AspireSR®

For epilepsy, the AspireSR®, and SenTiva™ VNS therapy systems are the two most recently developed VNS devices [1].

A VNS Therapy generator model, AspireSR®, was introduced and approved for CE Marking in February 2014. In enhancement of former models, the AspireSR has incorporated a cardiac-based seizure-detection (CBSD) algorithm that can detect ictal tachycardia and automatically trigger a defined auto-stimulation [2] [3].

The AspireSR® device 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. VNS with AutoStim achieves maintenance of prior-established seizure control with markedly less energy consumption and can also improve seizure control as compared to the former stimulator model [4].

The vagal nerve stimulator AspireSR 106 is also a responsive device which, in addition to basal stimulation, is activated by tachycardia. Deep brain stimulation of the anterior nucleus of the thalamus is used in Europe for intractable epilepsy and yields similar response rates to RNS using duty cycle stimulation [5].

The purpose of Tzadok et al. was to assess the outcome of the AspireSR® in a patient population managed in a pediatric neurology unit.

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.

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. The mean follow-up was 13 ± 7.5 months (range 2-29 months). The total cohort responder rate (patients with ≥a 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 an 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 a median follow up of 5 ± 1.3 months post-implantation. 67.4% experienced shorter seizure duration post-implantation.

The 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 [6].

Data were collected retrospectively from patients with epilepsy who had VNS AspireSR® implanted over a three-year period between June 2014 and June 2017 by a single surgeon. Cases were divided into two cohorts, those in whom the VNS was a new insertion, and those in whom the VNS battery was changed from a previous model to AspireSR®. Within each group, the seizure burden was compared between the periods before and after the insertion of AspireSR®.

Fifty-one patients with a newly inserted AspireSR® VNS model had a significant reduction in seizure frequency ($p < 0.001$), with 59% ($n = 30$) reporting ≥50% reduction. Of the 62 patients who had an existing VNS, 53% ($n = 33$) reported ≥50% reduction in seizure burden when the original VNS was inserted. After the battery was changed to the AspireSR®, 71% ($n = 44$) reported a further reduction of ≥50% in their seizure burden. The size of this reduction was at least as large as that resulting from the insertion of their existing VNS in 98% (61/62) of patients.

The results suggest that approximately 70% of patients with existing VNS insertions could have significant additional benefit from cardiac based seizure detection and closed-loop stimulation from the AspireSR® device. For new insertions, the AspireSR® device has efficacy in 59% of patients. The 'rule of thirds' used in counseling patients may need to be modified accordingly [7].

Analysis of electro-encephalographic (EEG) signals has revealed that seizures are accompanied by spatial synchronization of EEG electrodes that may persist for several minutes after the seizure. A quantitative feature was obtained from EEG data around ictal events collected during a 3-5day epilepsy monitoring unit (EMU) visit prior to VNS implantation and following one month after VNS implant. This feature was obtained from 15 patients who underwent implantation of the closed-loop AspireSR® VNS Therapy System [8].

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16 patients who underwent implantation of closed-loop VNS therapy system, namely AspireSR, we evaluated if automated delivery of VNS at the time of seizure onset reduces the severity of seizures by reducing EEG spatial synchronization as well as the duration and magnitude of heart rate increase. Unsupervised classification was subsequently applied to test the discriminative ability and validity of these features to measure responsiveness to VNS therapy.

Results of application of this methodology to compare 105 pre-VNS treatment and 107 post-VNS treatment seizures revealed that seizures that were acutely stimulated using VNS had a reduced ictal spread as well as reduced impact on cardiovascular function compared to the ones that occurred prior to any treatment. Furthermore, application of an unsupervised fuzzy-c-mean classifier to evaluate the

ability of the combined EEG-ECG based features to classify pre and post-treatment seizures achieved a classification accuracy of 85.85%.

These results indicate the importance of timely delivery of VNS to reduce seizure severity and thus help achieve better seizure control for patients with epilepsy [9)].

Patients (n=28) from the Seizure Detection and Automatic Magnet Mode Performance Study (E-36), a clinical trial of the AspireSR® VNS Therapy System® (NCT01325623), were monitored with ambulatory electrocardiograms (ECGs) ~2weeks before de novo VNS system implantation and following 2- to 4-week VNS titration during a protocol-specified 3- to 5-day epilepsy monitoring unit stay with concurrent EEG/ECG recordings. The TWA level was assessed interictally by the Modified Moving Average (MMA) method.

At preimplantation baseline, TWA was elevated above the 47-µV abnormality cutpoint in 23 (82%) patients with drug-resistant epilepsy. In 16 (70%) patients, TWA level was reduced during VNS treatment to <47µV, thereby converting positive TWA test results to negative. Peak TWA level in all 28 patients improved (group mean, 43%, from 72±4.3 to 41±2.3µV; p<0.0001). Vagus nerve stimulation was not associated with reduced heart rate (77±1.4 to 75±1.4beats/min; p=0.18). Heart rate variability was unchanged.

These findings suggest significant interictal cardiac electrical instability in this population of patients with drug-resistant epilepsy and suggest that VNS may be a novel approach to reducing risk [10)].

El Tahry et al. reported the experience with three patients in assessing the functionality of ictal stimulation, illustrating the detection system in practice. Detection of ictal tachycardia and variable additional detections of physiological tachycardia depended on the individual seizure-detecting algorithm settings [11)].

The E-37 protocol (NCT01846741) was a prospective, unblinded, U.S. multisite study of the AspireSR(®) in subjects with drug-resistant partial onset seizures and history of ictal tachycardia. VNS Normal and Magnet Modes stimulation were present at all times except during the EMU stay. Outpatient visits at 3, 6, and 12 months tracked seizure frequency, severity, quality of life, and adverse events.

Twenty implanted subjects (ages 21-69) experienced 89 seizures in the EMU. 28/38 (73.7%) of complex partial and secondarily generalized seizures exhibited ≥20% increase in heart rate change. 31/89 (34.8%) of seizures were treated by Automatic Stimulation on detection; 19/31 (61.3%) seizures ended during the stimulation with a median time from stimulation onset to seizure end of 35 sec. Mean duty cycle at six-months increased from 11% to 16%. At 12 months, quality of life and seizure severity scores improved, and responder rate was 50%. Common adverse events were dysphonia (n = 7), convulsion (n = 6), and oropharyngeal pain (n = 3). : The Model 106 performed as intended in the study population, was well tolerated and associated with clinical improvement from baseline. The study design did not allow determination of which factors were responsible for improvements [12)].

The intraoperative handling was comparable and did not lead to a significant increase in operation time. In our 14 operations, we had no significant short-term complications. Due to its larger size, patients with the AspireSR had significantly larger skin incisions. For optimal heart rate detection, the AspireSR had to be placed significantly more medial in the décolleté area than the Demipulse. The preoperative testing is a unique addition to the implantation procedure of the AspireSR, which may provide minor difficulties, and for which we provide several recommendations and tips. The price of the device is higher than for all other models. : The new AspireSR generator offers a unique technical improvement over the previous Demipulse. Whether the highly interesting CBSD feature will provide an additional benefit for the patients, and will rectify the additional costs, respectively, cannot be answered in the short-term. The preoperative handling is straightforward, provided that certain recommendations are taken into consideration. The intraoperative handling is equivalent to former models-except for the placement of the generator, which might cause cosmetic issues and has to be discussed with the patient carefully. Schneider et al. recommended the consideration of the AspireSR in patients with documented ictal tachycardia to provide a substantial number of patients for later seizure outcome analysis [13)].

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