Treatment of Medically Refractory Epilepsy: A Review Of Vagus Nerve Stimulator

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Citation

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Abstract

INTRODUCTION

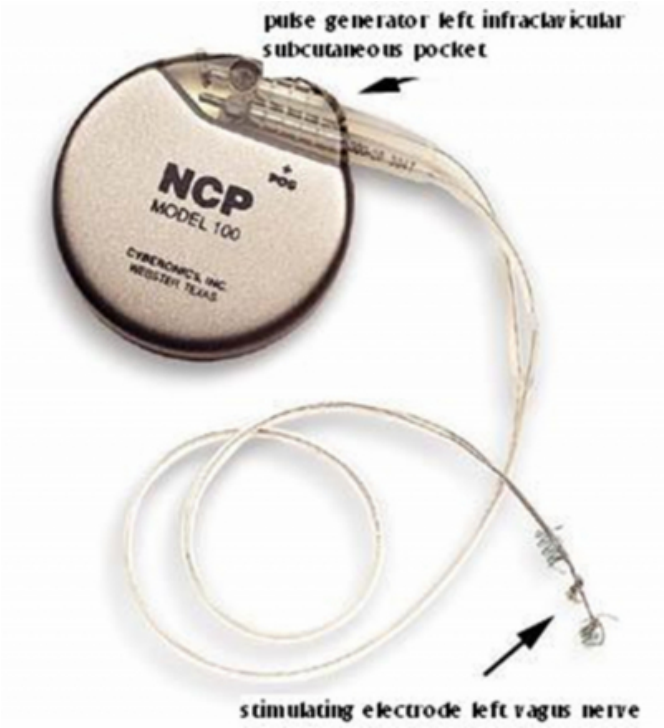
Epilepsy is among the most common disorder encountered by neurologists in their day-to-day practice. While the majority of seizures can be readily controlled with anti-epileptic drug (AED) therapy, there remains a small subset of patients who are refractory to AEDs. In these patients even polytherapy with three or more frontline AEDs does not achieve adequate seizure control. In the past the medical community had little to offer these medically intractable epilepsy patients whose quality of life was severely affected by ongoing chronic seizures. In the last decade nonpharmacological treatment options of vagus nerve stimulation (VNS) and responsive neurostimulation (RNS) have provided new ammunition in the fight against epilepsy. These options for medically refractory epilepsy shall be discussed in this article.

VAGUS NERVE STIMULATOR (VNS)

The vagus nerve stimulator (VNS) (manufactured by Cyberonics Inc, Houston, Tx) gained FDA approval in 1997 for the adjunctive treatment of patients over 12 years of age with medically intractable partial onset seizure disorder. Traditionally these are patients who have failed at least 3 frontline AEDs. VNS is a simple device consisting of 2 electrodes, an externally programmable pulse generator and a battery pack. The stimulating electrode is implanted around the midcervical portion of the left vagus nerve while the impulse generator along with the battery pack is implanted in a subcutaneous pocket in the left infraclavicular region. The left vagus nerve is the preferred site of stimulation due to the higher risks of cardiac arrhythmias with right vagus nerve stimulation. This is on account of the fact that the right vagus nerve innervates the sinoatrial node and thus influences heart rate and rhythm. The pulse generator is programmed externally through the skin via a magnetic wand. Different parameters of stimulation can be programmed such as current strength, pulse width, pulse train frequency, current on and off times as well as magnet current strength.

Figure 1

Figure 1: Vagus Nerve Stimulator (Cyberonics Inc, Houston, Tx)



MECHANISM OF ACTION OF VNS

The precise mechanism of action of VNS remains undetermined. The vagus nerve is a long cranial nerve with extensive distribution to head, neck, thoracic and abdominal viscera. In the brain it has extensive afferent inputs to many different areas such as the reticular formation, thalamus, limbic system and the neocortex. The VNS send electrical

impulses via the left vagus nerve to the nucleus of tractus solitaries (NTS). From the NTS are outflow tracts to different areas of the cortex as well as the brain stem such as to the reticular formation and to the locus ceruleus (LC). The LC is a major norepinephrine (NE) secreting nucleus in the brain. Increased release of norepinephrine and serotonin may underlie the antiepileptic actions of VNS by either increasing the release of gamma amino butyric acid or by inhibiting the release of glutamate. Research has shown that rats in which the LC is destroyed, VNS is no longer effective in controlling seizures.

