

Vagus Nerve Stimulation in Patients With Refractory Epilepsy: a case series

Estimulação do Nervo Vago em Pacientes com Epilepsia Refratária: uma série de casos

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ABSTRACT

Background: Approximately 33% of patients with epilepsy do not respond to treatment with a single antiepileptic drug. Many of these patients can benefit from neurosurgical treatment. However, not all patients are candidates for surgery, and in these cases vagus nerve stimulation (VNS) presents as a good therapeutic option. **Objectives:** Evaluation of efficiency, tolerability and safety in the control of seizures after VNS implantation in patients from a reference hospital. **Methods:** cross-sectional study examined 20 patients who underwent implantation of the VNS in our facilities between 2007 and 2014. Proportions and chi-square test were applied (statistical significance level set to $p \leq 0.05$). **Results:** Mean follow-up was 31.3 months. Seizure frequency decreased in 55% of the patients. Among them, 11 patients believed that VNS had improved their quality of life. The mean reduction reported by other patients was 78.3%. More than 30% reported no adverse effects. About 70% of patients no longer required hospitalizations and 95% reported reduction in the number of hospitalizations. **Conclusion:** In this population, VNS proved to be a good option in the treatment of refractory epilepsy and also in providing a significant improvement in quality of life, (reduction of seizures and hospitalizations), mood, attention and memory, which directly reflects on their social and cognitive.

Key-words: Vagus Nerve Stimulation, Drug Resistant Epilepsy, Epilepsy, Vagus Nerve

RESUMO

Introdução: Aproximadamente 33% dos pacientes com epilepsia não respondem ao tratamento medicamentoso com uma única droga. Muitos desses pacientes se beneficiam do tratamento neurocirúrgico. No entanto, nem todos os pacientes são candidatos à cirurgia, sendo o tratamento com a estimulação do nervo vago (VNS) uma opção. **Objetivos:** Avaliação da eficácia, tolerabilidade e segurança no controle de convulsões após implante de VNS em pacientes de um hospital de referência. **Métodos:** Estudo transversal que analisou 20 pacientes submetidos ao implante de VNS em um hospital de Curitiba entre 2007 e 2014. Proporções e teste do qui-quadrado foram aplicados (significância estatística quando $p \leq 0,05$). **Resultados:** O seguimento médio foi de 31,3 meses. A frequência de crises diminuiu em 55% dos pacientes. Entre eles, 11 pacientes acreditavam que o VNS melhorou sua qualidade de vida. A redução média de crises relatada por outros pacientes foi de 78,3%. Mais de 30% não relataram nenhum efeito adverso. Cerca de 70% dos pacientes não necessitaram mais de hospitalizações e 95% relataram redução no número de internações. **Conclusão:** Nessa população, o VNS mostrou-se uma boa opção no tratamento da epilepsia refratária, além de proporcionar melhora significativa na qualidade de vida, (redução de convulsões e internações), melhora do humor, atenção e memória, o que reflete diretamente em suas relações sociais e cognitivas.

Palavras-chave: Estimulação do Nervo Vago, Epilepsia Resistente a Medicamentos, Epilepsia, Nervo Vago

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INTRODUCTION

Approximately 33% of patients with epilepsy do not respond to treatment with a single antiepileptic drug, using a combination of antiepileptics¹. Even so, 20 to 30% of patients continue to have seizures that contribute to increased morbidity and mortality¹⁻⁶, characterizing what is called refractory epilepsy. When there is no therapeutic response, many of these patients may have some benefit from neurosurgical treatment, which is founded on the microsurgical resection of the epileptogenic zone, of the epileptogenic lesion or on its isolation with callosotomy or with hemispherectomy^{1-4,7}. The evolution in the presurgical evaluation and in the anesthetic and surgical techniques have led this approach to great success rates¹⁻⁸. However, not all patients are candidates for surgery, especially those with multifocal seizures. In this case, treatment with vagus nerve stimulation (VNS) has been advocated as a good treatment option. In 1997, the Food and Drug Administration (FDA) approved VNS as adjunctive treatment for refractory partial seizures in adults and adolescents^{1,3,4,6}, and in 1999 the American Academy of Neurology (AAN) followed this indication.

This paper aims to report our experience with VNS in the treatment of a population of patients with refractory epilepsy, to add information to the current literature and to make information about our experience with VNS available to other health care professionals.

