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Clinical outcomes of closed-loop vagal nerve stimulation in patients with refractory epilepsy

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ABSTRACT

Purpose: The AspireSR® is a vagal nerve stimulation (VNS) device that operates as a closed-loop system, delivering an automatic stimulation in response to an ictal heart rate increase that serves as a predictor for an imminent seizure.

Our purpose is to assess the outcome of the AspireSR® in a patient population managed in a pediatric neurology unit.

Methods: The records of patients who underwent transplantation during 2015–2017 and are continuously followed in one pediatric-epilepsy clinic, were retrospectively analyzed. Collected information included demographics, use of antiepileptic drugs and seizure type, frequency and duration before and after VNS implantation.

Results: 46 patients ages 5–31 years (mean 15.7 ± 5.8), mean age at implantation 14 ± 5.8 years, were included. 29 patients (63%) were new insertions and 17 of the patients (37%) underwent a VNS replacement to the AspireSR® model. Mean follow-up was 13 ± 7.5 months (range 2–29 months). The total cohort responder rate (patients with ≥50% reduction in seizure frequency compared to the pre-implantation period) was 60.9%. (62% in the new insertion group; while 59% in the replacement group had additional benefit over their former VNS model, p = 0.981). Epilepsy etiology, age, age at implantation and type of seizures pre-implantation showed no correlation to response-rate. Five patients (10.9%) experienced complete seizure-freedom following implantation (4/5 in the "new insertion" group). Responses were reported at median follow up of 5 ± 1.3 months post-implantation. 67.4% experienced shorter seizure duration post-implantation.

Conclusion: Our results suggest that the AspireSR® device provides an early and meaningful benefit to drug-resistant epilepsy patients, which is relevant for both patients with new insertions and those with replacements of former VNS devices.

1. Introduction

Epilepsy is a group of neurological disorders characterized by recurrent epileptic seizures with a prevalence rate of 0.5%–1% among children [1]. Most patients are successfully treated with anti-epileptic drugs, but about a third suffer from treatment-resistant epilepsy (TRE) [2]. Vagal nerve stimulation (VNS), approved by U.S Food and Drug Administration (USFDA) in 1997, is a safe and efficacious treatment for TRE, consisting of an implanted pacemaker-like generator and nerve stimulation electrodes, that delivers intermittent stimulation to the patient's left vagus nerve [2]. The indication for use of VNS outside of the U.S. is as an adjunctive therapy for reducing the frequency of seizures in TRE patients whose epileptic disorder is dominated by partial or generalized seizures once resective surgery is deemed not a viable option [3]. The mechanism of effect of VNS is currently unclear, but several pathways have been proposed and studied so far, including an increase in the release of neurotransmitters, such as norepinephrine and serotonin, increased cerebral blood flow to the thalamus and cortex and desynchronization of the alpha rhythms, as observed on EEG [4].

The first model of VNS device delivered stimulation in an open-loop fashion, consisting of continuous ON-OFF cycles with an on-demand stimulation magnet allowing patients and their caregivers to interrupt seizure activity by passing a hand-held magnet over the implanted device [5]. The reported responder rate of the open-loop VNS treatment

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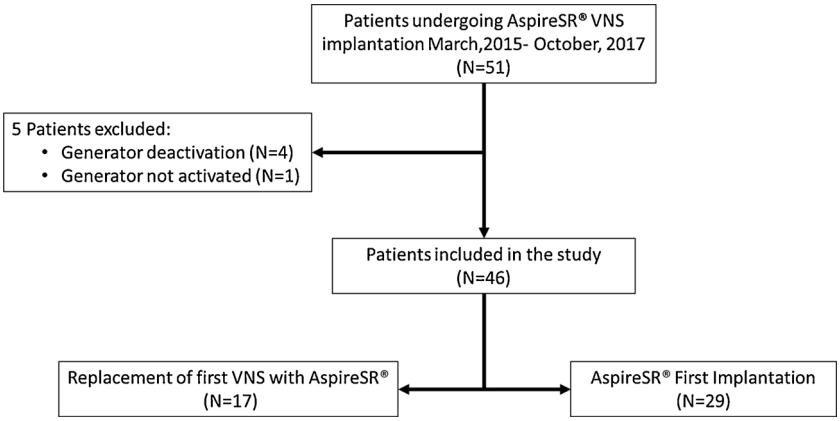

Fig. 1. Study flow chart.

varies between different studies, but according to a research done on 347 children, stands at 43.8% [6]. Elliott et al. have found VNS efficacy to be highest in patients suffering from partial seizures [2]. As for the magnet on-demand stimulation, it resulted in complete termination of seizures in 16.1% of children and adolescent patients, and a partial effect in 73.2% of them [7].

