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Research Article

The Benefit of Vagus Nerve Stimulation in Patients with Refractory Epilepsy, Experience in a Latin American Center

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Abstract

Background: Epilepsy is a neurological disorder caused by a discharge due to neuronal hyperexcitability, which causes seizures, affecting the quality of life in people who suffer from it, mainly because there is cognitive impairment due to seizures and physical limitations. Palliative treatment options for refractory patients are a ketogenic diet, Vagus Nerve Stimulation (VNS), and functional epilepsy surgery (resection surgery).

Aims: We Present the experience of the vagal stimulator implantation to reduce health expenses in the population with refractory epilepsy at the 20 De Noviembre National Medical Center, ISSSTE, in Mexico City; We sought to evaluate the percentage of improvement of patients with drug-resistant epilepsy to medical treatment, based on the percentage reduction in the frequency of seizures, quality of life, costs for medical services, and acquisition of antiepileptic drugs.

Materials and Methods: Data from patients treated with VNS at "20 de Noviembre" medical center, between January 2005 and December 2018, with a minimum follow-up time of 6 months, were included. The Vagal Neurostimulator was placed in 29 patients, of which 12 patients (41.4%) were female and 17 patients (58.6%) were male.

Results: The mean number of crises per day before implantation was 35; After implantation, the mean concerning the number of crises, was 12. The percentage reduction in the number of crises per day after the implantation of the VNS had a minimum of 33.3% and a maximum of 99.2%, the Mean was 65.2%, with a standard deviation of 16.4. The use of drugs in a general way by the 29 patients was reduced from 127 antiepileptic drugs before the placement of the vagus nerve stimulator (VNS), to 75 drugs used in a general way.

Conclusion: Results of the trials and the experience accumulated in recent years place the implant of the vagal neurostimulator (VNS), as an alternative in the treatment of refractory cases. It is now considered adjuvant, with few and transient adverse effects and a favorable impact on the frequency, duration of crises, and quality of life that justify its indication.

Keywords: *Vagus Nerve Stimulation (VNS); Refractory Epilepsy; Antiepileptic Drugs*

Introduction

According to Ropper, Samuels, Klein, Pinto and Martínez, 2017, epilepsy is a neurological disorder caused by neuronal hyperexcitability, which causes seizures, loss of consciousness, and convulsive movements, with alteration of perception, which causes an imbalance in

functions. psychic and that can occur without an apparent external stimulus [1]. It affects the quality of life of people who suffer from it, mainly because there is a cognitive deterioration, due to seizures and physical limitations.

Epilepsy is one of the most common neurological disorders in childhood, occurring in 0.5 - 1%, however, adequate control is not achieved in 20 - 30% of patients with antiepileptic drugs (FAEs), those Patients who do not have seizure control after being treated with multiple AED regimens are considered refractory.

Despite recent advances, pharmacological control of seizures is not satisfactory in 30 - 40% of patients, with 15% of these who could benefit to a greater or lesser degree from surgical treatment.

When refractory epilepsy is severe, it results in cognitive impairment, mainly in children, therein lies the importance of controlling seizures; Palliative treatment options for refractory patients, including adults, are a ketogenic diet, Vagus Nerve Stimulation (VNS), functional epilepsy surgery (resection surgery).

Neurostimulation of the Vagus Nevus in its cervical portion has been approved since 1997 by the FDA, for adults over 12 years of age, in cases of refractory epilepsy (drug-resistant epilepsy). Initially, vagus nerve stimulation was used experimentally from the late 1980s, when as many as 800 or more patients were implanted with the vagus nerve stimulator between 1988 and 1997. Studies by Murphy and Hornig reported that "vagus nerve stimulation was well tolerated by children and could lead to a significant decrease in seizure burden" [2].

The mechanism of antiepileptic action of VNS is not clear, however, A. Ulate Campos., *et al*. 2015, reported that "it could act by desynchronizing the thalamocortical circuits involved in the propagation of seizures when the left vagus nerve is stimulated" [3]. In another study, Robert S. Fisher., *et al*. 1997, explains that the possible mechanism of action involves several systems of the brain, since "it increases the expression of C-fos in the amygdala, in the posterior cortex, the cingulate gyrus, the ventromedial nucleus, and the arcuate hypothalamus", that of the vagus nerve, the locus coeruleus and the cochlear" [4].

With Vagal Neurostimulation, similar results have been reported in various studies: Robert S. Fisher., *et al*. 1997, found in their study that the low stimulation group experienced an average reduction in seizures of 11%, compared to the baseline, 19% of the patients experienced a 50% reduction in seizures [5]; Jason S. Hauptman., *et al*. 2012, reported that at six months, 55 patients experienced a median reduction of 31% in seizure load, at 12 months 51 patients experienced a median reduction of 34%, and at 18 months 46 patients experienced a median reduction of 42% [6]; George L. Morris., *et al*. 2013, associated VNS with > 50% seizure reduction in 55% of 470 children with partial or generalized epilepsy, > 50% seizure reduction in 55 of 113 Lennox-Gastaut syndrome (LGS) patients, and indicated that VNS is possibly associated with increased rates of seizure frequency reduction ≥ 50% from 7% 1 to 5 years after implantation [7].

In the pediatric population, the average reduction in seizures with vagus nerve stimulation (VNS) varies between 30 - 62%, and the percentage of improvement in the control of the frequency of epileptic seizures is between 26 - 77%.