METHODS

This is a cross-sectional study, which examined patients who underwent VNS implantation in a reference hospital at Curitiba between 2007 to 2014. Several variables were analyzed, such as ratio of genders, age, seizure type, and number of hospitalizations. Inclusion criteria were patients submitted to treatment by VNS who accepted to participate in the questionnaire via telephone.

Each patient was contacted through a telephone call by a trained and qualified person who read the informed consent. The patient had the option of accepting or denying to be enrolled in the study. All calls were recorded and archived.

Patients were questioned about: difficulty of reasoning, social limitation, memory difficulties, fear of seizures, improvement of the quality of life after implantation and adverse events.

Afterwards, the data were coded, inputted and systematized in the EpiData 3.0 and Microsoft® Excel 2010 softwares, using proportions and chi-square test aiming to correlate them for analysis and discussion. Statistical significance level was set at $p \leq 0.05$. This study was approved by the ethics committee.

RESULTS

Twenty patients with refractory epilepsy underwent VNS implantation at INC, in a period of 9 years. Mean follow-up was 31.3 months. Seizures were reduced to 50% or more in 78.3% of the patients. The smallest seizure frequency reduction reported was 40% (patient #16). More than 30% reported no adverse effects. Nineteen patients (95%) reported reduction in the number of hospitalizations and nine patients (45%) did not need to be hospitalized again. A significant improvement in quality of life was observed in 55% of the patients (Fig. 1).

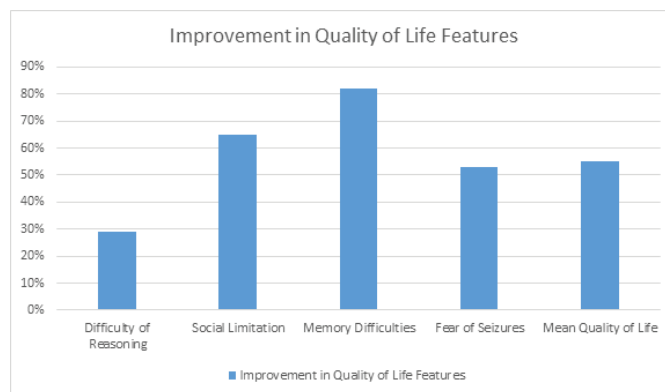


Figure 1. Improvement in features of quality of life reported by patient after VNS implantation.

DISCUSSION

Drug resistant epilepsy (DRE) is defined by the International League Against Epilepsy as failure of two adequate trials of tolerated, appropriately chosen and used antiepileptic drug schedules to achieve sustained seizure cessation⁹. Approximately 30 to 40% of the population with epilepsy is

drug-resistant¹⁰ representing a burden in terms of impaired cognitive function, brain damage, and other neuropsychiatric deficits to the patients and their families. Treatment options for DRE are resective surgery, in which the epileptogenic zone is targeted, trials of experimental antiepileptic drugs (AEDs) and palliative therapies, which include deep brain stimulation (DBS), corpus callosotomy (CC) and VNS^{5,11}.

Resective surgery is the preferred treatment for DRE in the pediatric population and the most likely surgical therapy to achieve seizure freedom⁷. The resection extension ranges from simple lesionectomy to single or multiple lobectomies and is based on seizure type, imaging findings, ictal and functional mapping of each patient⁷. However, patients with generalized epilepsy syndromes or epileptogenic zones which are poorly localized, multifocal or overlapped with eloquent brain areas are not obvious candidates for resective surgery. Thus, these patients could be benefited by palliative surgical options, such as VNS, DBS and CC.

In 2010, thalamic DBS was analyzed by the Stimulation of the Anterior Nucleus of Thalamus for Epilepsy (SANTE) trial in 110 adults¹². All of the patients had drug-resistant partial epilepsy. After a 3-month period, patients receiving DBS stimulation showed 40% of decrease in seizure frequency whereas only 15% of the patients in the control group had a decrease in seizure frequency. In a second part of the trial, all of the patients were treated with stimulation for 2 years and seizure frequency was reduced by 56%. After 5 years of follow-up, 69% of median seizure reduction was observed. The side effects during the first year of DBS included paresthesias (18%), surgical site pain (11%), local infections (9%) and need for lead replacement (8%)¹².

The principle of corpus callosotomy is to destroy the major connections between the two hemispheres to prevent contralateral spread of focal seizure activity and therefore impeding ictal loss of consciousness and drop attacks (tonic and atonic seizures). Seizure frequency reduction in one trial (seizure cessation or >90% reduction) was achieved in 85% of patients with drop attacks¹³. In this trial, overall daily function improved in 62% of patients.

