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Alberto Verrotti

Department of Pediatrics, University of Chieti, Italy

'Vagal nerve stimulation in intractable epilepsy: clinical experience on 100 patients and review of the literature'

Nelia Zamponi, Elisabetta Cesaroni, Cristina Petrelli, Claudia Passamonti, Roberto Trignani, Franco Rychlicki

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ORIGINAL ARTICLE

Vagal nerve stimulation in intractable epilepsy: clinical experience on 100 patients and review of the literature

Nelia Zamponi[1], Elisabetta Cesaroni[1], Cristina Petrelli[1], Claudia Passamonti[1], Roberto Trignani[2], Franco Rychlicki[2]

Abstract:
Introduction: Vagus Nerve Stimulation (VNS) is an effective alternative treatment for patients with refractory epilepsy. Nevertheless, information regarding VNS is still limited.
Materials and Methods: In the present non randomized, prospectic study we report our clinical safety and effectiveness of VNS in 100 patients (52 Males and 48 Females) with drug resistant epilepsy. Patient's age at implant ranged from 0,64 to 51,04 years (mean age 15.3 years). The mean follow-up time was 54,8 months (range 2 to 108,3 months).
Seventeen patients suffered from Lennox-Gastaut Syndrome, 34 patients suffered from partial epilepsy with drop attacks and secondary bysinchronism on the EEG (Lennox Gastaut-like) and 49 patients had Partial Epilepsy without drop attacks.
Data collection forms were designed for prospectively gathering data on each patient's history, seizures, drug therapy, implant device settings and side effects.
Patients were assessed prior the implant and 3, 12 and 24 months after surgery.
Results: Seventy-eight patients completed the 24 months follow-up session. VNS produced a mean seizure rate reduction of 32% at 3 months, 41% at 12 months, and 45% at 24 months. At 24 months, only the Partial Epilepsy patients showed a seizures reduction of 50%, which is considered clinically significant. Moreover both the age at implant and epilepsy duration were inversely correlated with the percentage of seizure reduction at 24 months.
Side effects were minor and transient; the most common were voice alteration and coughing during stimulation. In 7 patients electrode breakage occurred three years after the surgical procedure
Conclusion: In our study, clinical effectiveness is higher in younger children implanted before than 12 years with shorter epilepsy duration suggesting a precocious useful role of VNS. Patients with Lennox Gastaut Syndrome show a worse clinical response rather than other epileptic syndromes.

Key words: vagal nerve stimulation (VNS), epilepsy, children, efficacy, safety
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Introduction

Epilepsy is one of the most common disorders encountered by neurologists in their day-to-day practice. A subset of patients results refractory to antiepileptic drugs (AEDs) and even polytherapy with three or more front line AEDs does not achieve adequate seizures control. Drug-resistant epilepsy, defined as a failure to attain seizures control after 3 treatment attempts, is a significant problem affecting 25–40% of people with epilepsy.

[1] Pediatric Neurology Department, Ospedali Riuniti, Ancona, Italy
[2]Neurosurgery Department, Ospedali Riuniti, Ancona, Italy

Corresponding: Neila Zamponi, MD
Pediatric Neurology Department, Ospedali Riuniti, Via F Corridoni 11 Ancona, Italy.
Tel: +390715962684
Fax: +390715962502
e- mail: n.zamponi@tin.it

In the last ten years, Vagal Nerve stimulation (VNS) has significantly modified the surgical approach to the drug resistant epilepsy which cannot be treated by resective surgery. In 1988, Penry, Wilder, Ramsay and colleagues performed the first implant of a vagal stimulating device into a human. Because of these encouraging results, a randomized active control study (E03) was carried out in 1992. Other controlled studies were performed, including the pivotal E05. In 1994; the European Community approved the use of VNS for seizure prevention and control. [1-5] On July 16, 1997 the US Food and Drug Administration (FDA) approved the use of VNS as an adjunctive treatment for refractory partial-onset seizures in adults and adolescents older than 12 years.