The placement of the VNS as a palliative treatment is proposed for patients with syndromes that, due to their pathophysiology, are considered to have a poor prognosis from the point of cognition and crisis control; since it is safe and effective [8-15].

Adverse effects are presented in lower percentages, Robert S. Fisher., *et al*. 1997, reported: a hoarse voice, paralysis of the left vocal cord that persisted for at least one year; cable fracture, sore throat, cough, paresthesia, shortness of breath [16].

Material and Method

A descriptive, longitudinal, retrospective study was carried out in a single center, information was obtained by reviewing electronic records of the hospital administration system (SIAH) in the National Medical Center "20 de Noviembre", in Mexico City. Our population was

patients who underwent implantation of the vagal neurostimulator (VNS), during the period from January 2005 to December 2018. Records of patients with a diagnosis of refractory epilepsy, who were not candidates for functional epilepsy surgery or without subsequent improvement were selected. Using descriptive and inferential statistics to assess the effect on the frequency and intensity of seizures, quality of life (subjective scale), and related factors (sex, age, time of evolution, antiepileptic efficacy according to the type of epilepsy, the number/crisis type, stimulation parameters, associated with clinical response, and adverse effects in case they have developed, as well as the number of medications before and after the procedure. The selection criteria to implant VNS included: patients who failed multiple antiepileptic drugs (AEDs) (usually at least 3 AEDs) with multifocal or diffuse seizures not amenable to surgical resection, patients with persistent or recurrent seizures after surgery for intracranial epilepsy, AED toxicity or intolerable side effects, patients no candidates for intracranial surgery and patient preference or family for conservative measures before or instead of possible intracranial surgery.

We implanted the vagal neurostimulator on the left side (Image 1) since it is safer as various studies have indicated that implanting it on the right side can cause bradycardia [17].

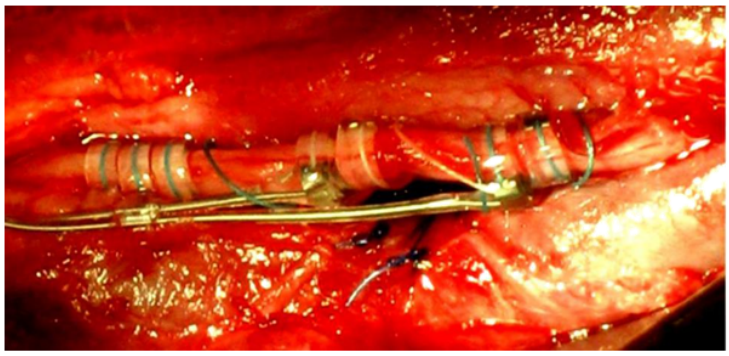


Image 1

Data from patients treated with VNS at "20 de Noviembre" hospital, between January 2005 and December 2018, with a minimum follow-up time of 6 months, were included. The Hospital Multidisciplinary Epilepsy Committee evaluated the patients who were candidates for VNS, according to the selection criteria established by the International League Against Epilepsy (ILAE), for patients with drug-resistant epilepsy who are not candidates for functional epilepsy surgery or who were candidates and did not present clinical improvement. The exclusion criteria were patients who did not meet the International League Against Epilepsy (ILAE) criteria for drug-resistant epilepsy; patients who are candidates for functional epilepsy surgery.18 As elimination criteria: patients where the outcome of VNS surgery cannot be evaluated, due to the lack of data necessary to measure.

The quantitative variables analyzed, before implantation: number. seizures/day pre-implantation, number of seizures/month pre-implantation, days of hospital stay (HSD), number of consultations, number of admissions to emergency departments pre-implantation, hospitalizations for other causes. To assess the effect of VNS were analyzed the quantitative variables after implantation: were frequency and intensity of seizures, number of seizures/day post-implantation, number of seizures/month post-implantation, percentage % reduction per day, percentage % reduction per month, days of hospital stay, number of post-implant consultations, number of admissions to post-implant emergencies, hospitalizations for other causes; the number/type of seizures, stimulation parameters, average neurostimulator battery life according to the start time of the implant. Qualitative variables analyzed: patient quality of life and related factors such as sex, age, time of evolution, and antiepileptic efficacy according to the type of epilepsy. And the variables regarding the factors associ-

ated with the clinical response: are adverse effects, cost-benefit, long-term cost-effectiveness, and cost-consequence of not implanting the stimulator.

The following data were obtained from the patients diagnosed with Drug-Resistant Epilepsy: age, sex, etiology of epilepsy, time of diagnosis, and drug treatment used; for patients who previously underwent treatment with functional surgery: date of surgery; and for patients who received the Vagal Neurostimulator: date of placement, parameters of the neurostimulator upon placement, the percentage reduction in seizure frequency, postoperative complications, adverse effects during follow-up, need for replacement neurostimulator battery, changes in antiepileptic drug treatment, number of outpatient consultations, number of reprogramming parameters, improvement in the patient's quality of life, number of hospital readmissions due to uncontrolled seizures.