In 2015, based on observations that 82% of epileptic patients present ictal or pre-ictal increases in heart rate (HR), a novel cardiac-based seizure detection algorithm was developed and incorporated into a new VNS model – VNS AspireSR® (SR - seizure response). The AspireSR® provides, in addition to the standard open-loop VNS features, an additional automatic vagal stimulation which is triggered in response to ictal HR increase of at least 20% and delivered in a closed-loop fashion [5]. In the E-36 study, a prospective study conducted by Boon et al, on 31 adult patients (ages 19–66 years), the sensitivity of HR-increase detection of this new model was found to be above 80% for at least one of the algorithm settings, and the automatic stimulation has immediately terminated 58.8% of the seizures [5]. It should be noted that the algorithm is designed to detect rapid HR changes, and thus, it distinguishes the dynamics of HR-increases associated with seizure activity from those associated with physical activity. Of all seizure types, focal onset seizures with impaired awareness were found to be more likely to be associated with higher HR-increases [9]. Furthermore, it has been found that earlier automatic stimulation following the ictal HR, was correlated with shorter duration seizures [10].

The U.S. E-37 trial, was one of the first studies performed to evaluate the AspireSR® clinical outcomes. It recruited 20 adult subjects (ages 21–69) with drug-resistant partial onset seizures and a history of ictal tachycardia. The study has found the responder rate to be 20%, 35%, and 50% at 3, 6, and 12 months follow-up respectively, higher than those reported following standard VNS therapy [9]. Seizure severity rated on a physician-scored severity scale as well as reported by patients and caregivers was significantly reduced at all three follow-up periods. Additionally, several quality of life indicators in epilepsy such as cognitive function and seizure worry showed significant improvement compared to baseline.

The aim of our study was to assess the long-term outcomes of AspireSR® therapy in a real-world patient population managed in a pediatric neurology unit. We describe findings from a retrospective cohort study performed in order to further understand the AspireSR® therapy effects on seizure profile.

Our primary objective was to examine the responder rates following implantation. We further sought to determine whether reduction of seizure frequency occurs with AspireSR® earlier post insertion than with the standard open-loop model VNS. An evaluation of a subgroup of patients who underwent open-loop VNS to AspireSR® replacement is also presented.

2. Materials and methods

2.1. Eligibility criteria

The study included patients that were referred to VNS AspireSR® implantation from the Pediatric Neurology Unit at Chaim Sheba Medical Center between March 2015 and October 2017 (N = 51). Indications for VNS implementation were resistance to ≥3 anti-epileptic medications in patients which were not considered appropriate candidates for epilepsy surgery. The indication for replacement of a previous VNS was insufficient reduction in seizure frequency with the existing devise, or in patients who approached battery expiration time. Eligibility criteria for the study included a minimum of 4 months of follow-up following device activation for naïve patients (patients whose closed-loop VNS was their first device), whereas those who had their VNS replaced, were eligible immediately following implantation. Five patients were excluded from the study, four of them due to generator deactivation, and one whose generator was never activated.

In total, 29 patients (63%) were first insertions and 17 patients (37%) underwent a VNS replacement to the new AspireSR® model (Fig. 1, Flow chart).

2.2. Device parameters

AspireSR® parameters were adjusted by the primary epileptologist during the follow-up according to a formal protocol, until steady therapeutic parameters were achieved (Table 1). For duty cycle, the mean was 20.2 ± 9.8% ON time, mean AC output current was 1.4 ± 0.55 mA. The means were calculated for parameters derived

Table 1
: Programmed device parameters.

Duty Cycle	% ON Time	N (%)
	10	16 (34.8%)
	15	1 (2.2%)
	16	15 (32.6%)
	25	10 (21.7%)
	35	4 (8.7%)
AC	**Output Current (mA)**	
	0.5	1 (2.2%)
	1.3	2 (4.3%)
	1.5	28 (60.9%)
	1.8	14 (30.4%)
	1.9	1 (2.2%)
Sensitivity	**Heart Rate Increase (%)**	
	20	30 (65.2%)
	30	14 (30.4%)
	40	2 (4.3%)

from the programmers at the Pediatric Neurology unit. In 65% of patients, device was set to a threshold of 20% increase in HR, in 30.4% of patients to 30% increase in HR and in 4.3% of patients to 40% increase in HR.