The advent of VNS has aroused a renewed interest in neurostimulation and opened up new perspectives in the treatment of the epilepsies [6]. It has become evident that VNS offers a substantial therapeutic benefit to some patients without causing major side effects. Therefore, it has become the first choice treatment for a great number of intractable epileptic patients for its reliability, low risk of complications, reversibility and lack of major side-effects. [7-10] Currently, VNS is considered a palliative treatment with the goal of reducing the frequency and severity of seizures, although a small proportion (about 5%) of patients have been reported to be seizure-free. [6,11-13]. Patients treated for three years were reported to have a median reduction in seizure frequency of ~40-45%. Similarly, there was an improvement in the percentage of patients with >50% reduction in seizure to about 45% [10,12-14].

Data about efficacy in children are less extensive than in adults and more limited informations are available regarding patients aged 18 years or younger. [15,12,16, 17-27]. However, the results are encouraging and clinical response seems to be the same or better than in adults.

At present time it is not possible to identify the patients who may be considered the "best responders" to the treatment. Furthermore, is not always possible obtain detailed information from the literature about the different types of seizures and epileptic syndromes included in the clinical trials and clinical results are often not homogeneous and sometimes conflicting.

In the present non randomized, prospectic study we report our clinical experience in 100 patients VNS implanted with refractory epilepsy. The aim was to evaluate safety and effectiveness of VNS, in different epileptic syndromes and identify clinical features correlated with better results.

Material and Methods

Patients population and study design

One hundred patients (52 Males and 48 Females) with drug resistant epilepsy were included. Patient's age at implant ranged from 0,64 to 51,04 years (mean age 15.3 years). The mean follow-up time was 54,8 months (range 2 to 108,3 months). Patients were eligible for the study if they met the following criteria:

- Lennox-Gastaut Syndrome
- Partial Epilepsy with multiple seizures, bysinchronous EEG and drop attacks (Lennox Gastaut-like)
- Partial Epilepsy with multiple seizures, without bysinchronous EEG and fall seizures
- Absence of progressive or systemic diseases
- Seizure frequency higher than 10 per month

Patients with severe swallowing difficulties, severe self-mutilating behaviour, recent onset epilepsy, progressive metabolic or degenerative disease, congenital heart defects, gastrointestinal diseases (mainly gastroesophageal reflux), or with poor parental compliance, were not included.

17 patients suffered from Lennox-Gastaut Syndrome, 34 patients suffered from partial epilepsy with drop attacks and secondary bysinchronism on the EEG (Lennox Gastaut-like) and 49 patients had Partial Epilepsy without drop attacks.

Etiology of epilepsy was cryptogenic in 34 patients and symptomatic in 66.

The etiology of symptomatic forms includes 11 patients with neurologic damage secondary to prematurity and perinatal anoxic/ischemic lesions, 1 patient with post traumatic lesion, 3 patients with herpethic encephalitis, 5 patients with neurological sequels of bacterial meningoencephalitis, 22 patients with cortical dysplasia, 13 patients with Bourneville Tuberous Sclerosis, 1 patient with vascular malformation of the middle cerebral artery, 1 patient with neurological sequels of near SIDS, 4 patients with chromosomopathy and 5 patients with Dravet's syndrome (SCN1A mutation).

Overall, mean seizure frequency was always very high. 76 patients had daily seizures up to a maximum of 40 seizures per day.

In all cases treatment with at least two antiepileptic drugs in variable associations had been tried unsuccessfully.

Interictal and ictal EEGs were available in all patients. The seizures' characteristics were assessed by video-EEG recordings in 77 patients.

The neuropsychological assessment showed severe mental retardation in 54 cases, moderate in 28 cases and mild mental retardation in 17.One patient had normal intelligence quotient (IQ). Focal neurologic disorders, including hemiparesis or tetraparesis, were present in sixty-tree cases.

Lennox Gastaut Syndrome

Seventeen patients (12M, 5F) have been diagnosed as Lennox Gastaut Syndrome.

