Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases

Clinical article

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Object. The authors undertook this study to analyze the efficacy of vagus nerve stimulation (VNS) in a large consecutive series of children 18 years of age and younger with treatment-resistant epilepsy and compare the safety and efficacy in children under 12 years of age with the outcomes in older children.

Methods. The authors retrospectively reviewed 141 consecutive cases involving children (75 girls and 66 boys) with treatment-resistant epilepsy in whom primary VNS implantation was performed by the senior author between November 1997 and April 2008 and who had at least 1 year of follow-up since implantation. The patients' mean age at vagus nerve stimulator insertion was 11.1 years (range 1–18 years). Eighty-six children (61.0%) were younger than 12 years at time of VNS insertion (which constitutes off-label usage of this device).

Results. Follow-up was complete for 91.8% of patients and the mean duration of VNS therapy in these patients was 5.2 years (range 25 days–11.4 years). Seizure frequency significantly improved with VNS therapy (mean reduction 58.9%, $p < 0.0001$) without a significant reduction in antiepileptic medication burden (median number of antiepileptic drugs taken 3, unchanged). Reduction in seizure frequency of at least 50% occurred in 64.8% of patients and 41.4% of patients experienced at least a 75% reduction. Major (3) and minor (6) complications occurred in 9 patients (6.4%) and included 1 deep infection requiring device removal, 1 pneumothorax, 2 superficial infections treated with antibiotics, 1 seroma/hematoma treated with aspiration, persistent cough in 1 patient, severe but transient neck pain in 1 patient, and hoarseness in 2 patients. There was no difference in efficacy or complications between children 12 years of age and older (FDA-approved indication) and those younger than 12 years of age (off-label usage). Linear regression analyses did not identify any demographic and clinical variables that predicted response to VNS.

Conclusions. Vagus nerve stimulation is a safe and effective treatment for treatment-resistant epilepsy in young adults and children. Over 50% of patients experienced at least 50% reduction in seizure burden. Children younger than 12 years had a response similar to that of older children with no increase in complications. Given the efficacy of this device and the devastating effects of persistent epilepsy during critical developmental epochs, randomized trials are needed to potentially expand the indications for VNS to include younger children.

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KEY WORDS • vagus nerve stimulation • epilepsy • epilepsy surgery • medically refractory epilepsy • medically intractable epilepsy • pediatric neurosurgery

THE prevalence of epilepsy is 0.5%–1% in the pediatric population, affecting millions of children and young adults worldwide.^{17,39,51} Although most patients are successfully treated with one or more AEDs, treatment-resistant epilepsy occurs in up to one-third of children with epilepsy and can be devastating to children and their families.^{10,20,25,29,41,46}

Abbreviations used in this paper: AED = antiepileptic drug; EEG = electroencephalography; VNS = vagus nerve stimulation.

Severe epilepsy is associated with cognitive decline and can be profound in children, disrupting developmental epochs essential to intellectual and social maturation.^{14,49} Retrospective studies in children with epilepsy suggest that better seizure control facilitates developmental progress and improves cognitive outcomes and quality of life.^{13,18,31,54}

Surgical treatment options include resective surgery, disconnection procedures, and stimulation procedures. The most widely used and studied neurostimulation procedure is vagus nerve stimulation (VNS). In 1997, the US

FDA approved VNS for the treatment of intractable partial epilepsy in adults and children over 12 years of age. The initial randomized studies of VNS were time-limited (3-month follow-up) and demonstrated a 25%–30% decrease in seizure frequency,^{8,21,23} but subsequent non-blinded, nonrandomized studies reported superior seizure control and demonstrated the efficacy and safety of VNS in adults and children with generalized epilepsy.^{7,9,25,36,38,41}

Most studies of VNS in children have involved a limited number of patients, often with only a short duration of follow-up. We report 141 consecutive cases involving children who underwent long-term VNS therapy for refractory epilepsy, analyze the efficacy and safety of VNS therapy, and examine predictors of VNS treatment success.

Methods

Patient Population

Between November 1997 and April 2008, 154 children (younger than 18 years of age) underwent VNS operations performed at the New York University and Saint Barnabas Medical Center Comprehensive Epilepsy Centers by a single surgeon (W.K.D.). Thirteen patients were referred for removal or revision of a device placed at other centers; 141 consecutive children with treatment-resistant epilepsy underwent primary insertion of a VNS device at our center and are reported on here. At the initial office visit, all patients were prospectively entered into a clinical registry, whose creation was approved by the New York University institutional review board. Data collected included demographic information, surgical history, physical and neurological examination findings, epilepsy characteristics, mean weekly seizure frequency (obtained from seizure logs), treatment history, and imaging findings. This report represents a retrospective analysis of this database.

