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Vagus nerve stimulation for partial and generalized epilepsy from infancy to adolescence

Clinical article

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Object. Vagus nerve stimulation (VNS) is approved by the FDA for the treatment of partial epilepsy in patients older than 12 years. Authors of the current study performed a large retrospective analysis and comparison of VNS outcomes in children with an age ≥ and < 12 years, including those with partial and generalized epilepsy.

Methods. A retrospective review of the records of pediatric patients (age < 18 years) who had undergone primary VNS system implantation between 2001 and 2010 by a single pediatric neurosurgeon was undertaken. Considered data included demographics, epilepsy type (partial vs generalized), seizure frequency, seizure duration, postictal period duration, and antiepileptic medication use.

Results. One hundred forty-six patients (49% female) were followed up for a mean of 41 months after VNS implantation. Thirty-two percent of patients had partial epilepsy and 68% had generalized epilepsy. After VNS system implantation, seizure frequency was reduced in 91% of patients, seizure duration in 50%, postictal period in 49%, and antiepileptic medication use in 75%. There was no significant difference in age, sex, or duration of follow-up according to epilepsy type. Neither was there any significant difference in seizure frequency reduction, seizure duration, postictal period, medication use, overall clinical improvement, or improvement in quality of life based on an age ≥ or < 12 years or epilepsy type.

Conclusions. Vagus nerve stimulation reduced both seizure frequency and antiepileptic medication use in the majority of pediatric patients regardless of sex, age cohort, or epilepsy type. Vagus nerve stimulation also reduced seizure duration and postictal period in approximately half of the pediatric patients. Contrary to expectation, children with partial epilepsy do not benefit from VNS at higher rates than those with generalized epilepsy.
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Key Words • **vagus nerve stimulation** • **generalized epilepsy** • **partial epilepsy** • **pediatrics**

Since its introduction in 1997, VNS has been widely used to treat medically refractory epilepsy in all age groups, including children and adolescents. Currently, the procedure is approved by the FDA for use as "an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years with partial onset seizures which are refractory to antiepileptic medications."[7]

Several groups, however, have reported substantial clinical improvement in patients who do not meet the FDA approval criteria, including children younger than 12 years and those with generalized epilepsy.[2–4,6,10,11,13] Nevertheless, little information exists to compare the relative efficacy of VNS therapy in children older or younger than 12 years of age and those with partial or generalized epilepsy. The impact of other demographic features on VNS efficacy, including comorbid diagnoses (such as cerebral palsy) and patient sex, are also poorly understood, with only limited data generally available from individual small series.[2–4,10,11,13]

We therefore analyzed a large consecutive series of children and adolescents who had been treated with VNS for epilepsy by a single surgeon, including all age groups less than 18 years of age and children with both partial and generalized epilepsy.

Abbreviations used in this paper: AVM = arteriovenous malformation; IVH = intraventricular hemorrhage; TBI = traumatic brain injury; VNS = vagus nerve stimulation.

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Methods

The Oregon Health & Science University Institutional Review Board approved this study. Patients included in this retrospective review had undergone primary implantation

of a NeuroCybernetic prosthesis system (Cyberonics) by the senior author (N.R.S.) between April 2001 and June 2010 and were younger than 18 years with a diagnosis of medically intractable epilepsy. All data were obtained from the patients' medical records. Collected information included demographic data (age, sex, seizure etiology, and previous epilepsy surgery), epilepsy type (partial vs generalized), seizure frequency, seizure duration, postictal period duration, antiepileptic medication use, seizure freedom, and VNS magnet use. Patients with mixed seizure disorder were categorized into the generalized epilepsy group. Pediatric neurologists determined epilepsy type by using clinical and electroencephalographic data. Patients were excluded from analysis if the follow-up post–VNS system implantation was less than 6 months.

All patients were implanted with a NeuroCybernetic prosthesis system generator in a left-sided subclavicular subcutaneous pocket. Vagus nerve leads were implanted through a small transverse left anterior neck incision in a standard fashion (Fig. 1). A protocol designed to reduce the risk of surgical site and device infection was used in all patients and is described elsewhere.[12] All patients were treated with approximately 24 hours of perioperative intravenous antibiotics: cefazolin (50 mg/kg) prior to 2006 and vancomycin (15 mg/kg) beginning in 2006.