Other researchers1-4 have suggested widespread cortical de-synchronization by the afferent volley of impulses leading to inhibition of recruitment of epileptic discharges. This increases the seizure threshold and thus aborts a seizure. Another mechanism proposed for VNS action is alteration of cerebral blood flow (CBF) in specific areas of the brain though this theory is not widely accepted. Effects on the amygdala may mediate the antidepressant effects and mood elevating effects of VNS.

STIMULATION PARAMETERS

Once the VNS device is in situ with the pulse generator in the subcutaneous pocket and the leads placed on the midcervical portion of the left vagus nerve, a number of parameters can be adjusted with the aid of the hand held interrogation device (wand). The output current, frequency, pulse width and signal on and off time are set on the generator. Activation is usually initiated at 0.25mA current and can be gradually increased in increments of 0.25mA till the desired effect is obtained. The other initial factory settings are as follows, pulse width of 250-500 microsec, 20-30 Hz frequency and signal on for 30 seconds and off for 3-5 minutes. 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 abort the seizure or prevent it from getting secondarily generalized. One must remember that the baseline output from the generator is always on.

STUDIES SHOWING CLINICAL EFFICACY OF VNS

A recent long-term descriptive prospective study from the Netherlands looked at the efficacy of VNS in patients with pharmacoresistant epilepsy. The study included 19 patients, 11 males and 8 females, aged 17-46 years who had received between 3-16 (mean 9) different AEDs and were not surgical candidates. Follow up after VNS implantation ranged from 2 to 6 years (mean 4 years). Efficacy was measured as the percentage change in seizure rate during 1 year and then after each year follow-up of VNS compared to 5 months baseline before implantation. Ardesch et al. found that mean seizure reduction at 1-6 years was, respectively, 14% (n = 19), 25% (n =19), 29% (n = 16), 29% (n = 15), 43% (n = 9) and 50% (n = 7). Two of their patients were able to live independently without supervision after VNS implantation. One patient died after 2 years of follow-up possibly as a result of SUDEP. Four patients had no apparent reduction in seizure frequency and two of these had their stimulator removed. The other two patients however had significantly reduced post-ictal periods and seizure time. One stimulator had to be switched off due to adverse effects, even though there was a positive effect on the patient's seizure frequency. Common adverse effects in their study were hoarseness and coughing during stimulation while one patient developed a temporary paralysis of his left vocal cord.

De Herdt et at2. presented efficacy data on 138 patients (67M/71F) in a multicenter study from Belgian. This was an uncontrolled, open-label retrospective study to evaluate long-term outcome in patients treated with VNS for refractory epilepsy in seven different epilepsy centers in Belgium. Inclusion criteria were a follow-up of at least 12 months and a documented seizure diary before implantation and at maximum follow-up. Primary outcome measures were the reduction in mean monthly seizure frequency and the percentage of patients with a seizure reduction of at least 50% (responder rate). The mean number of AEDs before implantation was 3 (range 1-5). About 117/138 patients had focal epilepsy, 21 patients had symptomatic generalized epilepsy. While 117/138 patients were older than 16 years, 21 patients were 16 or younger. They found that the overall reduction in mean monthly seizure frequency was 51%. Mean seizure frequency before implantation was 41 seizures/month (SD=61; range 1-300), mean seizure frequency after implantation at maximum follow-up was 7 seizures/month (SD=25; range 0-120). Responder rate was 59%. 13% of their patients had a seizure frequency decrease between 30% and 50%. About 28% had a seizure frequency decrease of<30% while seizure freedom was obtained in 12/138 patients (9%). The mean stimulation output current was 1.84mA (range 0-3.25).