Each patient underwent a presurgical evaluation that included history and physical examination, EEG, MR imaging and in most cases video EEG and functional imaging studies. Most children were reviewed at a presurgical multidisciplinary conference and deemed to be surgical candidates (Table 1). Selection criteria for the patients who had VNS insertion included patients who have failed multiple AEDs (typically at least 3 AEDs) with multifocal or diffuse seizure onsets not amenable to surgical resection, patients with persistent or recurrent seizures following intracranial epilepsy surgery, AED toxicity or intolerable side effects, patients medically unfit for intracranial surgery and patient or family preference for conservative measures prior to or in lieu of possible intracranial surgery was the selection criterion for VNS therapy. The multidisciplinary conference recommended VNS for the treatment of treatment-resistant epilepsy in 112 children and recommended intracranial epilepsy surgery for 29 children. Seventeen patients underwent intracranial epilepsy surgery and subsequently had VNS implantation due to persistent epilepsy (10 with nonresectable foci; 7 who underwent resection but had persistent or recurrent epilepsy). The families of 12 children chose VNS instead of recommended intracranial surgery.

TABLE 1: Multidisciplinary conference recommendations for 141 children with treatment-resistant epilepsy*

Recommendation	No. of Pts (%)
VNS	112 (79.4)
as primary treatment	103
after failure of intracranial op	9
intracranial op	17 (12.1)
bilat electrode monitoring	10
multistage electrode monitoring/resection	7
intracranial op/patient or family preference for VNS	12 (8.5)
bilat electrode monitoring	2
multistage electrode monitoring/resection	8
callosotomy	2

* Pts = patients.

Following institutional review board approval, patients undergoing VNS procedures were identified from within the database. Missing data were obtained from office and inpatient charts, operative reports, imaging and electrophysiological studies. Informed consent for this retrospective analysis was waived by the review board.

Surgical Procedure and Outcome Assessment

The surgical techniques for subcutaneous and subpectoral implantation of the VNS device have been previously described.⁵ Most children who underwent VNS implantation were discharged the same day. In the remaining cases the children were admitted to the epilepsy monitoring unit as planned for medication adjustment coinciding with VNS surgery. Since 1999, the stimulators were turned on at the time of surgery without adverse sequelae. Surgical follow-up typically occurred 2 weeks postoperatively and subsequently on a variable schedule as indicated. Long-term follow-up and adjustments of VNS parameters were conducted by the epileptologist.

Retrospective chart review was performed to collect follow-up and outcome data. At the time of last available clinical follow-up, the following data were collected: mean weekly seizure frequency (calculated from seizure logs kept by caretakers as an average of weekly frequencies from last 2 office visits or as an average of weekly frequencies over the 3 months prior to the visit), complications of VNS therapy, duration of VNS therapy, the timing and reason for revisions and removals of VNS devices, and all subsequent surgical procedures. A standardized questionnaire addressing complications and side effects was completed at each follow-up visit at our centers.

Telephone interviews were conducted with patients, families, or caretakers to determine most recent seizure frequency and current AED regimen. For patients who underwent device removal or had their devices turned off, the time of VNS therapy termination was used as the time of last follow-up. Given the demonstration of VNS effect by 3 months from the randomized trials, we considered patients who had VNS therapy for at least 3 months with

clinical follow-up data to have adequate follow-up. Patients who did not have follow-up of at least 3 months were excluded from outcome analyses.

Postoperative seizure outcomes assessed at the time of the last follow-up are expressed with a modified Engel scale¹⁶ and with a VNS-specific outcome scale proposed by McHugh et al.³⁴

Some children reported in this study were included in prior studies by our group on subpectoral and subcutaneous VNS generator placement⁵ (49 children) and VNS in patients with tuberous sclerosis complex (9 children).¹⁵

Vagus nerve stimulation therapy in patients with generalized epilepsies and children under 12 years of age is an off-label usage not approved by the US FDA.

