond more favorably than others. The lack of a significant reduction in number of AEDs used in this study, from 2.23 to 2.00, was unusual in comparison with some new AEDs.²⁷⁻²⁹

There is a question as to when VNS should be offered for the treatment of medically refractory epilepsy. Once at least 3 appropriately used AEDs have failed, further drug therapy is unlikely to be successful in providing complete seizure control.³⁰ At that point, therapeutic options are seizure surgery, other AEDs, the ketogenic diet, or VNS. Patients and their families should be made aware of each of these options, their potential for improved seizure control, and possible complications before implementing a therapeutic plan.

On the basis of these observations, we believe that VNS may be a consideration when a patient's condition is determined to be medically refractory, on the basis of failure of 3 AEDs.²⁹ It should be an available therapy for children younger than 12 years, as they appear to respond as well as older children. In the event that a patient responds for many years and then his or her condition deteriorates, implantation of a new generator should be considered even if all tests show the generator to be functional.

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Corresponding author and reprints: Jerome V. Murphy, MD, Neurology Section, Children's Mercy Hospital, 2401 Gillham Rd, Kansas City, MO 64108 (e-mail: jmurphy@cmh.edu).

REFERENCES

1. *Physician's Manual, NeuroCybernetic Prosthesis System, Models 100 and 101*. Houston, Tex: Cyberonics, Inc; January 2000:3.
2. Murphy JV, for the Pediatric VNS Study Group. Left vagal nerve stimulation in children with medically refractory epilepsy. *J Pediatr*. 1999;134:563-566.
3. Helmers SL, Wheless JW, Frost M, et al. Vagus nerve stimulation in pediatric patients with refractory epilepsy: retrospective study. *J Child Neurol*. 2001;16:843-848.
4. Murphy JV, Wheless JW, Schmoll CM. Left vagal nerve stimulation in six patients with hypothalamic hamartomas. *Pediatr Neurol*. 2000;23:167-168.
5. Parain D, Menniello MJ, Berquen P, Delangre T, Billard C, Murphy JV. Vagal nerve stimulation in tuberous sclerosis complex patients. *Pediatr Neurol*. 2001;25:213-216.
6. Labar D, Murphy J, Tecoma E, for the E04 VNS Study Group. Vagus nerve stimulation for medication-resistant generalized epilepsy. *Neurology*. 1999;52:1510-1512.
7. Ben-Menachem E, Hellstrom K, Waldton C, Augustinsson LE. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. *Neurology*. 1999;52:1265-1267.
8. Hosain S, Nikalov B, Harden C, Li M, Fraser R, Labar D. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. *J Child Neurol*. 2000;15:509-512.
9. Frost M, Gates J, Helmers SL, et al. Vagal nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. *Epilepsia*. 2001;42:1148-1152.
10. Aldenkamp AP, Van de Veerdonk SHA, Majoie HJM, et al. Effects of 6 months of treatment with vagus nerve stimulation on behavior in children with Lennox-Gastaut syndrome in an open clinical and nonrandomized study. *Epilepsy Behav*. 2001;2:343-350.

11. Fohlen MJ, Jalin C, Pinard J-M, Delalande OR. Results of vagal nerve stimulation in 10 children with refractory infantile spasms [abstract]. *Epilepsia*. 1998; 39(suppl 6):170.
12. Helmers S. Comparison of early and later initiation of vagus nerve stimulation for refractory epilepsy [abstract]. *Neurology*. 2002;56(suppl 3):A267.
13. Takaya M, Terry WJ, Naritoku DK. Vagus nerve stimulation induces a sustained anticonvulsant effect. *Epilepsia*. 1996;37:1111-1116.
14. Murphy JV, Hornig G, Schallert G. Left vagal nerve stimulation in children with refractory epilepsy: preliminary observations. *Arch Neurol*. 1995;52:886-889.
15. Hornig G, Murphy JV, Schallert G. Left vagal nerve stimulation in children: an update. *South Med J*. 1997;90:484-488.
16. Murphy JV, Hornig G, Schallert GS, Tilton C. Adverse events in children receiving left vagal nerve stimulation. *Pediatr Neurol*. 1998;19:42-48.
17. Handforth A, DeGiorgio CM, Schacter SC, et al. Vagus nerve therapy for partial-onset seizures: a randomized active control trial. *Neurology*. 1998;51: 48-55.
18. Schallert G, Foster J, Lindquist N, Murphy JV. Chronic stimulation of the left vagal nerve in children: effect on swallowing. *Epilepsia*. 1998;39:1113-1114.
19. Morris GL, Mueller WM. The Vagus Nerve Stimulation EO1-EO5: long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. *Neurology*. 1999;53:1731-1735.
20. Murphy JV, Wheelus JW, Schmoll CM. Left vagal nerve stimulation in six patients with hypothalamic hamartomas. *Pediatr Neurol*. 2000;23:167-168.
21. DeGiorgio CM, Schacter SC, Handforth A, et al. Prospective long-term study of vagal nerve stimulation for the treatment of refractory epilepsy. *Epilepsia*. 2000; 41:1195-1200.
22. DiGiorgio CM, Thompson J, Lewis P, et al. Vagus nerve stimulation: retrospective analysis of device parameters in 154 patients during the long term XE5 study. *Epilepsia*. 2001;42:1017-1020.
23. Rosner B. *Fundamentals of Biostatistics*. 3rd ed. Belmont, Calif: Duxbury Press; 1990:332.
24. Lai KK, Fontecchio SA. Infections associated with implantable cardioverter defibrillators placed transvenously and via thoracotomies: epidemiology, infection control and management. *Clin Infect Dis*. 1998;27:265-269.
25. Bruce DA, Alksne JF, Bernard E, Blume H, Fraser RAR, Li M. Implantation of a vagal nerve stimulator for refractory partial seizures: surgical outcomes of 454 study patients [abstract]. *Epilepsia*. 1998;39(suppl 6):92-93.
26. Clark KB, Naritoku DK, Smith DC, et al. Enhanced recognition memory following vagal nerve stimulation in human subjects. *Nat Neurosci*. 1999;2:94-98.
27. Marlow BA, Edwards J, Marzec M, et al. Vagus nerve stimulation reduces daytime sleepiness in epilepsy patients. *Neurology*. 2001;57:879-884.
28. Beydoun A, Sacjdeo RC, Rosenfeld WE, et al. Oxcarbazepine monotherapy for partial-onset seizures: a multicenter, double-blind, clinical trial. *Neurology*. 2000; 54:2245-2251.
29. Steiner TJ, Dellaportas CI, Findley LJ, et al. Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. *Epilepsia*. 1999;40:601-607.
30. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000; 342:314-319.