They showed the typical elettroclinical pattern of the syndrome and in eight patients spasms were present in the first five months of life.

Mean age at the implant operation was 13,2 years (5-25,2 years) with a mean epilepsy duration of 11,7 years (4-25 years).

Multiple seizures (atypical absences, tonic seizures, tonic-clonic generalized seizures) were present, with frequent and very disabling tonic or atonic drop attacks (average seizure number 330 per month).

All patients showed neurological focal deficits and mental retardation, severe in 15 cases and moderate in 2.

Lennox Gastaut like:

Thirty-four patients (17M ,17F) were affected by partial epilepsy with multifocal frontal or frontotemporal EEG abnormalities and important secondary bilateral synchrony. Multiple seizures were present, mainly partial complex or secondary generalized and drop attacks. Usually, falls followed a tonic asymmetric contraction of axial and leg muscles leading to a loss of balance. Mean age at the implant was 14,3 years (2,21-51 years) with a mean epilepsy duration of 12,5 years (2-29,4 years) and an average seizures number per month was 422. Mental retardation was severe in 27 patients, moderate in 6 patients and mild in 1 patient.

Partial Epilepsy

Forty-nine patients (23M, 26F) had Partial Epilepsy with polymorphic seizures mainly

complex partial or secondary generalized without tonic seizures and drop attacks.
The EEG pattern was characterized by focal or multifocal discharges without secondary diffusion.
Mean age at surgery was 16,7 years(0,64-50,8 years) with a mean epilepsy duration of 13,1 years (0,6-44 years) and an average number of seizures per month was 234.

Severe mental retardation was present in 12 patients, 20 children showed moderate mental retardation, 16 mild and 1 had normal IQ.

Study design

Data collection forms were designed for prospectively gathering data on each patient's history, seizures, drug therapy, implant device settings and side effects.
Patients were assessed prior the implant and 3, 12 and 24 months after surgery.

Medical outcome measures

Once the definitive target parameters of stimulation were reached the follow-up was extended to every 3 months in the first year and to every 6 months in the next years in order to evaluate the degree of tolerance and the clinical efficacy of VNS.

The clinical efficacy was determined by comparing the seizure frequency during the last 3 months of follow-up with the seizure frequency during the pre-implantation period, using the following formula: [seizures/month on VNS – baseline seizures/month] / [baseline seizures/month] x 100 [11]. Responder patient is a case with a seizure reduction of 50%. The best responder is a patient with seizure reduction ≥75%.

The seizures were encoded according to the International League against Epilepsy classification as follows: Complex Partial Seizures (CPS), Complex Partial Secondary Generalized (CPSG), Myoclonic seizures, Tonic seizures, Tonic- clonic seizures, Absence, Drop attacks. [22]

The antiepileptic therapy was not changed during the first 6 months after surgery.

Neuropsychological Outcome measures

Mental age was assessed using a battery test consisting of three different cognitive tests depending on the chronological age: Brunet Lezine Scale (0-2 years), Stanford- Binet (Terman-Merrill) Scales (2-6 years), WISC-R (above 6 years).

Statistical analysis

Seizure frequency changes in the three patients groups have been collected at baseline, 3 months, 12 months and 24 months. In order to evaluate the effect of VNS along time in groups with different epileptic syndromes, a repeated measures ANOVA, with "Groups" (Lennox, Pseudo-Lennox, Partial) as Between Factor, and "Sessions" (baseline, 3 months, 12 months and 24 months) as Within Factor, was carried out. Duncan-test was used for post-hoc comparisons.

The correlation between some clinical parameters (epilepsy duration and chronological age at implant) with the mean seizures reduction at two years was assessed by Pearson correlation Test.

Moreover, in order to evaluate the influence of the age at implant and the level of mental functioning on the percentage of seizure reduction at 2 years, an additional three -ways ANOVA was carried out.

The main factors were "Groups" (Lennox-Gastaut syndrome, Lennox-Gastaut like, Partial Epilepsy), age at implant (<12 years *vs*. ≥12 years) and level of mental functioning (mild retardation vs severe retardation).