Statistical Analyses

Averages are expressed as means $\pm$ SDs. Seizure frequency and number of AEDs before and after VNS lacked normal distributions; therefore, median values are reported and the paired-samples Wilcoxon signed-ranks test was employed to analyze pre- and postoperative seizure frequency and AED requirements (nonparametric data). Univariate and multivariate linear regression analyses were performed to determine the impact of the following independent variables (continuous, dichotomous, or multinomial) on mean percentage seizure reduction (dependent variable): age at epilepsy onset, age 5 years or less at onset of epilepsy (dichotomous), age at VNS implantation, age $\geq$ 12 years at VNS implantation (dichotomous), duration of epilepsy prior to VNS, duration of epilepsy $>$ 10 years prior to VNS therapy (dichotomous), prior intracranial epilepsy surgery (dichotomous), number of prior intracranial epilepsy surgery procedures, preimplantation seizure frequency, number of reported seizure types, partial seizures only (dichotomous), epilepsy classification and etiology (multinomial), underlying diagnosis if applicable (multinomial), EEG findings (multinomial; focal, multifocal, diffuse, diffuse and multifocal), number of preimplantation AEDs, number of failed AEDs and history of infantile spasms, febrile seizures, and developmental delay or status epilepticus (dichotomous variables). All statistical analyses were performed using SPSS 17.0 for Mac (SPSS Inc.). A *p* value $<$ 0.05 was considered statistically significant.

Results

Demographic and Clinical Data

Demographic characteristics and clinical data for the 141 patients who had primary implantations are summarized in Table 2. The group included 75 girls (53.2%) and 66 boys (46.8%), and the patients' ages at VNS implantation ranged from 1.3 to 18 years (mean 11.1 ± 4.7 years). Eighty-six children (61.0%) were younger than 12 years at time of VNS insertion (off-label usage).

The mean age at seizure onset for the cohort was 2.8 ± 3.6 years (range birth–16 years) and the mean duration of epilepsy prior to VNS therapy initiation was 8.4 ± 4.4 years (range 1 week–17.9 years). The median weekly seizure frequency was 10 seizures (range 0.1–2000 sei-

TABLE 2: Demographic and clinical data for 141 children who underwent VNS for treatment-resistant epilepsy

Variable	Value*
sex	
F	75 (53.2)
M	66 (46.8)
age at seizure onset (yrs)	
mean	2.8 ± 3.6
range	birth–16 yrs
duration of epilepsy prior to VNS	
mean (yrs)	8.4 ± 4.4
range	7 days–17.9 yrs
age at VNS insertion (yrs)	
mean	11.1 ± 4.7
range	1.3–18
pt age	
$<$ 12 yrs†	86 (61.0)
$\geq$ 12 yrs	55 (39.0)
seizure frequency (no. per wk)	
median	10
range	0.1–2000
no. of AEDs	
mean	2.6 ± 0.9
range	1–7
no. of AEDs failed	
mean	5.5 ± 2.9
range	2–15
prior failed intracranial epilepsy surgery	30 (21.3)
no. of seizure types	
mean	2.2 ± 1.1
range	1–6
developmental delay	112 (79.4)

* Values represent numbers of patients (%) unless otherwise indicated.

† Off-label usage.

zures) and the mean number of seizure types was 2.2 ± 1.1 (range 1–6 types). Treatment with an average of 5.5 ± 2.9 AEDs (range 2–15 AEDs) had failed in these children prior to VNS insertion and the children were taking an average of 2.6 ± 0.9 AEDs (range 1–7 AEDs) at time of insertion. Thirty patients (21.3%) had undergone a total of 38 intraoperative epilepsy surgery procedures prior to VNS therapy. One hundred twelve patients (79.4%) had developmental delay or neurocognitive impairment.

The classification of epilepsy type, EEG findings, and underlying etiologies in these children are summarized in Table 3. The most common types of epilepsy were multifocal partial epilepsy (39.0%), symptomatic generalized epilepsy (29.1%) and idiopathic generalized epilepsy (13.5%). The most common EEG findings were multifocal (44.0%) or diffuse/generalized (43.3%) onsets. Excluding children with unknown etiologies, the most common underlying diagnoses were cerebral palsy/static encephalopathy (10.6%), neuronal migration disorders/

TABLE 3: Epilepsy classification, EEG findings, and etiology in 141 children treated with VNS for treatment-resistant epilepsy*