The electronic medical record of each patient was reviewed to determine the following variables before and after VNS implantation: seizure frequency, seizure duration, postictal period duration, antiepileptic medication use, and quality of life. These outcomes were assessed by the patients' pediatric epileptologist and/or pediatric neurology nurse practitioner at the scheduled clinical follow-up closest to 6 months postoperatively (range 3–9 months). Data were collected from descriptive clinical notes, and the following categories were assigned. Decrease in seizure frequency was categorized as none, < 50%, or ≥ 50%. Seizure duration and postictal period duration were categorized as same, longer, or shorter. Antiepileptic medication use was categorized as more or less. Overall clinical outcome was categorized by the pediatric epileptologist and/or pediatric neurology nurse practitioner at 6 months postoperatively and at the time of the most recent documented clinical follow-up as the same, better, or worse, reflecting the above seizure management variables, patient and parent satisfaction, and parent/teacher reports of development and/or school performance. Quality of life, if it could be determined, was categorized as the same or better as judged by the patients' caregivers and/or the patient. No formal quality-of-life assessment tool was used during the clinical follow-up.

Seizure etiology was classified as follows: AVM, ischemic injury, Rett syndrome, other named syndrome (not specified to maintain patient anonymity due to the rarity of the disease), IVH, TBI, tuberous sclerosis, chromosomal abnormality, congenital abnormality not otherwise specified, cortical dysplasia, tumor, perinatal infection, and unknown (no identifiable etiology after a workup including MRI, electroencephalography, and metabolic analysis).

Outcomes were compared with the Student t-test, chi-square analysis, and Fisher exact test as appropriate by using SAS and STATA (StataCorp) software. Tests were 2-tailed and uncorrected for multiple comparisons. A Friedman test with the Dunn multiple comparison posttest was performed to compare outcomes at 6 months postoperatively and at the most recent clinical follow-up. Differences were considered significant if $p \leq 0.05$.

Results

Demographics and Overall Outcomes

One hundred eighty patients who met the general inclusion criteria were identified. Thirty-four of these patients were excluded because of inadequate follow-up, whereas 146 patients (74 males and 72 females) were included in our study. The mean follow-up was approximately 41 months. The most common seizure etiologies were unknown, congenital malformation, and cortical dysplasia in the generalized epilepsy group and unknown, ischemic injury, and congenital malformation in the partial epilepsy group (Table 1). Mixed seizure disorder was diagnosed in 51 patients and was included in the generalized epilepsy group for analysis. Indications for VNS in patients with partial epilepsy included no identifiable surgical target on MRI (32 patients), multiple or bilateral foci (6 patients), multiple tubers (4 patients), and refractory seizures after previous resection of seizure foci (4 patients). Thirteen patients had previously undergone resective epilepsy surgery including selective cortical resection (5 patients), tumor or AVM resection (4 patients), hemispherectomy (2 patients), corpus callostomy (1 patient), and temporal lobectomy (1 patient). Fifty-six percent of patients in the generalized group had multifocal epilepsy.

A reduction in seizure frequency was demonstrated in 91% of all patients, a reduction in seizure duration in 50%, a decreased postictal period in 49%, and a decrease in seizure medication in 75% at 6 months after the initiation of VNS therapy. In patients who were able to decrease antiepileptic medication use, the median amount of reduction was 1 medication in both epilepsy groups. Improved overall clinical outcome was demonstrated in 81% of patients at 6 months postoperatively and 80% of patients at the most recent clinical follow-up. The difference between the percentage of patients that improved at 6 months and at the most recent follow-up was not statistically significant ($p > 0.05$). Swiping the VNS magnet to abort seizures was successful in approximately 90% and 92% in patients with generalized and partial epilepsy, respectively, particularly within the first 6 months after implantation of the VNS system.

Four patients (2.7%) had postoperative generator site infection during primary generator implantation. These patients were treated with generator removal, intravenous antibiotics for lead salvage, and generator reimplantation, as described elsewhere.[12] No patient suffered permanent hoarseness, dysphagia, dysphonia, or other serious complication. Neither did any patient have increased episodes of status epilepticus following implantation of the VNS system.