Surgical procedure

The operation is typically performed with the patient under general anesthesia or regional cervical blocks. An incision is performed on the left side of the neck to expose the left vagus nerve. Subsequently an incision is made below the clavicle or in the lateral part of the chest and a pocket for the pulse generator is created just below the fascia of the pectoralis muscle to host the stimulating unit at the distance of about 7 cm from the electrodes. An electrode lead is passed from the neck to the chest incision.

Electrodes are then placed around the vagus nerve, the lead is attached to the pulse generator, and the construct is tested.

At this point, the anesthesia team should be notified that bradycardia, complete atrioventricular block, and asystole have been reported [28].

The first 10 patients of our series underwent a standard VNS procedure with a chest incision for pulse generator and a neck incision for electrode positioning.

Since 2001 the surgical technique has been modified by using a single cervical incision.

The device is tested for function and the electrode impedance is checked prior to leaving the operating suite. Usually the device is activated 3 days after the implantation. Prophylactic antibiotics are administered either preoperatively and 7 days postoperatively. Most patients are ready for discharge within 3 days and often earlier than that.

Stimulation Parameters

Children were discharged 72 hours after surgery with neurostimulator switched ON and thereafter re-evaluated as outpatients every week for 1 month for the ramp-up.

The VNS generator is non invasively programmed via an externally placed programming wand and software on a standard personal computer.

A number of parameters can be adjusted with the aid of the hand held interrogation device (programming wand).

The intensity of stimulation was increased step by step of 0.50 mA until the stimulation parameters reached 2 mA, at a frequency of 30 c/s, with OFF-period of 5 minutes alternating with ON-period of 30 seconds (standard stimulation setting). During this adjustment period, ECG-coupled poligraphyc EEG was systematically performed at the beginning of the activation, and while the intensity of stimulation reached 1 mA and 2 mA. In 67 cases, the standard stimulation setting was switched to an intermediate stimulation pattern (ON period 30 sec and OFF period 3 min) after 3 months for an unsatisfactory clinical response.

The patient is encouraged to swipe the hand held magnet over the generator at the onset of the epileptic aura. This triggers the release of a train of stimuli superimposed on the baseline discharge of the generator. This may aborted the seizure or prevent it from getting secondarily generalized. It must remember that the baseline output from the generator is always on. The stimulator battery would last 6-8 years.

It has been reported that as the battery reaches the end of its life, one can see increased seizures and changes in mood and attentiveness even if testing is unremarkable.

Results

Descriptive analysis

Seventy-eight patients completed the 24 months follow-up session. For this reason only data from these patients were considered for statistical analysis. Follow-up sessions were conducted at three months, 12 months and 24 months after VNS implant. In this

period, VNS produced a mean seizure rate reduction of 32% at 3 months, 41% at 12 months, and 45% at 24 months. At 24 months, only the Partial Epilepsy patients showed a seizure reduction of 50%, which is considered clinically significant. Lennox-Gastaut like patients showed a mean seizures reduction of 47%; Lennox-Gastaut patients gained the lowest seizure reduction (37%). (Figure.1)