Variable	No. of Pts (%)
epilepsy classification	
MFPE	55 (39.0)
SGE	41 (29.1)
IGE	19 (13.5)
MFPE/SGE	18 (12.8)
focal (frontal or temporal)	5 (3.5)
myoclonic epilepsy	2 (1.4)
EEG findings	
focal	5 (3.5)
multifocal	62 (44.0)
diffuse/generalized	61 (43.3)
diffuse/multifocal	13 (9.2)
epilepsy etiology	
idiopathic	54 (38.3)
cerebral palsy/static encephalopathy	15 (10.6)
neuronal migration disorders	14 (9.9)
infection	13 (9.2)
LGS	11 (7.8)
TSC	8 (5.7)
genetic/metabolic disorders	14 (9.9)
vascular lesion/tumor	3 (2.1)
TBI	3 (2.1)
LKS	4 (2.8)
HH	2 (1.4)

* HH = hypothalamic hamartoma; IGE = idiopathic generalized epilepsy; LGS = Lennox-Gastaut syndrome; LKS = Landau-Kleffner syndrome; MFPE = multifocal partial epilepsy; SGE = symptomatic generalized epilepsy; TBI = traumatic brain injury; TSC = tuberous sclerosis complex.

dysplasia (9.9%), genetic/metabolic disorders (9.9%), and infection (9.2%; encephalitis and/or meningitis).

Seizure Control Outcomes and Follow-Up

The mean duration of VNS therapy was 5.3 ± 3.1 years for the entire cohort (range 25 days–11.4 years). Two patients died during the follow-up period, and both deaths were related to the patients' epilepsy (21 months and 10 years following implantation). Eleven US patients and 2 patients from other countries had less than 3 months' postoperative follow-up and were unreachable by phone. Excluding these 13 patients with inadequate follow-up, data from 128 patients (91.8%) were available for outcome analyses. There were no significant differences between children with and without adequate follow-up in terms of sex distribution, age at seizure onset, duration of seizures, age at stimulator insertion, seizure types, seizure frequency, EEG findings, or past or present AED usage ($p > 0.05$ for all comparisons).

The mean percentage seizure reduction in these 128 children was 57.9% (range 0%–100%). The median

weekly seizure frequency was 3, significantly decreased from their preoperative baseline of 10 seizures per week ($p < 0.0001$). There was no significant difference in number of AEDs taken at time of last follow-up compared to the number taken preoperatively (median 3, range 0–7, for both; $p = 0.15$). Following VNS therapy, 26 children (20.3%) were taking fewer AEDs, 62 patients (48.4%) were taking the same number of AEDs, and 40 patients (31.2%) were taking a greater number of AEDs at last follow-up. Changes in AED regimen (medication and/or dosage) or stimulation parameters were made at many of office visits.

Table 4 summarizes the seizure control outcomes by modified Engel and McHugh classifications. Excluding 13 patients who lacked adequate follow-up, $\geq 90\%$ seizure control was achieved in 27 patients (21.1%), $\geq 75\%$ seizure control in 53 patients (41.4%), $\geq 50\%$ seizure control in 83 patients (64.8%), and $< 50\%$ seizure control in 45 patients (35.2%). Ten patients (7.8%) experienced no reduction in seizure burden and 3 patients (2.3%) had an increase in seizure activity from their presurgical baseline. Ten patients (7.8%) have remained seizure-free for at least 6 months prior to the last follow-up visit.

Vagus nerve stimulation resulted in a significant reduction in seizure frequency regardless of epilepsy type, etiology, and EEG findings (Table 5). Univariate linear regression analyses did not identify any demographic or clinical variables that predicted response to VNS; therefore, multivariate analysis was not performed.

Surgical Results and Complications

The leads were placed on the left vagus nerve in all patients. Generators were placed subpectorally in 91 patients (64.5%) and subcutaneously in 50 patients (35.5%). There were no urgent readmissions for acute complications or sequelae from same-day discharge.

The most common side effect was mild but tolerable neck pain associated with the duty cycle, which occurred in 18% of children. In all but a few cases, this resolved spontaneously over the course of a few weeks or with adjustment of the stimulation parameters.

Table 6 summarizes the neurological and nonneurological complications that occurred consequent to VNS implantation. Transient or minor neurological side effects included hoarseness in 1 child (0.7%), which resolved by 3 months, and intractable cough during stimulation in 1 child (0.7%). One child (0.7%) experienced moderate, permanent hoarseness. No child experienced dysphagia or vocal cord paralysis. Minor nonneurological complications included neck and arm pain unrelated to the duty cycle in 2 patients (0.5%) and neck pain related to the duty cycle in 1 patient (0.7%). In all 5 patients, the pain improved over time but persisted at a low level that was tolerable for them. Two patients (1.4%) developed superficial wound infections that were treated successfully with antibiotics alone and 1 patient developed a hematoma/seroma that was successfully treated with aspiration. Two children (1.4%) developed significant complications including infection requiring device removal in 1 case (0.7%) and pneumothorax in the other (0.7%). There was no difference in the incidence of major or minor com-