2.3. Study design

This was a retrospective cohort study. Data were collected on December 2017 from the computerized medical record system of Sheba Medical Center. Seizure frequency and duration data were obtained by reports from patients and caregivers, for the period following completion of device-adjustment/tuning. For patients who replaced a former standard VNS device with the AspireSR®, baseline was defined as the period following implantation of the original VNS device. Categories of reduction of seizure frequency following AspireSR® VNS implantation were: 25%, 50%, 75% reduction or complete seizure-freedom. The primary objective was the responder rate, the proportion of patients who experienced ≥ 50% seizure frequency reduction. Any patient who experienced ≥25% seizure frequency reduction was considered to have benefited from the AspireSR®. For this population, time to onset of frequency reduction was measured in months.

2.4. Statistical analysis

Categorical variables were described as frequency and percentage. Continuous variables were evaluated from normal distribution using histogram and reported as median and interquartile (IQR) range. Kaplan-Meyer curve was used to describe improvement during follow-up time. Mek-Nemar test was used to compare the duration of seizures between the periods prior to and following implantation. Mann-Whitney test was used to compare ordinal and continuous variables between implantation and re-implantation. Categorical variables were compared between implantation and re-implantation using Fischer exact test or Chi-square test. Etiology frequency was calculated by Kruskal-Wallis test. Seizure type was analyzed by Mann-Whitney test.

All statistical tests were two-tailed and p-values < 0.05 were considered as statistically significant. SPSS software was used for all analyses (IBM SPSS Statistics, version 23, IBM Corp., Armonk, NY, USA, 2015).

3. Results

3.1. Study population

The study was conducted at a pediatric neurology unit; however, 14 (30%) of the patients continued their follow-up and management in the unit into their adulthood (mainly those suffering from intellectual disability). Therefore, the analyzed cohort was comprised of 46 patients ages 5–31 years (mean 15.7 ± 5.8 years) of whom 30 (66%) were ≤18 years old. The mean age at implantation was 14 ± 5.8 years. There was no statistically significant difference between the first implantation and the VNS replacement cohorts in age, age at implantation, etiology of epilepsy or type of seizures. 52% of the patients (n = 24) suffered from intellectual disability. Mean follow-up was 13 ± 7.5 months (range 2–29 months). The demographic and clinical characteristics of the study population are presented in Table 2.

Mean number of anti-epileptic drugs (AEDs) failed prior to the implantation among patients was 4 ± 1.5. Patients were classified according to seizure types reported prior to the AspireSR® implantation; patients with several types of seizures could belong to more than one group. Sixty one percent of the study population reported Generalized Onset Seizures (Table 2).

3.2. Rate of responders

In total, after a mean follow-up of 13 months, the responder rate (patients with ≥50% reduction in seizure frequency) was 60.9% (28 patients) (Table 3). Five patients [10.8% of cohort] (of whom 4 had their first implantation) were seizure-free following the AspireSR® treatment. In addition, 31 patients (67.4%) experienced shortening of seizure duration following AspireSR® implantation.

Among patients for whom the AspireSR® was the first VNS, the responder rate was 62%. Among those who replaced a previous VNS with the AspireSR®, 59% experienced ≥50% reduction in seizure frequency compared to the period with the former VNS (p = 0.981).

Table 2
: Demographic and Clinical Characteristics of Study Population.

Variable		
Children (< 12 years) N (%)	13 (28%)	
Children (< 18 years) N (%)	30 (65%)	
Adults N (%)	14 (30%)	
Age mean (range)	15.7 (5-31)	
Age at VNS Implantation mean (range)	14 (4-29)	
VNS Replacement N (%)	17 (37%)	
Intellectual Disability N (%)	24 (52%)	
Prior epilepsy Brain Surgery N (%)	3 (7%)	
Etiology N (%)		
	Genetic	14 (30.4%)
	Immune	6 (13%)
	Infectious	1 (2.2%)
	Structural	10 (21.8%)
	Unknown	15 (32.6%)
No. of Failed Anti-Epileptic Drugs N (%)		
	2	3 (6.5%)
	3	5 (10.9%)
	4	8 (17.4%)
	5	7 (15.2%)
	6	23 (50%)
No of Failed Ketogenic Diet N (%)		10 (21.7%)
No of Failed CBD N (%)		17 (37%)
Types of seizure	Generalized Onset Seizures	61%
	Focal Onset with Impaired Awareness	25%
	Non motor Seizure	13%
	Myoclonic Seizures	4%
	Focal Onset Seizures	2%

Table 3
: Rates of Response (Reduction in Seizure Frequency).

Categories of Reduction* in Seizure Frequency	N (%)
No reduction	13 (28.3%)
≥25%	33 (71.7%)
≥50%	28 (60.9%)
≥75%	18 (39.1%)
Complete elimination of seizures	5 (10.9%)

* Compared to the Period preceding the AspireSR device implantation.