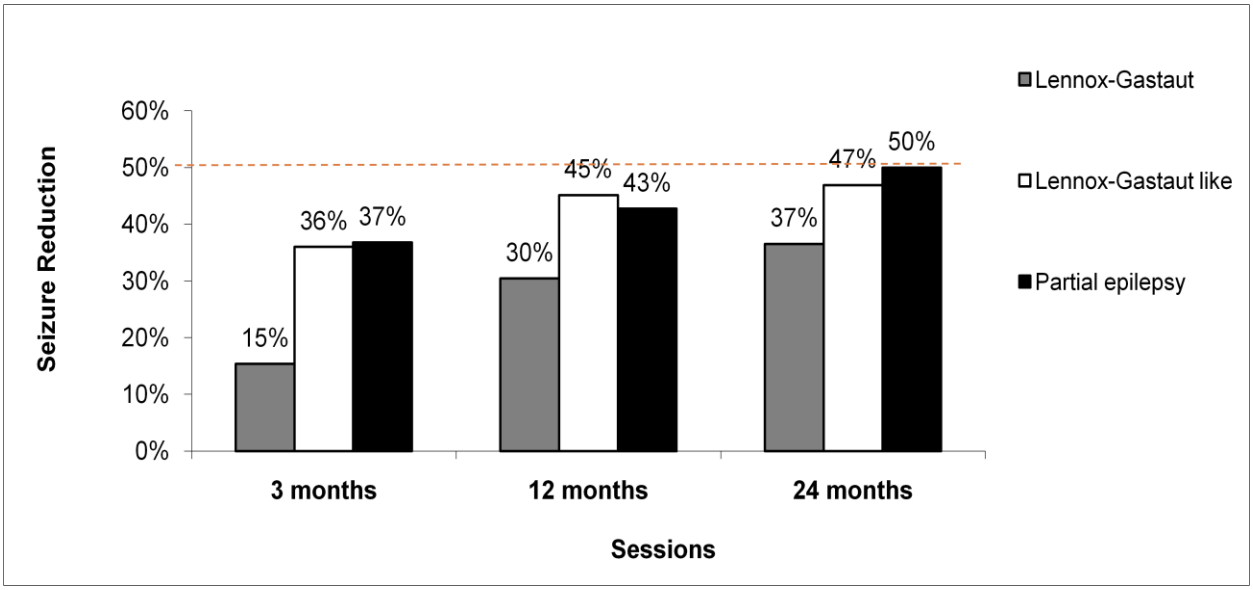

Figure 1. Percentage of seizures reduction in each clinical groups at each session.

At three months of follow-up, 12% of treated patients were considered best responder. The percentage increased to 14% and 24% at one year and two years respectively. (Figure 2)

Only 5 patients showed a transient worsening of seizure pattern during the first three months of treatment. Seven patients (7%) reported a seizure free period lasting more than 1 year.

Six of them were affected from partial epilepsy without drop attacks.

This result was obtained in the first 6 months post VNS without changing AEDs.

Statistical Analysis

ANOVA performed on seizures frequency showed a significant Group *Session interaction [F (6,102) =2,70, p=0,01].

In the group of Lennox Gastaut Syndrome no significant differences were found between seizure frequency at baseline (number of seizure per month: 330) and seizures frequency at 3 months (284, p= 0,4 n.s.), at 12 months (241, p= 0,1 n.s) and at 24 months (223, p=0.08). To be noted, in this latter follow-up session seizure reduction was close to significance.