TABLE 4: Seizure control outcomes by modified Engel and McHugh outcome classifications following VNS therapy in 128 children with complete follow-up*

Class	Modified Engel Description	No. of Pts (%)	McHugh Description	No. of Pts (%)
I	seizure-free; rare, nondisabling SPS	15 (11.7)	80%–100% reduction in seizure frequency	42 (32.8)
II	>90% reduction in seizure frequency; rare CPS	14 (10.9)	50%–79% reduction in seizure frequency	41 (32.0)
III	50%–90% reduction in seizure frequency	54 (42.2)	<50% reduction in seizure frequency	30 (23.4)
IV	<50% reduction in seizure frequency	45 (35.1)	magnet benefit only	2 (1.6)
V	—	—	no improvement	13 (10.2)

* CPS = complex partial seizure; SPS = simple partial seizure.

plications between children 12 years of age or older and those younger than 12 years of age (2 [3.6%] of 55 vs 1 [1.2%] of 86, $p = 0.56$, and 3 [5.5%] of 55 vs 3 [3.5%] of 86, $p = 0.69$, respectively).

Device Revisions and Removals

Forty-nine patients (34.8%) underwent a total of 61 device revisions after primary implantation at our center. Forty children had 1 revision, 9 children had 2 revisions, and 1 child had 3 revisions during the follow-up period. Of the 61 revision procedures, generator changes alone were performed in 51 cases and complete revision (generator and lead) in 10 cases. The most common indication for revision was generator power depletion, and it occurred at a

mean of 41.3 ± 18.1 months following implantation or last generator change (range 6.3–106 months). Lead fracture occurred in 4 devices, and the patients presented with delayed neck pain in synchrony with the duty cycle. In 2 patients, the indication for device revision included hardware displacement associated with an adolescent growth spurt. There were no complications following revision surgery.

At revision, generators were maintained in the subcutaneous location in 32 cases, maintained in the subpectoral location in 21 cases, and moved to a subpectoral location for improved cosmesis in 7 cases. A very short segment of the lead containing the electrodes is left attached to the vagus nerve during lead revisions.

Twenty-one children (14.9%) underwent device removal following primary insertion at our center at a mean time of 43.4 ± 29.4 months after insertion (range 8.5 months–9.5 years). Indications for device removal were nonefficacy (in 8 cases), MR imaging for possible or planned intracranial surgery (in 11 cases), infection (in 1 case), and AED success (in 1 case). There were no complications during device removal.

TABLE 5: Median seizure reduction by epilepsy classification, etiology, and EEG findings*

Variable	No. of Pts	Median Sz Reduction (%)	p Value†
epilepsy classification			
focal	5	86.2	0.042
MFPE	55	50.0	<0.001
MFPE/SGE	18	72.0	<0.001
SGE	41	62.5	<0.001
IGE	19	66.7	0.003
epilepsy etiology			
neuronal migration disorder	14	50.0	0.001
CP/static encephalopathy	15	68.9	0.016
LGS	11	51.0	0.008
infection	13	45.0	0.012
TSC	8	75.0	0.018
genetic/metabolic syndrome	14	66.7	0.003
unknown	54	65.0	<0.001
EEG findings			
focal	5	86.2	0.042
multifocal	62	54.6	<0.001
diffuse	61	64.8	<0.001
multifocal & diffuse	13	68	0.002

* CP = cerebral palsy; Sz = seizure.

† Analyzed via paired-samples Wilcoxon signed-rank test.

Discussion

Among 141 children with treatment-resistant epilepsy who underwent VNS device implantation, a 50% or greater reduction in seizure burden was achieved in over half of patients. While many patients noted hoarseness or pain during stimulation and the ramp-up period, most of these side effects resolved with time or alteration of stimulation parameters. Serious complications causing permanent neurological injury or leading to device removal were few (< 3%). Vagus nerve stimulation worked well for all types of epilepsy and age groups, including non-FDA approved indications like generalized epilepsies and in children under the age of 12 years. Purported markers of more severe epilepsy, such as duration of seizures, number of seizure types, number of failed AEDs, and failure of intracranial epilepsy surgery, did not correlate with VNS success.