Partial Versus Generalized Epilepsy

There was no significant difference in age distribu-

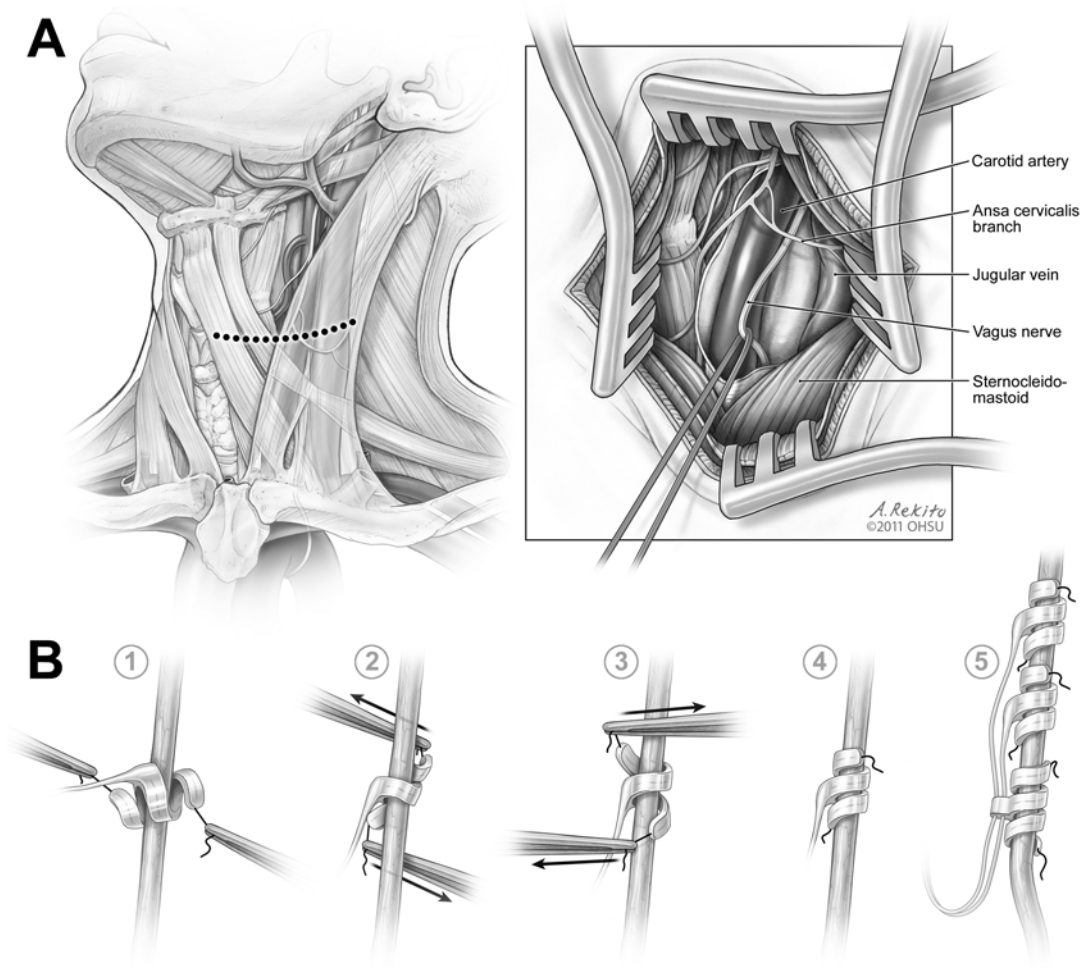

Fig. 1. Illustrations depicting the surgical procedure for implantation of a VNS system. **A:** The head is positioned in slight extension with a 15° rotation to the right *(left illustration)*. A left-sided transverse incision *(dotted line)* is created in a skin fold at approximately the C5–6 level, below the carotid artery bifurcation. After dividing the platysma, the sternocleidomastoid muscle and jugular vein are retracted laterally to reveal the vagus nerve (illustrated here elevated by a vessel loop, *right illustration*). The vagus nerve travels within the carotid sheath, while branches of the ansa cervicalis cross the exposure deep to the platysma but superficial to the sheath. **B:** Steps for implantation of the vagus nerve anchor and electrode coils. The coil is oriented perpendicular to the nerve and gently stretched using the attached tensioning sutures (1). The midpoint of the stretched coil is slid around the nerve (2). Each end of the coil, aided by its material "memory," is coiled around the vagus nerve (3 and 4). Proper configuration of the 3 coils (5). Printed with the permission of Andrew Rekito, 2012.

tion, sex, seizure etiology, or duration of follow-up in patients with partial versus generalized epilepsy (Tables 1 and 2).

