Seizure 59 (2018) 41–47

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Single-center long-term results of vagus nerve stimulation for epilepsy: A 10–17 year follow-up study

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ARTICLE INFO

Article history:
Received 27 January 2018
Received in revised form 12 March 2018
Accepted 26 April 2018
Available online xxx

Keywords:
Epilepsy
Vagus nerve stimulation
Long term follow up
Responder
Battery replacement

ABSTRACT

Purpose: The paper presents a long-term follow-up study of VNS patients, analyzing seizure outcome, medication changes, and surgical problems.
Method: 74 adults with VNS for 10 to 17 years were evaluated yearly as: non-responder – NR (seizure frequency reduction <50%), responder – R (reduction ≥ 50% and <90%), and 90% responder – 90R (reduction ≥ 90%). Delayed R or 90R (≥ 4 years after surgery), patients with antiepileptic medication changes and battery or complete system replacement were identified. Statistical analysis of potential outcome predictors (age, seizure duration, MRI, seizure type) was performed.
Results: The rates of R and 90R related to the patients with outcome data available for the study years 1, 2, 10, and 17 were for R 38.4%, 51.4%, 63.6%, and 77.8%, and for 90R 1.4%, 5.6%, 15.1%, and 11.1%. The absolute numbers of R and 90R increased until years 2 and 6. Antiepileptic therapy was changed in 62 patients (87.9%). There were 11 delayed R and four delayed 90R, with medication changes in the majority. At least one battery replacement was performed in 51 patients (68.9%), 49 of whom R or 90R. VNS system was completely replaced in 7 patients (9.5%) and explanted in 7 NR (9.5%). No significant predictor of VNS outcome was found.
Conclusions: After an initial increase, the rate of R and 90R remains stable in long-term follow-up. The changes of antiepileptic treatment in most patients potentially influence the outcome. Battery replacements or malfunctioning system exchange reflect the patient's satisfaction and correlate with good outcomes.

1. Introduction

Since the first implantation in humans in 1988 and Food and Drug Administration (FDA) approval in 1997, vagus nerve stimulation (VNS) has become an accepted palliative treatment modality for patients with drug-resistant epilepsy not suitable for resective surgery. The effect of VNS on seizure frequency and severity was confirmed by randomized controlled trials [1,2,3,4]. However the follow-up period in the first three studies did not exceed 26 weeks [1,2,3]. The last paper, a metanalysis of 74 studies with 3321 enrolled patients, proved a significant reduction of seizures at 3–12 months after surgery (36%) and an increasing effect of VNS on seizure reduction at >1year after surgery [4]. Other studies confirm a cumulative effect of VNS in medium-duration follow-up. For example, the median seizure reduction in 454 patients enrolled in five double-blind US studies improved from 35% to 44% at two years [5]. Similarly, a European study confirmed that treatment duration was significantly correlated with the percentage of seizure frequency reduction [6]. With increased experience, studies reporting post-VNS outcomes for up to 5 years [7,8] and studies covering follow-up periods exceeding 10–11 years have been published [9,10,11,12]. The effect of VNS on seizure reduction has been discussed in combination with other aspects of VNS: post-VNS quality of life [12] and surgical problems [9].

Abbreviations: FDA, food and drug administration; VNS, vagus nerve stimulation; ILAE, international league against epilepsy; MRI, magnetic resonance imaging; NR, non-responder; R, responder; 90R, 90% responder; DBS, deep brain stimulation.

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https://doi.org/10.1016/j.seizure.2018.04.022
1059-1311/

The first aim of the study is to present the results of VNS systems implanted for ≥ 10 years in patients with drug-resistant epilepsy followed in a specialized epilepsy center in a longitudinal time axis. The effect of VNS on seizure reduction is quantified yearly in terms of responder rates for the entire study period from stimulation onset to study completion. There were marked developments in the field of antiepileptic drugs during the study period. In terms of new medications during the study period (January 2000–November 2017), the date of levetiracetam registration was 29 Sept 2000, for zonisamide 10 Mar 2005 and for pregabalin 6 July 2004. The impact of medication changes during the follow-up period on seizure outcome is also studied, particularly in patients with late or delayed VNS response.

The satisfaction with VNS treatment can be quantified by sophisticated scales evaluating the different aspects of the quality of life [13], but a simple criterion – the frequency of battery replacement after depletion (indicating the patient's or the physician's will to continue VNS therapy in mutual agreement) – can provide a simplified answer. Moreover, surgical problems with the implanted system require revision and replacement and the rate of patients willing to undergo the surgery to continue the VNS therapy during the prolonged follow-up period also provide data about patient satisfaction with the results. Therefore the second aim of the study is the analysis of surgical problems of long-term VNS, with attention to reoperations and system complications in the long-term follow-up period, for which there are only a few comparable papers [10,12]. Finally statistical analysis of potential long- term VNS outcome predictors was performed; unfortunately there are currently no universally accepted outcome predictors for VNS. However, based on previously published papers aiming to find VNS outcome predictors, age, seizure duration, age at seizure onset, MRI findings (diffuse, focal, mesiotemporal sclerosis and negative) and the prevailing seizure type (complex partial seizure – focal aware – ILAE 2017, simple partial seizure – focal impaired awareness – ILAE 2017, and other), were selected as potential predictors for statistical analysis [4,14–16].