Seizure Control and Development

Severe treatment-resistant epilepsy is associated with cognitive decline.^{14,49} In children with treatment-resistant epilepsy, better seizure control can result in improved

TABLE 6: Minor and major complications following VNS implantation in 141 children with treatment-resistant epilepsy*

Complication	<12 Yrs of Age (86 pts)		≥12 Yrs of Age (55 pts)		Total	
	Minor	Major	Minor	Major	Minor	Major
neurological	2	0	0	1	2 (1.4)	1 (0.7)
hoarseness	1	—	—	1	1 (0.7)	1 (0.7)
intractable cough	1	—	—	—	1 (0.7)	—
nonneurological	1	1	3	1	4 (2.8)	2 (1.4)
neck pain related to duty cycle	—	—	1	—	1 (0.7)	—
superficial infection (antibiotics)	1	—	1	—	2 (1.4)	—
deep infection (removal/revision)	—	1	—	—	—	1 (0.7)
seroma/hematoma requiring aspiration	—	—	1	—	1 (0.7)	—
pneumothorax	—	—	—	1	—	1 (0.7)
subtotals	3 (3.5)	1 (1.2)	3 (5.5)	2 (3.6)	6 (4.2)	3 (2.1)

* Values represent numbers of patients (%). Minor complications were those that were managed conservatively or resolved spontaneously. Major complications included permanent neurological deficits or complications that required device removal or other invasive procedures.

developmental and cognitive outcome and quality of life.^{13,18,27,28,31,54} Moreover, numerous studies found that VNS can benefit attention, cognition, behavior, mood, and quality of life independent of reduced seizure burden.^{1,22,24,25,35,41} These findings suggest that consideration of VNS earlier in the course of refractory disease is warranted.⁴²

No randomized studies have demonstrated long-term benefits of VNS therapy on cognitive, social, or behavioral development or quality of life. However, it is uniformly believed that reduction in seizure burden during the critical early development of children will yield important benefits in long-term functional outcome. Although some patients in our series experienced improvements in development and behavior, formal preoperative and postoperative neuropsychological assessments were not available to quantify this benefit.

Efficacy of VNS

Although most studies on the efficacy of VNS have involved adult patients, many smaller pediatric series have shown comparable results (Table 7).^{1,2,9,15,25,26,30,33,36–38,40,41,43,45,47,52,53} Like other authors,^{25,36,38,41} we found no difference in VNS efficacy in children younger than 12 years compared with older children. Analyzing the efficacy of VNS in children, Levy et al.³⁰ retrospectively queried the Cyberonics, Inc. registry and noted a mean reduction in seizure frequency of more than 55% at 12 months of therapy. After 3 and 6 months of VNS treatment, Helmers et al.²⁵ found that children exhibited a mean reduction in seizure burden of 36% and 45%, respectively. Murphy and colleagues³⁸ also reported at least 50% reduction in seizure burden in 45% of 100 children with treatment-resistant epilepsy at a median follow-up of 32 months. Alexouploulos and colleagues² reported a mean reduction in seizure burden of 60% and a > 75% reduction in 43.5% of patients. Our current study demonstrates similar results with a larger number of patients and a significantly longer follow-up (> 5 years).

Cost-savings analyses were performed in small series

of cases.^{6,11,12,32} Authors reported significant decreases in hospital admissions, length of stay, intensive care unit admissions, and emergency room visits and estimated that the cost of the device and implantation (roughly \$10,000) can be recovered within 2–3 years after initiation of VNS therapy.^{6,11,12,32} Given the long life expectancy of children, these results may translate into a significant cost savings over time.

Although seizure reduction and hospital costs are the major clinical and economic considerations when considering the cost-effectiveness of any therapy for treatment-resistant epilepsy, other potential benefits may be equally important. Ancillary benefits of seizure control in children include health-related quality of life and cognitive improvements, fewer epilepsy-related injuries, decrease in sudden unexplained death in epilepsy patients (SUDEP), psychological improvements in anxiety and depression, improved school attendance, improvements in social and interpersonal relationships, and decrease in AED burden and side effects.⁴

Complications and Cosmetic Considerations

Dysphonia, throat or neck pain, and cough during stimulation are the most commonly reported side effects of VNS. Typically, these symptoms abate with time or alteration of the stimulation parameters.^{2,3,19,36,44,50} Significant or permanent injuries to the vagus nerve or development of dysphagia following implantation were rare (< 0.5%) in our series, and the rate is comparable to rates reported for other series (≤ 4%). The rate of infection was under 3%, which is comparable to rates reported in most large series (0%–8%) and similar to those reported for other implantable devices. In corroboration of the results reported by Murphy and colleagues,³⁸ we found no difference in the rate of adverse effects in children younger than 12 years of age, compared with older children. This documentation of the safety of VNS in younger, smaller children is an important initial step toward expanding the FDA-approved indications for VNS.