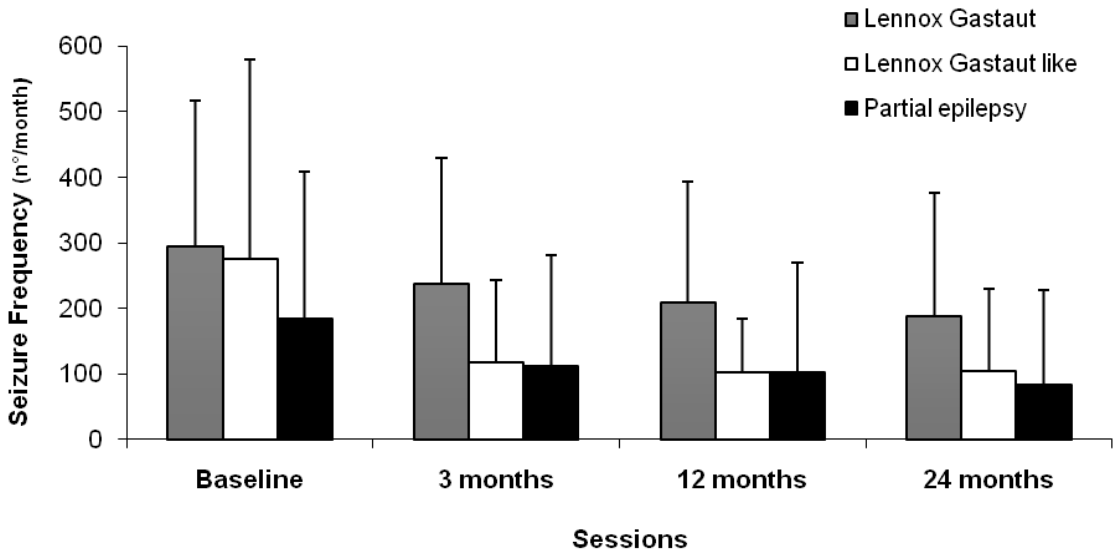

Figure 2. seizure frequency per month in the three groups along session.

On the contrary, patients with Lennox Gastaut like showed a highly significant reduction in seizures frequency at 3 months (97, p<0.0001), at 12 months (101, p<0.0001) and at 24 months (122, p<0.0001) compared to baseline (422).

Similarly to the previous group, in patients with Partial Epilepsy a significant reduction was found at 3 months (130, p=0.05), at 12 months (121, p=0.05) and at 24 months (107 p=0,04) compared to baseline(234) (Fig.2).

Both the age at implant (r:-.39, p<0,001) and epilepsy duration(r:-.34, p=0,002) were inversely correlated with the percentage of seizure reduction at 24 months. That is, the amount of seizure reduction was greater for patient implanted earlier and with shorter epilepsy duration. Furthermore, these two clinical parameters were highly positive correlated one to each other (r: .9, p<0,001). ANOVA revealed a significant effect of main factor "Age at implant" [F(1,72)=5,42, p=0,02], but no significant effect of the level of mental functioning, nor any significant interaction. Therefore, patients implanted before 12 years gained a significantly higher seizures reduction (56,5%) compared to patient implanted after 12 years (35%, p=0,009).

Therapy

Patients assumed an average of 2.9 antiepileptic drugs (AEDs) before operation. At the cut off date the mean number of AEDs is reduced to 1.8. At 2 years follow-up, 33% of patients were able to simplify their drug therapy as AEDs number or dosing reduction without compromising seizure control.

Side effects

The side effects of the short and long term VNS are of mild entity. Common adverse effects such as cough, hoarseness, voice alteration tend to improve and disappear with time. In our series transient pain was reported in 11 patient at the site of implantation of the neurostimulator. 47/100 patients reported hoarseness and coughing during the setting phase when increasing the stimulation parameters. Both these events resolved in 1 to 2 days after the stimulations adjustment.

Lead breakage must be considered an important complication rarely reported in the literature [29], but in our series occurred in 7% of patients (7/100) three years or more after surgical implantation without history of trauma or drop-attacks. The breakage has been discovered accidentally performing a lead test that showed high impedances and did not present as an absence of perceived stimulation.

When clinical results is satisfying it becames mandatory to perform a new surgical procedure after removing all the previous device, but sometimes it's not possible to take away the coils without damaging vagal nerve, yet could be not so easy to find a free nerve tract to host the coils.

Discussion

VNS was initially approved by the FDA for patients aged 12 years and older with refractory partial onset seizures. However in the next years VNS was also successfully used for generalized seizures [30,31], pediatric population [8,19,32-35], Lennox-Gastaut Syndrome [36] Tuberous Sclerosis [37], severe epileptic encephalopaties [21].

Currently, VNS is not regarded as a front-line therapy but instead is considered only after medical therapy has failed and a patient has been deemed an unsuitable candidate for resective surgery or is unwilling to accept the risks of surgery.

The reason of this is due in part to a lack of understanding with respect to the mechanism of action and because the indications of which patients will benefit and which will not still very clears. Overall, the results of these controlled clinical trials with VNS are comparable to what is seen with many of the new antiepileptic drugs in intractable epilepsy patients, but are not as favorable compared to traditional resective epilepsy surgery [4,38,39]

Long-term follow-up of patients with VNS suggests that efficacy may improve with continued use, although this conclusion is based on uncontrolled, "open-label" studies that are subject to certain biases limiting interpretation of the data.