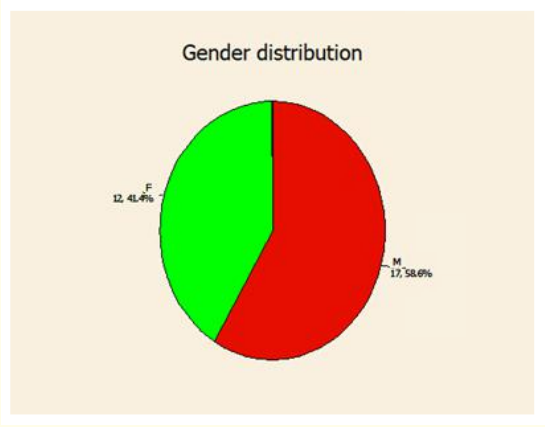
The Vagal Neurostimulator was placed in 29 patients, of which 12 patients (41.4%) were female and 17 patients (58.6%) were male, with the initial parameters: initial output current of 0.25 mA, signal frequency of 30 Hz, pulse width: 500 µsec, signal on time: 30 sec, signal off time: 5.0 min.

Statistical analysis was performed using SPSS 25.0 statistical software, GraphPadPrism version 8.0.2. and Excel. The Student's T-statistical test was used for quantitative variables with normal distribution, and U Mann-Whitney for quantitative variables with non-normal distribution, to demonstrate differences in the same group of patients before and after placement of the Vagal Neurostimulator; the Chi-Square statistical test for the qualitative variables. A Confidence Interval (CI) of 95% was established.

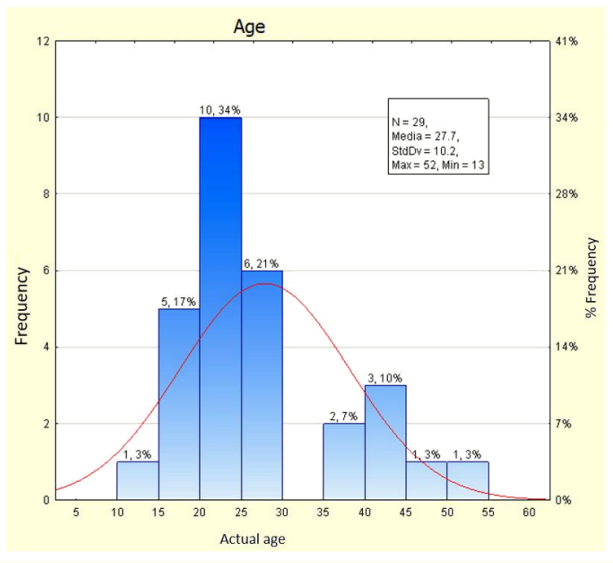
The data was organized in frequency tables; measures of central tendency: Arithmetic mean, median, and mode; dispersion measures: range, interquartile range, standard deviation, and percentiles; crosstabs; graphs: ANOVA graphs for the comparison of averages. Fisher's analysis of variance (Parametric ANOVA); post Hoc test or post ANOVA Tukey's test for multiple comparisons.

Results

In our sample it was found from our study, according to the selection criteria of the multidisciplinary group with a diagnosis of drug-resistant epilepsy, 29 patients were considered, of which they were distributed in 12 female patients (41.4%) and 17 male patients (58.6%) (Graph 1). The current age of the sample of patients, ranged from a minimum of 13 years to a maximum of 52 years, with a mean and standard deviation of 27.7 ± 10.2 years (Graph 2).



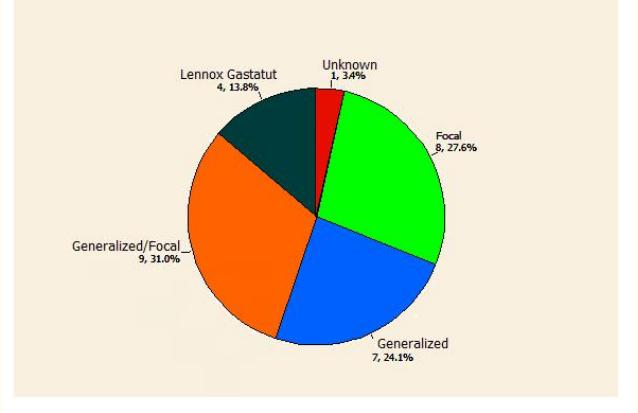
Graph 1: *The 29 patients were considered as the universe, of which they were distributed in 12 patients (41.4%) of the female gender (women) and 17 patients (58.6%) of the male gender (men).*



Graph 2: *The current age of the sample, oscillated between the minimum of 13 years and the maximum of 52 years, with a mean and standard deviation of 27.7 ± 10.2 years. The current age was recorded by increasing ranks.*

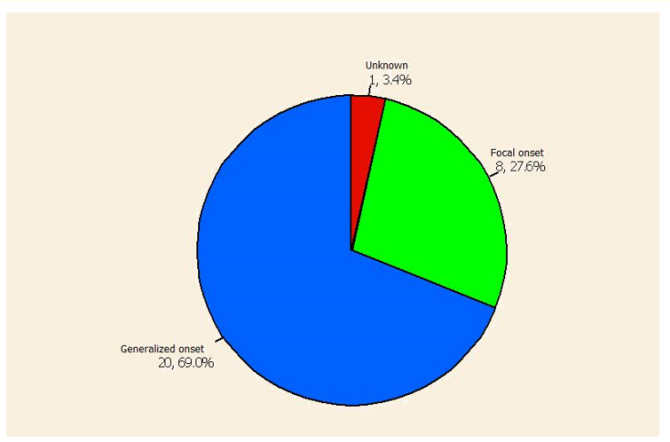
A review was made of the diagnoses of the 29 patients, these diagnoses were classified for a better understanding, according to the Operational Classification of Epilepsy, and the types of seizures were reviewed, by the International League Against Epilepsy, according to the 2017 ILAE terminology [18].