3.3. Time to response onset

Time to response onset, analyzed with the Kaplan-Meier method, is presented in Fig. 2. 65% of the patients responded within the first 6 months following AspireSR® implantation. Median time to improvement was 5 ± 1.3 months. Statistical analysis revealed no effect of etiology of epilepsy or type of seizure on time to response.

Seizure reduction was first noticed within 3 months after implantation in the majority of the VNS replacement cohort (53%), as compared to 6 months or less for most of the first implantation cohort (55%). Mann-Whitney test revealed that those who underwent VNS replacement to AspireSR® responded significantly faster after device activation (shorter onset period), than patients who had their first implantation (p = 0.028). Nevertheless, the responder rates at the end of

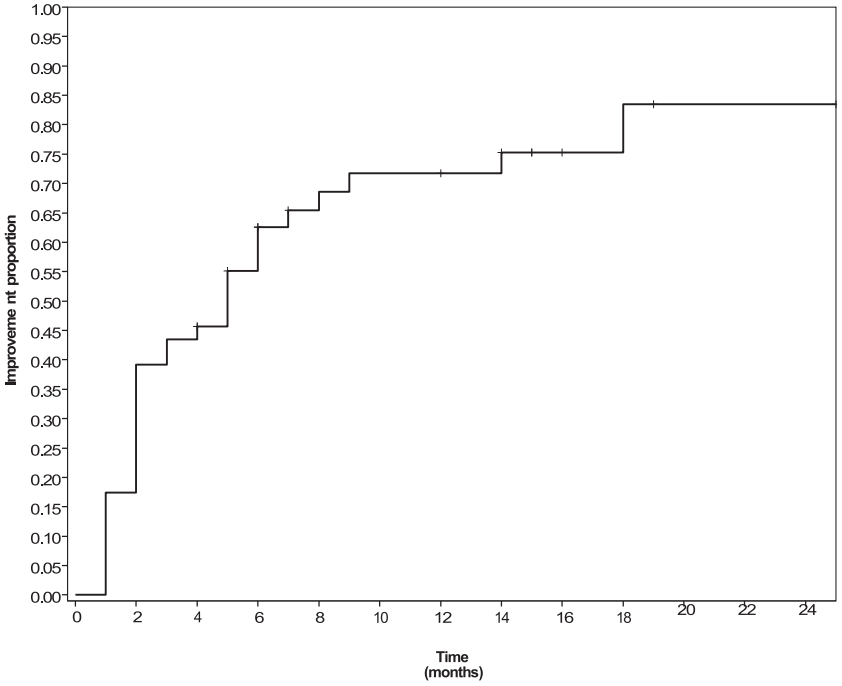

Fig. 2. Time to response.

follow-up were similar across the two cohorts (62% for the VNS replacement group vs. 59% for the first implantation group).

4. Discussion

In this study, we retrospectively analyzed the efficacy of AspireSR®, a VNS device that operates as a closed-loop system, delivering an automatic vagal stimulation in response to an ictal HR increase of at least 20% that serves as a predictor for an imminent seizure [5]. The responder rate in our population was 60.9%. In this cohort of patients with severe epilepsy, resistant to multiple anti-epileptic drugs, 5 patients (10.9%) became seizure-free following implantation, providing strong evidence for the efficacy of the therapy. In addition, 67.4% of patients experienced shortening of seizure duration.

Among the first-insertion cohort, 62% were responders, and 59% of patients who replaced a previous VNS with the AspireSR®, experienced ≥50% reduction in seizure frequency on top of any benefit provided by the former VNS. This is of specific importance showing the added value of the AspireSR® device over the previous open loop model especially when taking into account that patients who agreed to replace a VNS with a newer model are most likely those who have experienced improvement with their previous one.

In our study, improvement was observed early, at a median follow-up time of 5 months, and a responder rate of 60.9% was achieved after a maximal follow-up of 29 months. Response was achieved faster among the replacement cohort than the new-insertion cohort, suggesting a potential cumulative effect. The rapid, relatively high rates of response and seizure freedom in our cohort may be attributed to the higher device sensitivity threshold that we used. At the end of the device ramping-up period, < 5% of the study population remained with our initial device setting of a threshold to 40% increase in heart-rate. Close to 95% of devices were set to a threshold of 20–30% increase in ictal HR. The increased sensitivity of the Auto-Stimulation was not accompanied by elevated rates of adverse effects. Moreover, in none of the patients worsening of seizures was reported after implantation.