Vagus nerve stimulation and childhood epilepsy

TABLE 7: Outcomes of VNS therapy in published case series involving pediatric patients*

Authors & Year	No. of Pts	Design	FU (mos)†	% Sz Reduct†	% Sz Reduct (% of pts)				Worse Szs (%)	Hoarseness (%)		VC Paral/ Dysphagia (%)	Neck/Throat Pain (%)			Infection (%)
					≥50	≥75	≥90	100		Trans	Perm		Trans	In-tract	Cough (%)	
Murphy et al., 1995	12	R	7.4	—	25	25	25	—	—	0	0	0	0	0	0	16.7
Hornig et al., 1997	19	R	3.5	—	53	—	32	5.3	11	100‡	0	0	0	0	0	0
Murphy et al., 1999	60	R	>18	42§	—	—	—	—	6	21.7	13	0	0	0	25	18.3
Patwardhan et al., 2000	38	R	12	—	68	—	29	—	—	—	—	—	—	—	—	—
Helmers, et al., 2001	125	R	3–6	45	51¶	—	—	0¶	2¶	57.9	0.8	0.8	1.1	—	37.9	—
Parain et al., 2001	10	R (TSC)	22	—	90	—	50	0	0	0	0	0	0	0	—**	0
Aldenkamp et al., 2002	19	R (LGS)	24	20.6	21	—	—	—	—	—	—	—	—	—	—	—
Zamponi et al., 2002	13	R	13.6	66††	77††	—	—	0	0	—††	0	0	7.7	0	—	0
Murphy et al., 2003	100	R	32.4	—	45	—	29	18	5	—	1	0	—	—	—	3
Smyth et al., 2003	74	R	26.4	—	—	—	—	—	—	1.4	0	1.4	0	0	1.4	7.1
Major & Thiele, 2005	12	R (TSC)	52.4	—	50	—	—	0	0	0	0	0	8.3	0	8.3	16.7
Alexopoulos et al., 2006	49	R	24	60	59	43.5	—	10.1	—	—‡‡	0	0	—‡‡	0	—‡‡	0
Benifla et al., 2006	41	R	31	—	41.5	—	38	—	0	14.6	2.4	0	—	2.4	14.6	4.9
Rychlicki et al., 2006	34	R	30.8	49¶¶ (61§§)	—	—	—	8.8	—	44.1	0	4	11.8	0	—	0
Zamponi et al., 2008	6	age <3 yrs	41.6	50.8	50	33.3	16.7	0	0	0	0	0	0	0	0	0
Rossignol et al., 2008	28	R	24	53§§	68	—	—	14	—	—¶¶¶	—	4.2	—¶¶¶	—	—¶¶¶	8.3
Shahawan et al., 2009	26	R	36	—	54	31	11.5	3.8	0	3.8	0	3.8	7.7	3.8	—	0
Elliott et al., 2009	8	R (TSC)	38.1	71.3	87.5	78.1	25	12.5	0	0	0	0	25	12.5	0	0
Levy et al., 2010 ^a																
Group A	315	registry	12	55.6	48.6	28.3	15.9	4.4	21.6	—	—	—	—	—	—	—
Group B	78	registry	12	62.5	48.7	29.5	18	5.1	19.2	—	—	—	—	—	—	—
present study	141	R	63.6	57.9	64.8	41.4	21.1	7.8	2.3	0.7	0.7	0	18	2.1	0.7 ^b	2.1

* All studies are retrospective in design. Abbreviations: FU = follow-up; Intract = intractable; Paral = Paralysis; Perm = permanent; R = retrospective; Reduct = Reduction; Trans = transient; VC = vocal cord.

† Mean or median values (with exception of duration of follow-up for Helmers et al. [range]).

‡ All patients had hoarseness during stimulation only.

§ At 18-month follow-up in 46 of 60 patients.

¶ At 6-month follow-up.

** Cough occurred when current was being increased but resolved with reduction in current. Number of cases was unreported.

†† At 3-month follow-up. All 13 patients experienced change in vocal timbre during stimulation but this was not a significant problem for the patients.

‡‡ 56.5% of patients experienced throat pain, hoarseness, cough, or drooling that resolved spontaneously or responded to changes in stimulator settings.

§§ At 24-month follow-up.