Graph 3a represents, according to the operational terminology of the International League Against Epilepsy (ILAE) [18], the most frequent diagnosis is generalized/focal 31% (9 patients), followed by focal 27.6% (8 patients), generalized in 24.1% (7 patients), predominant syndromic epilepsy were Lennox Gastaut 13.8% (4 patients), finally, unknown only 1 patient corresponding 1.34%.



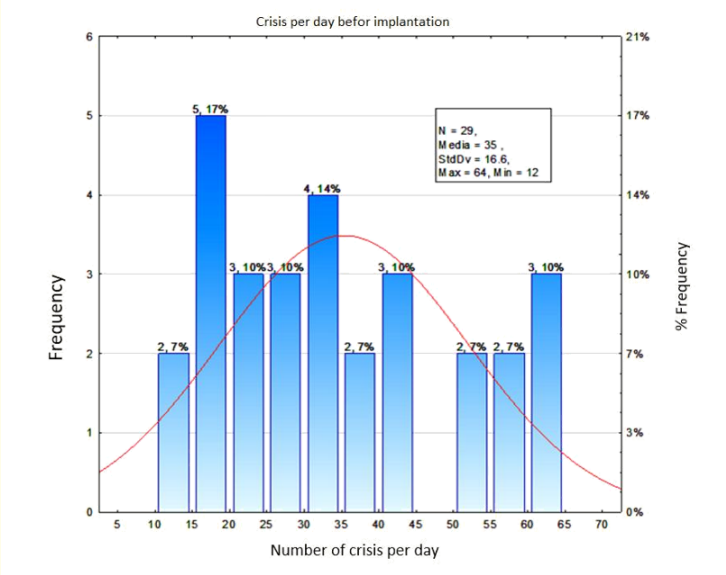
Graph 3a: *It is represented according to the operational terminology of the International League Against Epilepsy (ILAE). The most frequent diagnosis is Generalized/Focal (9 patients) 31%, Focal (8 patients) 27.6%, Generalized in (7 patients) 24.1%, Syndromes as the predominant diagnosis of Lennox Gastaut (4 patients) 13.8%, finally, Unknown only 1.34%. (1 patient).*

In graph 3b, it is represented according to the operational terminology of ILAE, the type of seizure, predominant generalized onset (20 patients) 69.0%, focal onset (8 patients) 27.6%, unknown onset (1 patient) 3.4%.

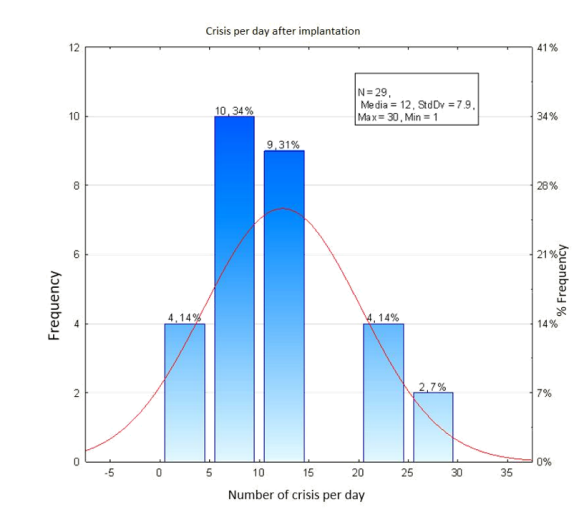


Graph 3b: *The most frequent onset is generalized (20 patients) 69.0%, focal onset (8 patients) 27.6%, and unknown onset (1 patient) 3.4%.*

The mean number of crises per day before implantation was 35 (Graph 4); After the implant, the Mean, concerning the number of crises, was 12 (Graph 5).

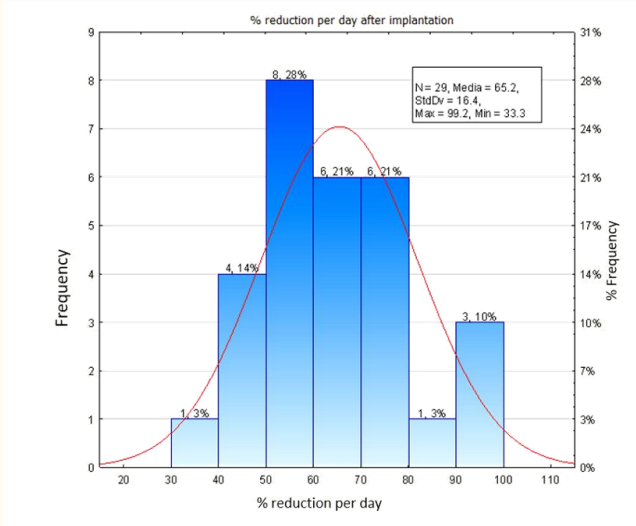


Graph 4: *Before vagus nerve stimulation (VNS), the number of seizures per day ranged from 12 to 64; with a mean and standard deviation of 35 ± 16.6 seizures per day.*



Graph 5: *The number of seizures per day post-implantation ranged from 1 to 30 events; with a mean and standard deviation of 12 ± 7.9 seizures.*

The percentage reduction in the number of seizures per day after VNS implantation had a minimum of 33.3% and a maximum of 99.2%, the mean was 65.2%, with a Standard deviation (StDv) of 16.4 (Graph 6).