There was no significant difference in the rates of seizure frequency reduction, seizure duration, postictal period, overall clinical outcome, or quality of life between patients with partial epilepsy and those with generalized epilepsy (Table 3). There was a weak trend ($p = 0.119$) toward a greater reduction in seizure duration in patients with generalized epilepsy. Notably, only 3 patients with generalized epilepsy and 0 patients with partial epilepsy were seizure free ($p = 0.551$).

Other Variables

An age ≥ or < 12 years did not affect any VNS outcome measure (Table 4), although there was a trend toward a greater improved quality of life in the younger group ($p = 0.054$). Nor was there any effect of age when patients were divided into groups from birth to 6th birthday, 6 years to 12th birthday, and 12 years and above (data not shown). Only 3 patients younger than 12 years and no patients older than 12 years were seizure free ($p = 0.562$). Neither patient sex nor seizure etiology significantly affected any outcome measure (data not shown).

Discussion

Although VNS therapy is only FDA approved for patients with partial epilepsy who are 12 years of age or older, the present study demonstrates equal benefits of VNS therapy accruing to both younger children and those with generalized epilepsy.

The presence of comorbid neurological diagnoses, including cerebral palsy, did not affect the quality of re-

TABLE 1: Comparison of demographics by epilepsy type*

Parameter	No.		p Value
	Generalized Seizures	Partial Seizures	
mean age in yrs	8.5 ± 4.6	8.8 ± 4.6	0.780
total no. of patients	100	46	0.410
M	53	21	
F	47	25	
diagnosis			0.103
AVM	2	0	
ischemic injury	5	8	
named syndrome	1	2	
IVH	3	1	
Rett syndrome	7	0	
TBI	1	2	
tuberous sclerosis	6	2	
chromosomal abnormality	1	1	
congenital malformation	10	6	
cortical dysplasia	8	4	
tumor	2	0	
unknown	50	16	
infection	4	4	
mean FU in mos	41.9 ± 28.8	39.8 ± 36.3	0.970

* FU = follow-up.

TABLE 2: Comparison of demographics by patient age

Parameter	No.		p Value
	<12 Yrs	12–18 Yrs	
epilepsy type			0.677
partial	33	13	
generalized	75	25	
total no. of patients	108	38	0.780
M	54	18	
F	54	20	
diagnosis			0.492
AVM	0	2	
ischemic injury	12	1	
named syndrome	0	3	
IVH	4	0	
Rett syndrome	5	2	
TBI	2	1	
tuberous sclerosis	6	2	
chromosomal abnormality	1	1	
congenital malformation	12	4	
cortical dysplasia	8	4	
tumor	2	0	
unknown	48	15	
infection	5	3	
mean FU in mos	41.1 ± 31.7	41.1 ± 31.7	0.992

TABLE 3: Comparison of outcomes by epilepsy type*

Parameter	No. (%)		p Value
	Generalized Seizures	Partial Seizures	
seizure frequency reduction			0.227
none	8 (8)	5 (11)	
<50%	31 (31)	20 (43)	
≥50%	61 (61)	21 (46)	
seizure duration			0.119
shorter	54 (54)	19 (41)	
same	46 (46)	26 (56)	
longer	0	1 (2)	
postictal period			0.256
shorter	51 (51)	20 (43)	
same	49 (49)	25 (54)	
longer	0	1 (2)	
medication use			0.497
less	73 (73)	36 (78)	
more	27 (27)	10 (22)	
overall clinical outcome at 6 mos postop			0.807
better	82 (82)	36 (78)	
same	15 (15)	8 (17)	
worse	3 (3)	2 (4)	
overall clinical outcome at most recent FU			0.388
better	83 (83)	34 (74)	
same	13 (13)	8 (17)	
worse	4 (4)	4 (9)	
quality of life			0.728
same	50 (50)	17 (37)	
better	25 (25)	10 (22)	
indeterminate	25 (25)	19 (41)	

* Percentages are displayed with 2 significant digits and may not equal 100.

sponse to VNS therapy in the present study. Thus, the higher proportion of children with cerebral palsy in the partial epilepsy group is unlikely to translate into worsened outcomes in this group. Furthermore, the outcomes reported here for patients with partial epilepsy are comparable to those in previous studies of VNS therapy in children.[6,8,9,13] Surprisingly, the only trends toward an improved outcome in response to VNS therapy for seizure frequency and duration, which do not approach statistical significance, accrued to patients with generalized epilepsy. This finding runs counter to the expectations reflected in the FDA approval language.