Bunch et al3 did a study to find out whether acute response of VNS in terms of reduction in seizure frequency correlates with the amplitude of the output current. This was a

retrospective analysis of a multicenter randomized trial employing three unique paradigms of VNS carried out in patients with intractable partial onset epilepsy. Low currents were defined as <1mA and high currents >1 mA. Sixty-one subjects, age greater than12 years were randomized into one of the three groups differing primarily in their on/off times. Group A, 7 s on/18 s off; Group B, 30 s on/30 s off; Group C 30s on/3 mins off with no change in pulse duration or frequency. No correlation was found between output current ranging from 0.25 to 1.5 mA and reductions in seizure frequency, or with >50% reduction in seizures. Six of their initial seven non-responders experienced > 50% reductions in seizures after the current was increased suggesting that initial non-responders may respond to an increase in output current.

Labar4 looked at seizure rates after 3 and 12 months of VNS therapy in a cohort of 269 patients from the VNS treatment outcome registry who stayed on exactly the same AEDs, at exactly the same doses for the entire first year after VNS implantation. Seizure rates improved between 3 months (median=45%) and 12 months (median=58%). No differences were found between patients on standard (off-time > 3.0 min) versus rapid (off-time <1.8 min) cycling or those who were switched from standard to rapid cycling. Patients were also stratified according to the output current as low (0.25-1.00mA), medium (1.25-2.0mA) and high (>2.25mA). Seizure rates were found to decline with increasing VNS duration but no particular stimulation parameter was found to affect the seizure rate. Labar4 found VNS responsiveness to be associated with older age (p=0.016), longer duration of epilepsy (p=0.033) and syndromes other than Lennox-Gastaut (p=0.003).

The efficacy of VNS in pediatric intractable epilepsy was assessed in a bicentric study from Korea5. Sixteen patients were implanted with a VNS and followed up for at least 12 months. VNS resulted in a >50% reduction in seizure frequency in 50% (8/16) of children with 31.3% (5/16) of patients having a greater than 90% reduction in seizure frequency. Additionally enhancements in quality of life occurred as follows: memory in 50% (8/16), mood in 62.5% (10/16), behavior in 68.8% (11/16), alertness in 68.8% (11/16), achievement in 37.5% (6/16), and verbal skills in 43.8% (7/16) of the patients. Adverse events were few with hoarseness in 2 patients, dyspnea during sleep in 2 and sialorrhea in one patient. Adjusting the current settings controlled these events.

NEW VNS DEMIPULSE MODEL 103 GENERATOR

New VNS demipulse model 103 and model 104 generators were launched in 2007. As compared to the older models 102 and 102 R which weighed 25 gms and 27 gms respectively, model 103 weighs only 16 gms with model 104 tilting the scales at 17 gms. Their predicted battery life at 2mA, 20 Hz and 500 microsecs is 6+ years. The newer models are much smaller in size (volume 8cc as compared to 14-16 cc for the older generators). This reduction in thickness and generator volume gives improved post-implant cosmetics as compared to the older models. The software is significantly improved too with improved diagnostics namely the lead impedance is measured directly and displayed accurately in Ohms. The lead impedance is measured once every 24 hours and a warning message appears when the device is interrogated if the impedance is high or low. The device predicts the expected battery life at current settings with instant update to a new end of service projection when new device settings are chosen. A warning message is displayed when battery life is within 6 months of end of life thus assisting in replacement decision process making.

SIDE EFFECTS AND CONTRAINDICATIONS OF VNS

Patients with VNS should be warned not to use short-wave diathermy, microwave diathermy or therapeutic ultrasound. Diagnostic ultrasound can be carried out though. VNS implantation is not an absolute contraindication for an MRI study, though it is recommended that the device be switched off prior to the MRI study as the heat induced in the lead by the MRI scanner may damage the vagus nerve. In fact MRI compatibility was demonstrated using a 1.5 T GE Sigma Imager with a Model 100 device. The device should be interrogated both before and after a patient undergoes an MRI study. The company recommends that patients exercise reasonable caution and avoid devices which generate strong electric or magnetic fields. Devices like electrocautery, radio frequency ablation devices, therapeutic radiation machines like cobalt machines and linear accelerators and even extracorporeal shockwave lithotripsy may damage the VNS generator.