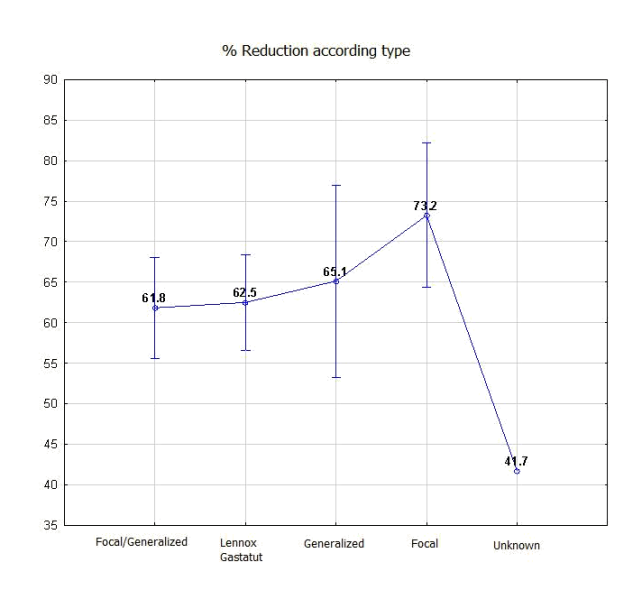


Graph 6: *The percentage reduction of seizures/day for each patient ranged from 33.3% to 99.2%; with the number of seizures per day with a mean and standard deviation of 65.2 ±16.4%. It was calculated following the formula ((Number of seizures Pre - Number of seizures Post) / Number of seizures Pre) * 100.*

Using variance analysis (ANOVA) using pre-post implantation as a factor, the mean response of the number of convulsive crises/day was compared. This analysis revealed a statistically significant difference ($p < 0.00001$). This indicates that the use of VNS was significant in our study population, with a reduction in the number of seizures with an average of 65.2% (maximum percentage of 99.2% and a minimum of 33.3% post-implantation) considering that our population had diagnoses of different types of epilepsy and types of epilepsy seizures, as well as the varied age, both pediatric and adult. Obtaining results with statistical significance about the decrease in the number of seizures.

Statistically, T-tests were used, and in most cases, the P value of .05000 indicates that our results with the placement of the VNS implant in patients with drug-resistant epilepsy are not by chance. It has an acceptable level of significance in the treatment of these patients with complex treatment, this type of therapy being effective.

The mean response in seizures per day according to the type of epilepsy was: 61.8% for generalized/focal epilepsy, 62.5% in Lennox Gastaut syndrome, 65.1% in generalized epilepsy, 73.2% for focal epilepsy, and 41.7% for unknown epilepsy (Graph 7).

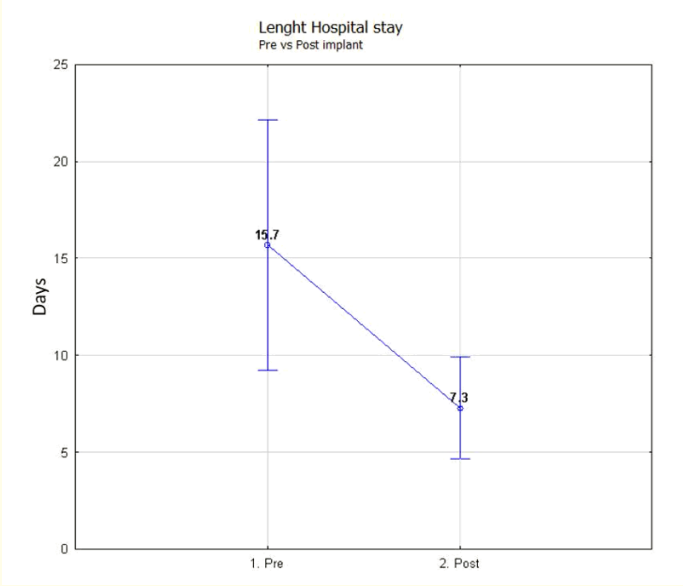


Graph 7: *With variance analysis (ANOVA) of one factor (Type of Epilepsy), the average performance of the percentage reduction in the number of seizures/day tends to be increasing as shown in the graph, except for the drop in the type of unknown epilepsy.*

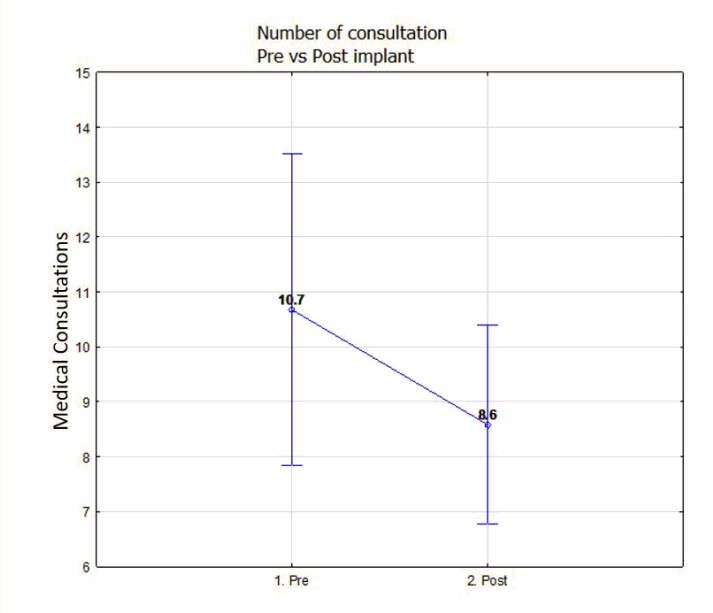
The mean response of the hospital stays days from pre to post-implantation was: 15.7 pre-implantation, and 7.3 post-implantation (Graph 8). The mean response of the number of consultations from pre to post-implantation was: 10.7 before implantation, and 8.6 after implantation (Graph 9).