Another recent large retrospective study of VNS therapy outcomes also showed no significant difference between pediatric patients younger or older than 12 years of age.[6] That study and the present study document nearly equivalent numbers of children with very similar demographic and clinical characteristics. Both studies also report quite

TABLE 4: Comparison of outcomes by patient age*

Parameter	No. (%)		p Value
	<12 Yrs	12–18 Yrs	
seizure reduction			0.746
none	11 (10)	2 (5)	
<50%	37 (34)	14 (37)	
≥50%	60 (56)	22 (58)	
seizure duration			1.000
shorter	53 (49)	19 (50)	
same	54 (50)	19 (50)	
longer	1 (1)	0	
postictal period			1.000
shorter	52 (48)	19 (50)	
same	55 (51)	19 (50)	
longer	1 (1)	0	
medication use			0.254
less	78 (72)	31 (82)	
more	30 (28)	7 (18)	
overall clinical outcome at 6 mos postop			0.404
better	85 (79)	33 (87)	
same	18 (17)	5 (13)	
worse	5 (5)	0	
overall clinical outcome at most recent FU			0.866
better	85 (79)	32 (84)	
same	17 (16)	4 (11)	
worse	6 (6)	2 (5)	
quality of life			0.054
better	53 (49)	11 (29)	
same	23 (21)	12 (32)	
indeterminate	32 (30)	15 (39)	

* Percentages are displayed with 2 significant digits and may not equal 100.

similar overall results. For example, Elliott and colleagues[6] found > 50% reduction in seizure frequency in 65% of pediatric patients, as compared with 56% of patients in the current study. Additional smaller series have also demonstrated a generally consistent pattern of results.[5,13]

Linear regression analysis by Elliott et al.,[6] including consideration of 6 categories of epilepsy type and 11 categories of epilepsy etiology, failed to demonstrate any differences in VNS outcome based on these or other clinical characteristics. Those authors did not, however, categorically analyze the influence of partial versus generalized epilepsy on outcomes. Thus, our finding that children with generalized epilepsy benefit from VNS therapy at least as much as those with partial epilepsy represents an important and novel finding in a large pediatric series.

In our study, only 2.7% of patients experienced an infection during primary implantation of the VNS system. Previous reports of VNS hardware infection in pediatric patients have ranged from 0.7% to 7.7%.[1–3,6] The lowest infection rates reported for primary implantation of a VNS device in children have occurred in the largest series of patients—that for Elliott et al.,[6] 0.7%, and that for the present report, 2.7%—suggesting that surgical volume may contribute to beneficial technical outcomes for VNS therapy. In the present series, other than hardware infection, no patient suffered a serious, permanent complication.

One could postulate that additional therapeutic attention around the time of surgical VNS system implantation might improve the overall clinical status of pediatric patients. The improved overall clinical outcome noted in our patients 6 months after VNS system implantation, however, persisted at unchanged levels during the most recent clinical follow-up (mean 41 months postoperatively).

This study is limited by its retrospective nature and the difficulty of accurately assessing seizure frequency and severity. Additionally, no objective quality-of-life evaluation tool was used during follow-up, and the compromised functional and cognitive status of many patients precluded accurate assessment. Findings in the present study nevertheless suggest that limitations on the FDA-approved indications for VNS therapy, which reflect the design of the original preapproval prospective studies, may not accurately delineate the patient population able to benefit from this approach. Further prospective study of VNS therapy in younger children and those with generalized epilepsy appears warranted.

Conclusions

Vagus nerve stimulation therapy appears to be at least as effective in treating children and adolescents with generalized epilepsy of all ages as it is in treating patients with partial epilepsy. In this large series, VNS reduced seizure frequency and antiepileptic medication use and improved both short- and long-term clinical outcomes in the majority of pediatric patients regardless of sex, age cohort, or epilepsy type. Vagus nerve stimulation also reduced seizure duration and postictal period in approximately half of the patients. Given the results of this and multiple other smaller studies, we advocate the use of VNS in patients younger than 12 years and in those with generalized epilepsy when otherwise indicated.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Selden, Thompson, Wozniak, Roberts, Kao. Acquisition of data: Thompson, Wozniak, Roberts, Kao. Analysis and interpretation of data: all authors. Drafting the article: Selden, Thompson, Wozniak, Roberts, Kao. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Selden. Statistical analysis: Thompson, Anderson.

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