Patients with VNS implanted for three years were reported to have a median reduction in seizure frequency of ~40-45%. Similarly, there was an improvement in the percentage of patients with >50% reduction in seizure to about 45% [10,12-14]. De Herdt presented efficacy data on 138 pts in a multicenter study. This was an uncontrolled, open label retrospective study to evaluate long term outcome in patients treated with VNS for refractory epilepsy .They found that the overall reduction in mean monthly seizure frequency was 51% while seizure freedom was obtained in 12/138 patients (9%). [40] Labar looked at seizure rates after 3 and 12 months of VNS therapy in a cohort of 269 patients. Seizure rates improved between 3 months (median 45%) and 12 months (median 58%). [41]

Data about efficacy of VNS in children are less extensive than in adults.

In a study on 60 children, with mean age of 15 years, Murphy reported a median reduction in seizure frequency of 44%[20]. In 2001 a six centers retrospective study evaluating the effectiveness of VNS therapy in 125 children with Lennox-Gastaut Syndrome (LGS), reported an average seizure reduction of 36.1 % at 3 months and 44.7% at six months [34]. Kabir retrospectively reviewed the data of 69 children who had insertion of vagal nerve stimulator (VNS) for medically intractable epilepsy. Outcome was based on the Engel's classification. Thirty-eight patients (55 %) had a satisfactory outcome (Engel class I, II or III) and in 31 patients (45 %) there was no worthwhile improvement of seizures (Engel class IV). There was no statistical significance

between the type of seizure and outcome ($p = 0.351$).

Statistical analysis also showed that the following parameters did not significantly influence the outcome ($p > 0.05$): age at insertion of VNS, age of first fit, duration between first fit and insertion of VNS and the length of follow-up. [42]

Zamponi et al reported six very young patients, less than 3 years old (mean age at implant 1.6 years). All patients suffered from severe cognitive impairment and catastrophic epilepsy. The mean follow-up time was 41.6 months. Four of six children have shown a significant, persistent improvement in seizure control (range, 60-90%). [43]

The VNS has been used for patients who have generalized severe symptomatic epilepsy.

Hornig reports a positive response (reduction in total seizure number >90%) in 83% of 6 children with Lennox-Gastaut syndrome, without specifying the typology of their seizures [17]. Parker et al does not report positive results in the 11 children with Lennox-Gastaut that they examined [21].

Frost describes the results of a multi-centre study that includes 50 pediatric and adolescent patients diagnosed with Lennox-Gastaut syndrome. He found an 88% reduction in drop attacks after 6 months of VNS while partial complex seizures fell by only 20%. [36]

The global outcome of VNS treatment in our patients series confirms earlier reports of the literature. Our data showed that seizure free patients or those who experienced a seizure reduction more than 75 % are a more consistent group. At three months 12% of treated patients were considered best responders. The percentage increased to 14%, and 24%, at one year and two years respectively.

The positive response was achieved very early after surgery and progressively improved with time, confirming that the duration of stimulation is an important factor in clinical long term improvement as result of a cumulative effect of the continue electrical stimulation on vagus nerve [44,45].

The aim at the present study was to evaluate safety and effectiveness of VNS in different epileptic syndromes, and identify clinical features correlated with better results.

At the moment data reported in literature do not allow to identify which kind of epilepsy is most suitable for surgical treatment by VNS.
Our series includes three types of epileptic Syndromes that are Lennox Gastaut Syndrome, Partial Epilepsy and Lennox Gastaut like Syndrome.

The clinical effectiveness of the VNS seems greater in the group of patients with partial epilepsy and Lennox Gastaut like Syndrome, whereas Lennox-Gastaut patients do not obtain a significant improvement.

It is important to notice that only patients with partial epilepsy syndrome reach the clinical criterion of 50% seizure reduction.