Discussion

Currently, we have as never before the availability of AED, which have improved their effectiveness, optimizing better control of epilepsy, even reducing the use of 2 different drugs, avoiding what we commonly call polypharmacy, and even improving patient tolerability, causing fewer side effects. Up to 63 - 70% of patients may be seizure-free [19].



Graph 8: *Length hospital stay mean response comparison. It is read that it dropped from 15.7 days to 7.3 days. Thus, a reduction of 50% is concluded.*



Graph 9: *The number of consultations dropped from 10.7 consultations to 8.6 consultations. A reduction of 19.62% is concluded.*

The treatment of epilepsy, in recent years, has an arsenal, in pharmacological treatment, as well as neurosurgical, consequently, there is a favorable control of convulsive crises. However, epilepsy is one of the most frequent chronic neurological diseases. It affects at least 50 million people worldwide. Although much has been understood about its causes, and the aforementioned treatments have improved, epilepsy continues to be a brand disease or social signaling and many patients are victims of prejudice and social exclusion. The quality of life of people affected by the disease is significantly compromised due to seizures, antiepileptic drugs (AEDs), cognitive impairment, and physical limitations [20].

Currently, medically resistant epilepsy is considered a health problem worldwide, since it is presented by approximately one-third of epileptic patients.

So, the financial burden is substantial, and among all uncontrolled patient health costs, almost 50% is related to the costs of drug-resistant epilepsy care. A high percentage still does not have a precise diagnosis, so the data can reach even more alarming figures [21].

For these patients with a diagnosis of drug-resistant epilepsy, whose treatment is generally complex, functional epilepsy surgery may be indicated, obtaining a benefit of up to 80% control of seizures, depending on different aspects such as follow-up time and location of the epileptic focus [20] However, even with the success percentage of functional epilepsy surgery, there is a percentage of patients who continue to have seizures, so treatment becomes even more complex, requiring new treatment alternatives, one of them is vagus nerve stimulation (VNS), considered a palliative therapy, but currently represents coadjuvant treatment, with effectiveness in patients diagnosed with drug-resistant epilepsy of different etiologies [22].

Vagus nerve stimulation (VNS) plays a very important role in cases where epilepsy exceeds the complexity of standardized treatment. In these cases, where first-line treatments are not enough to achieve control of seizures, with all that it entails for the patient and family members of not having control of the evolution of the pathology. Safe and effective treatment is required, even if it is only palliative. VNS is considered a palliative treatment that tries to reduce the frequency of seizures in highly disabled patients, and its effectiveness is comparable to, or even greater than, that of some of the new ones AEDs. Patients undergoing VNS experience a reduction in the frequency of seizures of 50% in general, it is worth mentioning that this percentage is even higher in some patients, achieving control of up to 80% [22,23].

VNS was approved by the US Food and Drug Administration (FDA) in 1997 as an adjunctive neuromodulatory treatment for patients older than 12 years with drug-resistant partial epilepsy. In patients with severe and disabling drug-resistant epilepsy, who are not candidates for functional epilepsy surgery, the placement of VNS is proposed as an alternative or palliative treatment, given that it is safe and effective, with studies carried out with human beings ending up demonstrating its clinical utility in patients with this diagnosis [23]. However, the multiple studies carried out worldwide have observed clinical improvement concerning a decrease in seizures, as well as the quality of life, from patients aged 1 month to adulthood, with greater efficacy in pediatric patients, not only in drug-resistant partial epilepsy but in all types of epilepsy, as well as epileptic syndromes, have better control of seizures, to VNS it is not limited to one type of epilepsy [24].

Most studies have observed stable functional cognitive status during treatment and some have even reported additional beneficial effects with VNS, improving general mood and reducing depression, regardless of whether the frequency of seizures decreased. Thus, early and more effective seizure control may improve cognitive outcomes and quality of life in children [25]. Although initial studies had shown that VNS appeared to be an expensive therapy, long-term evaluations duration of emergency department visits and intensive care unit admission costs showed that these exceed the costs of VNS during and after implantation, as well as other parameters such as decreased use of antiepileptic drugs, either in number or dose thereof.

Currently, one of the main goals in improving therapy is to reduce patient risks, which can be achieved by increasing battery life and reducing the number of procedures to replace the generator. According to the manufacturer's manual, setting decreases could increase the durability of the device. A considerable percentage of patients with (VNS) improve with low output currents, even after a late course, since the stimulation effects are not immediate. Furthermore, decreasing the frequency from 30 to 20 Hz and the pulse width from 500 to 250 μs does not reduce the number of fibers stimulated and, consequently, does not interfere with the efficacy of the treatment [26]. Another approach to improve patient care and increase battery life is the use of a rechargeable generator. This is already used in some stimulation devices for the treatment of Parkinson's disease, dystonia, and pain and allows the stimulation to last approximately nine years, compared to three years with non-rechargeable batteries. Despite this can significantly reduce costs, the rechargeable system has some disadvantages, mainly related to the need for routine battery charging, which does not represent a cost-benefit disadvantage, rather than the familiar routine to perform.