A few studies have retrospectively analyzed the data of pediatric drug-resistant epilepsy patients, following the implantation of a standard open-loop VNS. Elliott and colleagues evaluated 141 consecutive cases and found a response rate (≥50% reduction in seizure frequency) of 64.8%, of which 41.4% of patients reported a reduction of ≥75% [2]. Orosz and co-authors analyzed the data of 347 cases and found responder rates of 32.5%, 37.6%, and 43.8% at 6, 12, and 24 months after implantation, respectively [6]. Majkowska-Zwolińsk and group have analyzed the data of 57 cases, and found responder rates of 46.4%, 50% and 55.6% at 6, 12, and 24 months [7]. The difference in responder rate between these studies may be correlated to the differences in follow-up periods, as response to VNS has been found to increase progressively with time [11]. In the Elliott study, the mean duration of VNS therapy was 5.3 ± 3.1 years for the entire cohort (range 25 days–11.4 years), compared to a maximal 2 years in the Orosz and Majkowska-Zwolińsk studies. The positive effect that we observed in our patients with the closed-loop VNS was obtained sooner: response was observed at a median follow-up of 5 months post-implantation.

In our study, 62% of patients for whom the AspireSR® was the first implanted VNS device were responders. This result is in line with a recently-published study conducted in adults with the same device and same mean follow-up time (13 months) by Hamilton and colleagues [12]. These authors showed a 59% (N = 30) response-rate among patients for whom the AspireSR® was the first implanted VNS ("new-insertion cohort", N = 51). In the Hamilton study, the replacement group responders rate increased from 53% (patients with ≥50% reduction in seizure frequency compared to the pre-implantation period) to 71% demonstrating a 32% additional benefit with the AspireSR. Whereas in our population, the additional benefit for the replacement cohort was 59%.

Hamilton and colleagues reported a 6% (3 patients) seizure-freedom among the new-insertion cohort, whereas in our new-insertion cohort, the rate of seizure-freedom was 13.8% (4 patients). In the future, as more experience with the AspireSR® will be accumulated, it will be possible to reach more accurate characterization of the specific populations and treatment settings that will lead to maximal benefit from the device. In our sample, most patients were children, and no significant differences were found between patients over 18 years of age and pediatric patients. Hamilton's study recruited only adults. Taken together, results of the Hamilton study and ours suggest that the benefit of the AspireSR® is relevant for a wide range of patient ages.

In our sample, 13 patients (28.3%) reported ≤ 25% reduction in seizure frequency following implantation of the AspireSR® and no patients reported worsening in seizure frequency. By comparison, in the Orosz study with the standard open-loop VNS, 136 patients (39.3%) had a ≤ 25% reduction in seizure frequency and an increase in seizure frequency was reported in 21 patients (6.1%) [6]. At 24 months of follow-up, Majkowska-Zwolińsk reported no effect of the VNS on seizure frequency in 12 patients (22.2%) [7]. These sub-groups seem to represent a patient population with extremely refractory disease, unresponsive to therapy. Among our patients who experienced ≤ 25% reduction in seizure frequency, 9 patients (31% of the cohort) were new-insertions, and 4 patients (23.5% of the cohort) were replacements. These rates are higher than observed in the Hamilton study (10% in new-insertions and < 2% in replacements). Further research is needed to ascertain the underlying reason for these differences that may include differences between adult and pediatric epilepsy populations or differences in follow-up period between the studies.

Our study was limited by the small sample-size and by its retrospective design. We evaluated the efficacy of the device based on medical records and retrospective interviews with patients' care-givers. This type of design predisposes data to biases, including recall-bias of the care-givers as well as selection bias resulting from lack of randomization. Moreover, data was available from routine clinic visits, which differ in number between patients, and not pre-planned, at the same time intervals. Large-scale prospective studies, using standardized seizure-information collection methods and device management data, can provide a more accurate estimate of the device efficacy and overall effect on patient well-being.

In conclusion, our results suggest that the closed-loop AspireSR® VNS device provides a benefit to drug-resistant epilepsy patients managed in a pediatric and young adults neurology unit once resective surgery is deemed not a viable option, with a responder rate of 60.9% of the study population. The benefit was observed both in patients for whom this was the first implanted VNS and those for whom the AspireSR® was a replacement for a previous VNS. Complete seizure freedom was achieved in 13.8% of new-insertions and 10.8% of complete cohort. Response was achieved rapidly, with a median of 5 months post-implantation, potentially due to the use of threshold to as low as 20% increase in ictal HR. This increased sensitivity setting did not cause elevation in adverse event rates. Should this connection be corroborated by larger-scale prospective studies, it can direct physicians to choose a setting of higher sensitivity to HR increases in most patients, in pursuit of better results.

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Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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