In our series, statistical analysis shows a significant effect of the age at implant on seizure frequency reduction. In fact, patients implanted before 12 years gain a significantly higher seizure reduction compared to patient implanted after 12 years.

Moreover, ages at implant and epilepsy duration are both inversely correlated with the percentage of seizure reduction at 24 months.
That is, the amount of seizure reduction is greater for patient implanted earlier and with shorter epilepsy duration.

The positive effect of young age on clinical outcome is supported by various pediatric series. [8,32-35]

Side effects

Placement of a stimulator is generally safe, with few complications or side effects. The surgical procedure was well tolerated in all cases without noticeable complications.

The aesthetic damage related to the size of the stimulator was acceptable in all the cases. Adverse effects of VNS can be divided into acute perioperative and long term.

One of the most dramatic and rarest is asystole that can occur during intraoperative lead testing. [28] The manufacturer reports the occurrence rate in approximately 0.1% or less.

Other acute complications include bleeding, vocal cord paralysis occurring in about 1% of patients, wound seromas and dehiscence and infection.

In published trials, infection was the most commonly observed surgical complication of either the generator site or lead implantation site. The overall infection rate was 3% but only about 1% required explantation of the device being the other patients successfully treated with antibiotic therapy only. In our experience no infection was observed perhaps for the use of a prolonged antibiotic therapy. Transient side effects of chronic VNS occurred frequently and include hoarseness, cough, voice changes, dyspnoea, headache, nausea and neck spasms. They are usually dose-dependent and occur during stimulus delivery only. All these side effects are reversible, well tolerated and did not precipitate discontinuation of the treatment. [29,38]

More recent adverse events reported such as the effects of VNS on sleep-related breathing and heart rate. Respiratory pattern changes in sleep with VNS were seen in seven of eight children reported by Nagarajan but the changes did not meet the criteria for apnoea/hypopnoea and there were no significant hypoxia or hypercapnia. [46]

Late-onset bradyarrythmia must be regarded as an extremely rare complication. Two patients have been reported in the recent literature. [47,48]

In our series, transient pain at the site of implantation of the neurostimulator and hoarseness and coughing during the setting phase when increasing the stimulation parameters were present. Both these events resolved in 1 to 2 days after the stimulations adjustment.

A change in the vocal timbre was reported in all patients during the stimulation period, however this never represented a significant problem.

Lead breakage occurred commonly in the early history of vagus nerve stimulation with a rate of 0.12-2.7%. It was due to “fatigue” of the lead wire and the electrode contact.

Some unusual circumstances may rarely cause lead breakage such as drop attacks, trauma, self manipulation, excessive generator movement, and suturing directly to the lead body. In addition, the normal growth during childhood could place additional strains on the leads and damage them.

In our series (100 patients implanted), a lead breakage occurred in 7 patients three years or more after surgical implantation without history of trauma or drop-attacks. The generator device may be easily taken away, but removal of the electrodes would injury vagal nerve because they are wrapped around the nervous trunk. Is our experience that the removal of the stimulation electrodes may be possible even after a prolonged period of implantation in spite of the presence of a marked fibrosis in the nerve. In this circumstance we found that it is less traumatic to cut the spiral electrodes piece to piece than to unwind them from the nerve. [9]

Conclusions

Vagus Nerve Stimulation is an effective palliative treatment for patients with refractory epilepsy. Although we do not yet know the mechanism of action or the ideal combination of device parameters, drugs, and diet, VNS certainly appears to have a positive effect in the patients with epilepsy without distinguish which kind of epilepsy is most suitable for surgical treatment.
Clinical response was early evident and efficacy progressively improved with the duration of treatment up to 24 months postoperatively.

In our study, clinical effectiveness is higher in younger children implanted before than 12 years with shorter epilepsy duration suggesting a precocious useful role of VNS. Patients with Lennox Gastaut Syndrome show a worse clinical response rather than other epileptic syndromes.

Long term clinical studies with larger homogeneous series of patients are needed to further define the best responders in the epilepsy syndromes and to guide the search for the operation time.

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