VNS is considered a good alternative to drug treatment in patients with refractory epilepsy in several previous studies. However, although many studies have evaluated the efficacy of the technique with quite heterogeneous results up to now, these studies fundamentally evaluate the decrease in frequency, leaving aside such important parameters as the intensity of the seizures, their duration, reduction in medication or quality of life, and cost-benefit [27]. This is largely due to the difficulty in collecting these variables in retrospective studies. In our study we included variables with these parameters, observing favorable results in these little-evaluated variables, but fundamental in the long term in the pathology of such complexity.

A high percentage of our patients have significantly reduced the number of seizures, in the study as described in the number of seizures in frequency per day and, in each patient (29) diagnosed with drug-resistant epilepsy, before implantation of the vagus nerve stimulator (VNS), the number of seizures per day ranged between a minimum of 12 and 64 events per day; with a mean and standard deviation of 35 ± 16.6 seizures per day.

After the placement of the vagus nerve implant (VNS), the results with the improvement or reduction in the number of seizures, we obtained that the number of seizures per day post-implantation ranged between 1 and 30 events per day; with a mean and standard deviation of 12 ± 7.9 seizures, as shown in the graph in the results section.

The significant reduction of epileptic seizures, reduction of seizure events in percentage per day, with a mean of 65.2% reduction of seizure events, with a maximum percentage of 99.2% and a minimum of 33.3%, post-implantation of the vagal neurostimulator (VNS), concerning the pathology and comorbidities of each patient.

These results indicate that vagus nerve stimulation (VNS) is historically considered palliative, however, it has become a safe and effective adjuvant therapy for patients with drug-resistant epilepsy. Even though VNS was approved for focal epilepsies, our study included patients from pediatric age to adulthood, obtaining efficacy in the treatment of focal epilepsy and various types of generalized epilepsy, including idiopathic generalized epilepsy and the Syndrome of Lennox Gastaut. Similar to previous studies, we observed the efficacy of VNS therapy in cases of cryptogenic epilepsies or epileptic syndromes and those with lesions undergoing functional epilepsy surgery without improvement.

Compared to the early series (studies EO1 and EO2) they comprised 15 patients in an open trial and a study by Uthman., *et al*. The average reduction in seizures from the first day to the last day of the 90 days was 43.6% [28].

The EO3 study, a blinded, randomized, parallel-group study of VNS in the treatment of partial seizures conducted at 17 sites in the United States, Canada, and Europe. To be eligible, subjects had to be 13 to 60 years of age, male or female with simple or complex partial seizures, recurring at least 6 or more times per month despite medical treatment, and free of progressive disease. The average age of the

patients studied was 33 years with seizures for an average of 21 years. Candidates had a 12-week baseline follow-up and were subsequently implanted with the left vagus nerve stimulator. The published report analyzed the first 67 patients who completed the 14-week acute phase. The high-stimulation group (n = 31) experienced an average seizure reduction of 31%, and 39% of them experienced a 50% or greater seizure reduction. The low stimulation group experienced an average seizure reduction of 11%, compared to baseline, 19% of patients experienced at least a 50% seizure reduction. It was reported that, in the high-stimulation group, 21% of the seizures were prevented thanks to the contingent activation of the magnet, compared with only 9% in the low-stimulation group. Only 26 of 31 patients in the high-stimulation group and 18 of 36 patients in the low-stimulation group had secondarily generalized seizures. The differences in the frequencies of secondarily generalized seizures were not significant. The follow-up study examined the response to stimulation of the 67 patients, all were converted to high stimulation parameters for open-label treatment lasting up to 18 months: 44% of patients had more than 50% reduction in crisis, which is similar to the initial response of 39%. Mean seizure frequency was reduced to 52% from the 12-week baseline. Overall, a trend toward continued improvement was described in the opening tag portion of the study [29].

Subsequent studies carried out: EO4 and EO5 included another 124 and 196 patients, respectively. EO4 was an open study as a treatment in patients diagnosed with partial or generalized epilepsy. The results in patients with generalized epilepsy mean seizure reduction was 46%, and 11 patients had a reduction greater than 50%. Those who were older at the time of the onset of the seizures and those with more frequent seizures responded better [30].

The EO5 study was the second randomized, blinded study in patients between 13 and 60 years of age, with partial seizures poorly controlled by antiepileptic drugs. Two groups were randomly established: one, with high stimulation, and the other, with low stimulation. The decrease in seizures was significantly higher in the high-stimulation group (28% vs. 15%, $p < 0.04$). The percentage of patients with a 50% reduction in seizures was similar in both groups, although the percentage of patients with a 75% reduction was significantly higher among those with high stimulation [31].

In children, the experience is less, although it seems equally optimistic. Hornig., *et al*. in a study of 19 children, found that 10 (53%) improved their seizure frequency by more than 50%, and six of them (32%) presented a reduction in the number of seizures of more than 90% [32]. Lundgren., *et al*. cite that of six children with Lennox-Gastaut syndrome, five presented a seizure reduction greater than 90%. Other authors confirm this efficacy and report a slightly lower improvement, with six patients out of 13 with an improvement greater than 50% and a single patient without significant improvement [33]. The selection of adolescent patients from studies EO1 to EO5 yields similar results to those of grown-ups; It is worth noting that, after twelve months of follow-up, 17% of patients improve more than 90% in the number of seizures. Recently, data from 38 patients between the ages of 11 months and 16 years indicate efficacy and safety similar to those in adults, broadening the spectrum of seizures that improve to tonic seizures and the absence of them. Also patients with hypothalamic hamartomas and gelastic crises improved in the frequency of crises (three of the six patients) or in autistic behavior (four patients) [34].