Adverse events reported during VNS usage include dyspnea, increased coughing, laryngismus (throat and larynx spasms), pharyngitis, nausea, throat pain, dysphagia and hoarseness of voice. Cyberonics recommends that the device be used with caution in patients with underlying pulmonary diseases like

chronic obstructive airway disease and asthma.

VNS therapy also affects respiration during sleep and has been shown to worsen pre-existing obstructive sleep apnea hypopnea syndrome (OSAHS) by increasing the number of apneas and hypopneas6,7. Consistent sleep-related decreases in airflow and effort coinciding with VNS activation have been documented with apneas and hypopneas found to be more frequent during VNS activation than during nonactivation. How VNS affects respiration during sleep has still not been fully delineated. Both central and peripheral mechanisms have been postulated. Stimulation of peripheral vagal afferents activates motor efferents with cell bodies in the dorsal motor nucleus of the vagus nerve and in the nucleus ambiguus. These efferents may alter neuromuscular transmission to the upper airway muscles of the pharynx and larynx producing upper airway narrowing and obstruction. VNS may also modulate central projections to the brainstem reticular formation altering the rate and depth of respiration. At relatively low current and frequency settings VNS increases REM sleep predisposing the patient to apneas and hypopneas. VNS has been shown to cause left vocal cord adduction and torsion at frequencies above 40 Hz while lower frequencies (below 20 Hz) cause left vocal cord abduction. Why vocal cord position is frequency dependent is unclear. VNS may also interfere with effective CPAP titration in patients with OSAHS. With the increasing use of VNS and the known association between VNS and sleep apnea, increased attention needs to be paid to effective ways of treating apnea in patients with comorbidities of intractable epilepsy and OSAHS. Nasal CPAP remains the most effective treatment for OSAHS. It appears that for some patients at least, attempting to begin effective nasal CPAP titration with the VNS turned on may prove to be a difficult task. This may be due to a combination of sleep fragmentation both from VNS stimulation and from the anxiety of using CPAP for the first time. Therefore, it may be helpful to intially have the VNS turned off to help find a somewhat effective CPAP pressure. Patients should then be restudied with the VNS tuned on after they have adapted to the use of CPAP. Another possibility is to reduce VNS stimulation parameters both frequency and current or increasing the off-time off (e.g., activation every 5 minutes rather than every 3 minutes). This though may worsen seizure control in these medically refractory epilepsy patients.

Infection may follow VNS implantation. These may be difficult to treat requiring at times explantation of the device. Patients should be given antibiotics preoperatively and strict antiseptic precautions should be maintained during VNS implantation.The safety and effectiveness of VNS has not been established for use during pregnancy. VNS should be used during pregnancy only if the advantages clearly outweigh the risks.

RESPONSIVE NEUROSTIMULATION (RNS) DEVICE

An investigational study of a responsive neurostimulator (RNS) has been sponsored by NeuroPace, Inc for the treatment of patients with refractory epilepsy. Once placed underneath the scalp, the RNS electrodes are placed in the area of potential epileptogenicity (seizure foci). Ideally no more than two epileptogenic foci should be present. The device is designed to continuously monitor the electrocorticogram (EcoG). When the onset of a seizure is “detected” by the machine, it is programmed to deliver a train of brief electrical stimulus with the intention of aborting the seizure. RNS device functions as a semi-closed loop with the device responding to the electrical milieu of the brain (responsive neurostimulation). The device has the capacity to store the EcoG data which can be retrieved at a later date. The RNS can be programmed by a modified laptop computer via a hand-held wand. Seizure detection settings and the amount of electrical stimulus delivered can all be programmed with respect to a patient's seizure type. Patient's currently enrolled in the study include those experiencing three or more disabling partial seizures (motor), complex partial or secondary generalized seizures and who have failed a minimum of two frontline AEDs. Efficacy date from the RNS study is keenly awaited and shall determine whether this may someday become a viable armament in the battle against intractable epilepsy.

CONCLUSIONS

VNS is an effective non-pharmacological treatment for patients with medically refractory partial onset seizure disorder. A greater than 50 % reduction in seizure frequency rate is achieved in most patients. With newer devices like the RNS on the horizon, the battle against intractable epilepsy may yet be won.

SUGGESTED READING

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