2. Material and methods

Adult patients (age ≥ 18 years) with VNS systems (Cyberonics, Inc., Houston, Texas, USA) implanted at the author's department for ≥ 10 years ago were retrospectively identified from a prospectively constructed database of the patients who had surgery for drug-resistant epilepsy at the comprehensive Brno Epilepsy Center. Prior to VNS implantation, all patients underwent a detailed preoperative investigation at the center and were ruled out as suitable candidates for resective epilepsy surgery. After standard implantation of the left vagus nerve stimulation system (ZN, JC), all the patients were followed at the First Department of Neurology at regular intervals (2, 4, 6, 12 and 18 months; then yearly). VNS parameter adjustments and modifications of antiepileptic medication were made strictly according to the clinical decision of the epileptologist.

Based on post-VNS seizure reduction, the patients were graded at the follow-up visits as non-responders – NR (seizure frequency reduction <50%), responders – R (reduction ≥ 50% and <90%), or 90% responders – 90R (reduction ≥ 90%). When the VNS system was switched off due to a response that was not clinically relevant, the patient was moved to the "stimulation off" category and remained there until the end of the follow-up period; other patients were categorized as having had system explantation ("explantation"), as lost to follow-up care ("patient lost"), or as having died for any reason ("dead"). Missing data for a single follow-up visit moved the patient to the "data missing" category for that particular follow-up point. Patients with late response to VNS (shifting from the NR category to the R category, or from the R to the 90R category at ≥ 4 years after surgery), as well as patients with fluctuating or worsening response to VNS during the follow-up period, were identified. The percentages of R, 90R, and Good outcomes (R + 90R) for each study year were related to all the patients with follow-up results available for the defined study year (excluding patients categorized as "dead", "data missing", or "lost").

The medical reports of late responders were checked for medication changes during the year prior to the improved response. The percentage of patients with medication changes (including permanent dosage changes) during the follow-up period was also calculated.

Patients with battery replacement during the follow-up period were identified from the database and confirmed from surgical reports. Similarly, patients requiring complete VNS system replacement (including the helical electrode) were identified, and the cause of system failure was determined from the surgical report. The rates of 90R and Good outcomes were selected as the endpoints of the statistical analysis. The time points for analysis were defined at year 10 and final follow up. Absolute and relative frequencies were accepted for the description of endpoints occurrence. Logistic regression was used for the analysis of relation between predictors and endpoints; odds ratios, their 95% confidence intervals and statistical significance were used for the description of this relationship.

3. Results

The study included 74 adult patients (33 males, 41 females) who had VNS implanted between January 2000 and November 2007. The mean patient age at implantation was 31.1 years (range 18–59 years; standard deviation 10.65 years). There was a history of previous neurosurgical operations in 20 patients (simple lesionectomies in six patients, failed extratemporal or temporal resections in four patients, stereotactic lesional surgeries in seven patients, stereoelectroencephalography not providing adequate data for resective surgery in three patients). Two patients had brain hypothermia. The first case was a 35-year-old male with seizure onset at the age of 2 years (frontal absences with secondary generalization). Hypothermic treatment was administered at the age of 17 years, but without effect on seizure frequency or severity. MRI showed gliotic changes after ventricular punctures. Because the investigations failed to localize the epileptogenic focus, the patient had VNS system implanted, and was categorized as a Responder. The second patient (a 37-year-old male) was treated at another department for multifocal epileptic seizures by stereotactic surgeries (coagulation of the right Forel field, rostral cingulum, and right thalamic nuclei) and with brain hypothermia. After VNS, he was graded as 90R.

Six patients were lost to follow-up before study year 10 (one 90R and five R at the last follow-up). Two patients died before study year 10 (one NR suffered a severe brain injury after epileptic seizure and one NR due to malignant retroperitoneal tumor). The outcome data at the year 10 follow-up visits were available for 66 patients.

Follow-up data of patients with VNS implanted for 17 years were available for nine patients (two patients were lost to follow up; one patient died from neurodegenerative disease).

During the whole study period, there were 8 patients lost to follow-up care (one 90R and 7 R at the last follow-up). Five patients died during the follow-up period. In three patients, the cause of death was unrelated to epilepsy (retroperitoneal malignancy, urinary bladder cancer, and neurodegenerative disease). In one patient, the death was related to epilepsy: a fatal brain injury caused by a fall during an epileptic seizure. The possibility of SUDEP could not be excluded in one patient who reportedly died from heart failure.