The results are quite similar in studies conducted in response to seizure reduction. Follow-up for 25 months of the patients included in the studies with a 46% reduction in seizures, and 35% of patients with an improvement of more than 50% in the acute phase. After a 15-month follow-up in the same patients after the acute phase, the medium-term results were 39% reaching a reduction of 50%; Of these, 30% presented a reduction greater than 75%, as well as cases of variable response with a reduction in seizures of 35% to 40%.

Taking as reference the most important studies with short and medium-term follow-up, with patients of varying ages, as well as types of epilepsy of different etiologies, including epileptic syndromes. Similar results were obtained with the use of vagus nerve stimulation (VNS), it was significant in our study population, with a reduction in the number of seizures with a mean of 65.2%, (maximum percentage of 99.2% and a minimum of 33.3%, post-implantation). Using analysis of variance (ANOVA) of a Factor (Pre-post implantation) the mean response of the number of convulsive crises/day was compared. This analysis revealed a statistically significant difference ($p < 0.00001$).

Although the studies have focused on the results of the reduction of convulsive crises in the short, medium, and long term, above all this variable, has been considered a pillar in the treatment with vagal stimulation, the results being based on the reduction of seizures. seizures, to achieve control in patients with drug-resistant epilepsy.

In our study, an evaluation of variables was carried out, focusing on everything that this type of therapy entails as an alternative in the treatment of drug-resistant epilepsy.

These variables were evaluated, and in general, the results were positive, even higher than we expected. These data obtained are the context of the following variables were included:

I. Days of hospital stay (DEIH).

II. Number of Consultations (Before)/(After) VNS implant.

The surgical intervention for VNS implantation is considered a low-risk surgery, the side effects were often mild and mainly related to the associated post-surgical pain or foreign body, there was no infection of the surgical site, most were without morbidity repercussions in the immediate postoperative period. Being an effective and safe procedure in patients with drug-resistant epilepsy.

The main major complications such as asystole, cardiac arrhythmias, sudden death, bronchial aspiration, hiccups, changes in cerebral blood flow, and some effects on the airway. Side effects with high morbidity and mortality are considered, and described in the placement of the VNS however, in the world literature it is rare for them to occur, with a higher risk in those patients who have comorbidities associated with drug-resistant epilepsy [35]. In our study there were no cases with severe side effects.

On the other hand, it is worth mentioning again the statistical analysis of the control of convulsive crises, the correlation of the best control of the convulsions can result in a better development and cognitive result and the quality of life for the patient and family VNSironment. The results in this first study are similar in comparison with the studies described in centers of recognized prestige in the treatment of VNS. It should not be forgotten that, despite the effectiveness of (VNS), many patients will have to continue with their medical treatment indefinitely.

Conclusion

In recent decades, progress has been made in the development of surgical techniques with greater knowledge of the pathophysiology of the disease, as well as the development of surgical techniques directed at each type of specific epilepsy, allowing better results together with the use of a better diagnosis. with the use of videoencephalograms with more accurate localization of the epileptogenic focus.

At present, despite the advent of new antiepileptic drugs in the treatment, as well as functional epilepsy surgery with its unquestionable improvement in recent decades. The treatment of epilepsy, in recent years, has an arsenal of both pharmacological treatment, as well as neurosurgical, with control of seizures, and even in severe cases have shown a control greater than 80%, first-line treatments have been considered. line in pharmacological order, followed by functional surgery with good results.

The financial burden is substantial, and among all uncontrolled patient health costs, almost 50% are related to epilepsy care costs. Resulting in a pathology of great complexity in its treatment, for which new therapies are necessary for these patients. The results of the trials and the accumulated experience in recent years place (VNS) as an alternative in the treatment of refractory cases, being considered as palliative therapy, however, as has been shown in studies, it works as an adjuvant therapy, not as a last resort after the failure of primary pharmacological or surgical therapy.

We believe that (VNS) has been shown in our study to reduce the number of seizures. With the safety of the procedure during the surgical procedure, with mild, tolerable complications, without forgetting that there are severe complications that, although they are very

rare, are commonly associated with comorbidities if they do occur, achieving control of seizures at any rate. type, as well as in the variability of the different types of epilepsy, even in complex epileptic syndromes, not only in partial focal seizures as was its indication in its beginnings.

It is an effective technique, which not only contributes to the reduction in the frequency of epileptic seizures but also reduces the duration, intensity, and consumption of drugs, days spent in the hospital, and days spent in the emergency room as a result of lack of control. In addition, quality of life is another aspect that should be considered when evaluating therapy (VNS), since psychosocial factors also contribute to improvement. After evaluating the quality of the subjectively in the patient and family, on memory, physical and emotional well-being, depression, and functional limitations.

This study confirms that VNS is a treatment that, historically considered palliative, is now considered adjuvant, with few transient adverse effects and a favorable impact on the frequency, duration of seizures, and quality of life. that justify its indication.

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