The Israeli Retrospective Multicenter Open-Label Study Evaluating Vagus Nerve Stimulation Efficacy in Children and Adults

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ABSTRACT: **Background:** The management of intractable epilepsy in children and adults is challenging. For patients who do not respond to anti-epileptic drugs and are not suitable candidates for epilepsy surgery, vagal nerve stimulation (VNS) is a viable alternative for reducing seizure frequency.

Methods: In this retrospective multicenter open-label study we examined the efficacy and tolerability of VNS in patients in five adult and pediatric epilepsy centers in Israel. All patients had drug-resistant epilepsy and after VNS implantation in 2006–2007 were followed for a minimum of 18 months. Patients were divided into two age groups: ‹ 21 and › 21 years old.

Results: Fifty-six adults and children had a stimulator implanted in 2006–2007. At 18 months post-VNS implantation, none of the patients was seizure-free, 24.3% reported a reduction in seizures of ≥ 75%, 19% reported a 50–75% reduction, and 10.8% a 25–50% reduction. The best response rate occurred in patients with complex partial seizures. Among these patients, 7 reported a ≥ 75% reduction, 5 patients a 50–75% reduction, 3 patients a 25–50% reduction, and 8 patients a ‹ 25% reduction. A comparison of the two age groups showed that the older group (‹ 21 years old) had fewer seizures than the younger group.

Conclusions: VNS is a relatively effective and safe palliative method for treating refractory epilepsy in both adults and children. It is an alternative treatment for patients with drug-resistant epilepsy, even after a relatively long disease duration, who are not candidates for localized epilepsy surgery.

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In recent years vagus nerve stimulation has become an accepted method to treat patients with refractory epilepsy who are not candidates for epilepsy surgery or in whom surgery has failed [1]. From the accumulated experience of centers using VNS, one-third of patients have a reduction in seizure frequency of at least 50%, another third have a lower but still significant reduction, while in the remaining third there is little or no effect [2]. Despite increasing clinical data, it is still not possible to predict which patients will benefit from VNS. Identifying prognostic factors possibly related to outcome is needed due to the invasive nature of the procedure, the possible hazards of chronic implantation, and the relatively high cost of the treatment [3,4].

Two studies compared the duration of a patient's epilepsy and the results of VNS and found that patients with a history of epilepsy exceeding 6 years had a significantly smaller chance of being seizure-free on VNS treatment than those with a less than 6 year history of epilepsy [5-8]. Different studies have also reported adverse effects related to VNS implantation and treatment, with rates ranging from 3% to 13.3% [8,9]. Frequently reported complications include interruption of stimulation due to mechanical injury to the electrode, hoarseness, dysphonia, dysphagia, transient tingling sensations or coughing, local inflammation at the insertion area, and transient vocal cord paralysis.

This retrospective multicenter study conducted in Israel summarizes data from 42 adults and children implanted with VNS and evaluated at least 18 months post-surgery. Previously reported predictive factors were used to assess procedure success as measured by a reduction in seizure frequency.

VNS = vagus nerve stimulation

Table 1. Stimulation parameters

	Stimulation current (mAmp)	Pulse width (μsec)	Stimulation frequency (Hz)	Stimulation On time (sec)	Stimulation Off time (sec)
Mean	1.13	406.25	24.22	25.63	195.38
Median	1.00	500	22.50	30.00	180.00
Minimum	0.25	250	10	10	18
Maximum	2.00	500	30	30	200

PATIENTS AND METHODS

A retrospective multicenter open-label study examined the efficacy and tolerability of VNS in patients from five adult and pediatric epilepsy centers in Israel. Seizure intractability was defined as failing two different anti-epileptic drug treatments and having at least one seizure per month for 18 months. VNS implantation was performed between 2006 and 2007 and patients were at least 18 months post-surgery.

PATIENT POPULATION

The patient population derived from both pediatric and adult epilepsy clinics. Patients were classified by age into two groups: 7–21 years old (group 1) and 22–53 years (group 2). Prior to VNS implantation, all patients underwent a detailed clinical evaluation, brain magnetic resonance imaging, and electroencephalography or video-EEG. Video-EEG monitoring was performed in 13 of the 42 patients to characterize their seizures and epilepsy syndromes, while the other 12 had repeated EEGs that were sufficient to diagnose their epilepsy syndrome or seizure semiology. Epileptic syndrome diagnoses were made in accordance with accepted ILAE (International League Against Epilepsy) definitions [3].

FOLLOW-UP PROTOCOL AND DATA COLLECTION

Identical questionnaires were sent to all participating physicians between April and November 2008. For each patient, data related to epilepsy syndrome, pre-implant seizure frequency, prior surgical procedures, duration and type of seizures after implant, anti-epileptic drugs before and after implantation, concurrent medication dose changes, and complications during the procedure or during the device settings. Reported changes in mood, behavior and sleep quality were also recorded.