¶¶ Most children had minor side effects like throat or chest pain, voice change, dyspnea, coughing, or mild dysphagia.

^a Study was conducted via retrospective query of the voluntary registry of Cyberonics, Inc., and compared 315 children with treatment-resistant epilepsy (Group A) with 77 children with treatment-resistant epilepsy and autistic spectrum disorder (Group B). Mean seizure reduction recorded at 12 months following implantation.

^b Many children experienced coughing during the ramp-up period but only 1 patient had persistent cough with stimulation.

Compared with the potential neurological deficits from resective surgeries and the risk of disconnection syndrome from corpus callosotomy,⁴⁸ the relative risks of a “minimally invasive” and fully reversible procedure like VNS implantation are minor, often self-limited and well-tolerated by children. Importantly, the most common adverse effects associated with VNS (cough, voice change, and throat pain during stimulation) are not dangerous to the patient.

Another important factor when choosing VNS in children is the cosmetic impact of having a subcutaneous generator in the infraclavicular region. Children typically have less adipose tissue to cushion the generator and also may tend to tamper with the wound or device. We have previously described our technique for subpectoral insertion of the generator and noted increased soft-tissue coverage, improved cosmesis, lower risk of tampering or trauma, and a comparable risk of infection. We strongly believe the subpectoral technique for generator implantation should be considered in children, especially younger children.

Study Limitations

Our study was limited by the retrospective query into a prospective database and is subject to biases inherent to such methodology. Nearly 8% of patients were unavailable for follow-up. Determination of seizure frequency relied on the reports of patients or caretakers and is inherently subject to error and bias. This limitation is common to many studies measuring seizure frequency and treatment outcomes. We tried to improve our estimates by using LVCF (last value carried forward) analysis instead of declining-n analysis, which is prone to nonresponder attrition.⁵⁰

Detailed information on the effects of VNS on mood, quality of life, and qualitative aspects of seizures (duration, severity, clustering, postictal period, and magnet usage) were either not systematically reported or could not be derived from this retrospective analysis. Moreover, we did not determine if a mean reduction in seizures of nearly 50% translates into caretaker and patient satisfaction and overall improvements in quality of life. Future prospective studies are needed to better ascertain baseline mood assessments, quality-of-life metrics, and caretaker satisfaction and to determine the impact of VNS on these parameters and their relation to seizure control.

Another confound concerns the unknown impact that changes in AED regimens have on seizure frequency over time in the setting of VNS. Many office visits were accompanied by VNS setting changes and, more frequently, by AED regimen adjustments. We could not control for these changes but believe AED treatment plays a major role in the success of any treatment plan, including long-term VNS therapy. Further study is needed to better understand the relative contributions of effective VNS therapy, AED regimen adjustments, and regression to the mean.

To our knowledge, however, this is the largest case series involving VNS therapy in children with the longest reported follow-up duration (mean > 5 years) in the literature. Our treatment protocol and outcomes arise in

the setting of a high-volume epilepsy center using a multidisciplinary approach. Approximately 25%–30% of patients who are deemed surgical candidates at our center undergo VNS instead of intracranial epilepsy surgery. We agree with authors from other centers^{12,41} and stress that VNS—despite its apparent simplicity and safety—should be considered as a palliative treatment option for children with treatment-resistant epilepsy but only after thorough evaluation to exclude those children who may benefit from intracranial surgery.

Conclusions

Vagus nerve stimulation is a safe and effective palliative treatment option for treatment-resistant partial and generalized epilepsy in children. When it was used as part of a multidisciplinary and multimodality treatment regimen including aggressive AED regimens and epilepsy surgery, more than 50% of children with treatment-resistant epilepsy experienced at least a 50% reduction in seizure burden. Given the potential for developmental, cognitive, and behavioral improvement with or without improved seizure control, VNS should be considered early in the course of treatment-resistant epilepsy for possible improved outcomes and quality of life. The rate of complications and VNS efficacy were similar in patients younger than 12 years of age and those 12 years of age or older. Prospective, randomized trials are needed for patients with generalized epilepsies and for younger children to potentially expand the FDA-approved population of patients who may benefit from this palliative treatment.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Elliott, Doyle. Acquisition of data: Elliott, Morsi, Doyle. Analysis and interpretation of data: Morsi, Geller, Carlson, Devinsky, Doyle. Drafting the article: Elliott, Rodgers, Bassani, Morsi, Carlson. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Elliott. Administrative/technical/material support: Geller, Devinsky, Doyle. Study supervision: Devinsky, Doyle.

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