Our literature review reported response rates (reduction in seizures $\geq$ 50%) at 1 year with VNS therapy in refractory epilepsy ranging from 37%¹⁴ to 57.6%¹⁵. A meta-analysis of 74 clinical studies with 3,321 patients reported that after VNS

the seizure frequency was reduced by 45% on average. This study also showed that reduction in seizure frequency tends to increase with time: at 3–12 months after surgery a 36% reduction in seizure frequency was described, a rate that was increased up to 51% after 1 year¹⁶. In our series, 45% of the patients referred a higher than 50% improvement in seizure frequency. Sixty-six per cent of these patients had either generalized or multifocal neocortical irritative activity, while 50% of the patients who did not refer improvement in seizure frequency had a localized epileptogenic zone. Our results show accordance with the main indications for VNS - multiple or non resectable epileptogenic zones, previous unsuccessful epilepsy surgeries and generalized epilepsy syndromes¹⁷. Arcos et al.¹⁵ recently found temporal lobe discharges on video-EEG as a predictor of a sooner and higher response to VNS. These evidences suggest the high impact that seizure semiology and location of epileptogenic zone can have on the outcome of patients treated with VNS.

Among acute adverse effects of VNS implantation are infections, vocal cord paresis, lower facial weakness and, more rarely, bradycardia and asystole¹⁴. The most common long-term adverse effects are stimulus-induced cough, throat pain, and hoarseness¹⁸. Regarding this matter, our case series diverged from the literature. The most common adverse effects in our sample were worsening of seizure frequency or quality, falls, hoarseness, agitation and local pain or discomfort (Fig. 2). Since our interviews were conducted through telephone calls, this correlation between some of the referred adverse effects and device implantation could be questioned.

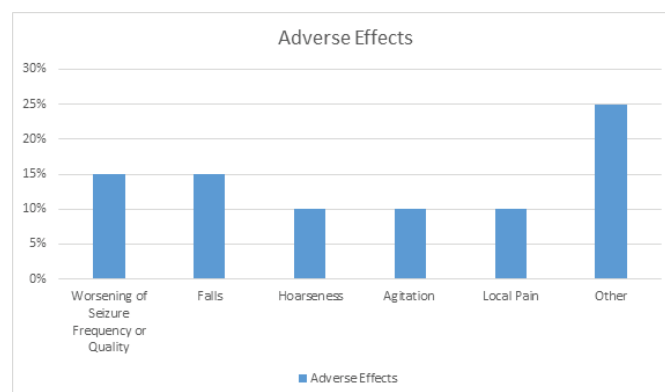


Figure 2. Adverse effects referred by the patients after VNS implantation.

A study compared seizure outcomes postimplantation of VNS between patients that had undergone prior resection and those who had not. At 24 months follow-up the reduction in seizure frequency was 51% among those who were submitted to previous surgery and 67% among those who had not undergone previous procedures¹⁹. This is an important information, both to clinicians and surgeons, since many of the patients suitable for VNS implantation have been submitted to different epilepsy procedures in the past.

Besides this effect on seizure frequency reduction, VNS appears to have a positive effect on memory²⁰, mood and quality of life²¹. Klinkenberg et al. reported that 6 months after VNS implantation, mood (Profile of Mood States, POMS) and quality of life (Quality of Life in Epilepsy Inventory, QOLIE-89) increased significantly²¹. Faught et al.²² found in their study with pediatric population a decrease in seizure-related hospitalizations post-VNS implantation, both in children and adolescents, with an adjusted incidence rate ratio (IRR) of 0.66 and 0.46, respectively (IRR < 1 indicates a lower incidence of the event taking place during the Post-VNS period). In our own case series 55% of the patients referred improvement in quality of life after VNS implantation, thus being consonant with previous series. Furthermore, 45% of our patients reported a reduction in hospitalization after the procedure, and 40% remained without needing hospitalization. Burke et al. found a global decrease in health care utilization after VNS implantation, with a 21% decrease of in-patient bed-days, a 7% decrease of elective in-patient episodes and a 14% decrease of non-elective in-patient episodes²³.

In spite of been seen as an extraordinary treatment modality by most neurologists and neurosurgeons, VNS efficacy in controlling seizures should bring it to the frontline of therapies of refractory epilepsies. The consistent numbers of reduction in seizure frequency, of hospitalization and the increase in quality of life indicators and scores place it as a major treatment option for this quite handicapped population.

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