Chronic stimulation began within 2–4 weeks of surgery. The output current was increased for each patient according to clinical status and adverse events. The VNS stimulation parameters were adjusted in line with standard medical practice for implanted patients. Initial stimulation parameters were: output current = 0.25 mA, frequency = 30 Hz, pulse width = 500 μs, On/Off cycle of 30 seconds On and 3 or 5 minutes Off. The On/Off cycle was also changed based on the clinical condition of each patient.

EEG = electroencephalography

Magnet output was started at 0.50 mA with a pulse width of 500 ms and an On-time of 60 seconds. The stimulus intensity was increased stepwise by 0.25 mA up to a maximum of 2.00. Stimulation parameters were analyzed at the last follow-up visit in 36 of the 42 patients. The range of the output current was 0.5–2.00 mA (mean 1.43 ± 0.41 mA). The range of the duty cycle was 10%–35% (from 30 sec On/5 min Off to 30 sec On/1.1 min Off). The most frequent duty setting (n=20) was 30 sec On/3 min Off [Table 1].

Assessment also included a quality of life questionnaire (reported by the patients or their caregiver), and a question on the general impression of the physician regarding the well-being of the patient before and after implantation. Reported side effects, duration, and the procedures undertaken to correct them were also listed. Since VNS has been reported to possibly worsen normal sleep patterns by aggravating obstructive sleep apnea in both children and adults, questions were included on the subjective sleep quality of the patients.

OUTCOME EVALUATION

The primary objective of this retrospective study was to evaluate the efficacy of VNS in reducing various types of epileptic seizures after 18 months of stimulation and to identify possible predictive factors related to efficacy. Reductions in seizure rates after VNS implantation were classified as follows: < 25%, 25–50%, 50–75%, and > 75%.

STATISTICAL ANALYSIS

We performed a statistical analysis of the change in seizure frequency at predefined visits. Wilcoxon signed ranks test was performed to evaluate the differences between individual visits. SPSS 13.0 was used to perform the statistical analysis. $P < 0.01$ was considered statistically significant.

RESULTS

PATIENT POPULATION

Altogether, 56 adults and children were implanted from June 2006 to December 2007. Only 42 patients had at least 18 months of comprehensive post-implant medical data. Ages ranged from 7 to 53 years (mean SD 36.4 ± 21.6 years). There were 22 patients, 12 males and 10 females, younger than 21 years old (group 1), and 22, 11 males and 11 females, older than 21 years (group 2). Fourteen patients from the original group of 56 were excluded due to insufficient medical data or the lack of 18 months follow-up. Group 1 included 14 patients who were mentally retarded and 4 who had learning disabilities with normal cognition. Group 2 comprised 11 patients diagnosed as having mild-to-moderate mental retardation with the remaining 9 having no mental impairment.

Since the total number of patients was small and ethnically as well as economically diverse, no assessment of socioeco-

Figure 1. Etiology of seizures (n=34)

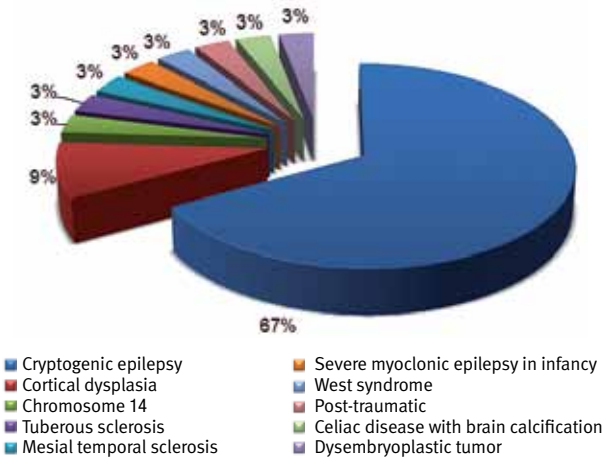
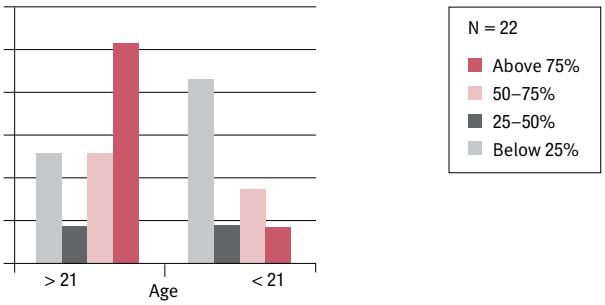


Figure 2. Seizure reduction according to age group



nomic impact following VNS implantation could be undertaken. The age of epilepsy onset ranged from 2 months to 39 years (mean 9.7 years).

Mean duration of epilepsy at the time of VNS implantation was 14.8 years in group 1 and 30.2 years in group 2. Using the ILAE classification system, 33% had remote symptomatic epilepsy while the remaining 67% were defined as cryptogenic epilepsy [Figure 1]. The most common seizure type in both patient groups was complex partial seizures.

Patients were treated with four to eight anti-epileptic drugs prior to VNS surgery, a mean of 6.8 drugs per patient, an indication of the population's intractability. No statistical difference was found between the number of anti-epileptic drugs in either of the age groups, or between male and females before and after the implant. Nine patients in Group 1 and six in group 2 had been treated with a ketogenic diet with varying degrees of success. Prior to VNS implantation, epilepsy surgery had been attempted with unsatisfactory results in four of the group 1 patients and three of the group 2 patients.

SEIZURE REDUCTION

At 18 months post-VNS implantation none of the patients was seizure-free. There was a reduction in overall seizure frequency, with 24.3% reporting a ≥ 75% reduction, 19% a 50–75% reduction and 10.8% a 25–50% reduction

SEIZURE ACCORDING TO ETIOLOGY

In the symptomatic group, one patient with mesio-temporal sclerosis and one with cortical dysplasia reported a ≥ 75% reduction in seizure frequency. One patient with brain calcification secondary to celiac disease had a 50–75% reduction and one patient with cortical dysplasia reported a 25–50% reduction. Five other patients with different seizure etiologies reported a < 25% reduction. In the cryptogenic group, 6 patients reported a ≥ 75% reduction, 5 patients a 50–75% reduction, 8 patients a 25–0% reduction and 8 patients < 25%. The correlation between the reduction in seizures and the reported seizure etiology was examined. The best improvement in seizures was reported in patients with complex partial seizures, all of whom were in the cryptogenic group (22 of 27 patients). In the complex partial seizures group, 7 patients reported a ≥ 75% reduction in seizure, 5 patients a 50–75% reduction, 3 patients a 25–50% reduction and 8 patients < 25% reduction.

A comparison of seizure reduction between group 1 (< 21 years old) and group 2 (≥ 22 years) showed a ≥ 75% seizure reduction in one patient in group 1 versus six in group 2, a 50–75% reduction in one patient in group 1 vs. three in group 2, a 25–50% reduction in two in group 1 vs. one in group 2, and < 25% seizure reduction in five in group 1 vs. three in group 2 [Figure 2].

QUALITY OF LIFE

Quality of life was assessed 18 months post-VNS implantation using the Quality of Life Inventory version 4.04. All questionnaires were routinely filled by the treating epileptologist during the patients' follow-up visits. Of the 35 patients or families who answered the question on quality of life, 29% in group 1 and 32% in group 2 reported an improvement. Improvement in quality of life was not found to be correlated with degree of seizure reduction.

Assessment of sleep problems was taken from the primary caregiver's report for children using a sleep-validated questionnaire from Ferber and Kryger's *Principles and Practice of Sleep Medicine in the Child*. For adult patients we used their own report of their sleep quality. These reports were also completed 18 months post-implant in all the participating hospitals. Of the 32 patients who answered the question on their quality of sleep, 31 did not report any changes. Only one patient reported a subjective feeling of sleep worsening and was referred for a sleep study, which did not reveal any sleep abnormality.

ILAE = International League Against Epilepsy

Table 2. Side effects and complications

Side effects	No. of patients
Behavior problems	2
Tingling	5
Cough	4
Hoarseness	4
Dysphagia	1
Device removal	3

COMPLICATIONS

Data on possible side effects and complications of VNS therapy were gathered from the chart at each post-implant visit. Minor side effects including vocal alterations during stimulation were observed in two patients, and a sensation of tingling or hoarseness was reported by nine patients. Varying degrees of coughing were reported in four patients. All these complaints started when patients reached the output current of 1 microampere (mA) during VNS stimulation. A reduction in the output by 0.25 mA for 2 weeks to 1 month resolved these complaints. Three devices had to be removed prematurely. In two cases the implant was removed because of wound infections resistant to intravenous antibiotics. In three cases the device was removed following the parent's request due to pain at the generator site and lack of improvement in seizure control [Table 2].

DISCUSSION

This multicenter study reviews the clinical data of a group of children and adults with intractable epilepsy implanted with VNS in Israel. All patients had a minimum of 18 months follow-up after implantation. Although none of the patients were seizure-free after VNS implantation, 24.3% reported a 75% or more reduction in seizures, 19% a 50–75% reduction and 10.8% a 25–50% reduction. This is comparable to other studies of mixed populations of children and adults, which report a ≥ 50% reduction of seizure frequency in 40–50% of patients and very infrequent complete seizure freedom [10].

No particular seizure type is reported in the literature to have a significantly better seizure reduction with the use of VNS therapy [11]. Previous studies found that patients aged 21 years and older with complex partial seizures had better seizure control with up to 75% reduction than patients with other seizure types [11,12].

Data on the efficacy of VNS in children are less extensive than for adults. The small number of articles show that children under age 16 have particularly low response rates when compared to older age groups [13,14]. Some of these studies also report a very poor response among children under 16 with Lennox-Gastaut syndrome [15]. Some studies noted that children with severe learning disabilities and more disturbed EEG background patterns responded less favorably to VNS therapy [16,17]. In the present study, the best response rate occurred in patients with cryptogenic complex partial seizures as compared to patients with different forms of symptomatic epilepsies. This finding is supported by other authors who found that patients with complex partial seizures respond relatively better to VNS implantation than other forms of epilepsy [18]. It must be remembered, however, that most of these studies were observational non-randomized open-label trials. Benifla et al. [19] described their experience with VNS implantation at the Hospital for Sick Children in Toronto. They noted that after a mean follow-up of 31 months, 38% of the patients had a reduction in seizure frequency of more than 90%. They also observed that 38% of children were non-responders. Murphy [20] reported that 45% of the children with VNS experienced > 50% reduction in seizure frequency at 6 months, with 18% of the children being seizure-free [20]. Rossignol and colleagues [21], who followed a cohort of 28 adolescents and children implanted with VNS for non-surgical refractory epilepsy, found that 68% experienced a > 50% reduction in seizure frequency at 2 years, with 14% being seizure-free.

Several articles discuss seizure outcome and pre-surgical duration of epilepsy [19]. Murphy [20] found that the outcome in patients with epilepsy duration of either less than or more than 7 years was not significantly different [20]. A larger study by Colicchio and co-authors [8] examined VNS efficacy in 135 patients with refractory epilepsy, of whom 81 were children. The children's cohort consisted of patients with Lenox-Gastaut syndrome, multifocal epilepsy, and partial epilepsy. All experienced a statistically significant reduction in seizure frequency, with an increase in response over time. In contrast, and supporting the notion that early implantation results in better outcome, Helmers et al. [22], who conducted an analysis of outcome data in the Cyberonics VNS patient registry, found significantly better outcomes in patients treated with VNS within 6 years of seizure onset. In the current study, the mean duration of epilepsy at the time of VNS implantation was 14.8 years in group 1 and 30.2 years in group 2. This prolonged time before implantation is due to the fact that VNS technology was only introduced and approved by Israel's Ministry of Health in 2006, and awareness of the potential benefits of this procedure within the Israeli medical community is recent. Despite the prolonged time to implantation, the overall reduction in seizures did not show any significant difference in outcome compared to other reports in the literature where implantations took place earlier. This finding summarizes results of the first children and adults groups with intractable epilepsy, emphasizing that even children and adults with prolonged epileptic disease can be good candidates for VNS implantation [23].

We speculate that since VNS implantation will be accepted in Israel as a means of treating intractable epilepsy, physicians will likely refer patients earlier than previously. We may then

see better reductions in seizure frequency and outcome as these patients will have fewer years of the "epileptic burden."

The stimulation parameters in this study were in the same range as those of other controlled studies [25]. Data showing the relationship between chronic response and stimulation parameters of VNS are still lacking. Improvement or change in the perception of quality of life was reported in only some of the responding patients: 29% in group 1 and 32% in group 2. Other studies have shown that VNS therapy may have a positive effect on mood and behavior, often independent of reduction in seizure frequency [21]. The relatively small number of patients in both groups who reported improvement in quality of life may indicate that more time after VNS implantation is needed to reflect a positive effect on life quality or, alternatively, that the question was not appropriately presented.

One of the most discussed issues in VNS implantation is safety and tolerance during the implantation procedure, as well as acute and chronic adverse effects of stimulation [5,8]. Side effects of various severities have been reported in 5.4–80% of cases in several studies in children and adults [25]. The complication rate in our study is comparable to others, as removal of the device occurred in only three patients due to late postoperative infection or lack of effectiveness. Other side effects such as cough, tingling around the neck, and hoarseness were mild and in all cases resolved spontaneously several weeks after implantation.

CONCLUSIONS

We reviewed the Israeli experience with VNS therapy for refractory epilepsy in children and adults with a minimum follow-up of 18 months. We found VNS to be modestly more helpful in patients with complex partial seizures due to cryptogenic (idiopathic) causes and in patients in the relatively older age group. Despite its limitations, the merits of this study include a relatively large number of patients with lengthy follow-up of up to 18 months post-implantation. As shown here, VNS should be considered a palliative surgical procedure for patients with drug-resistant epilepsy, even after a relatively long duration of disease, who are not candidates for localized epilepsy surgery.

We speculate that as VNS implantation will become an available and recognized treatment in Israel, implantation will be considered somewhat earlier, which may improve the outcome.

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