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Vagus Nerve Stimulation in Refractory Epilepsy: State of the Art

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1. Introduction

Even if the notion of refractory epilepsy is difficult to define precisely, it is widely admitted that it corresponds to the failure of two or more drugs and occurrence of one or more seizures per month over 18 months. Approximately 30 to 35% of epileptic patients will experience refractory epileptic periods in their lifetime despite maximal antiepileptic medications or they will suffer from serious side effects of their medical treatments. Indeed neurosurgical resection procedures including cortectomies and temporal lobe surgeries may result in a dramatic improvement of seizure frequency in selected patients, but these procedures carry a non-negligible rate of potentially serious risks with a mortality rate reaching more than 3% in some centers.

Another surgical option with less risks and reversible action for these patients is represented by vagus nerve stimulation (VNS), mainly in those patients that are not candidates for a surgical resection. VNS consists in the chronic and intermittent stimulation of the tenth cranial nerve (vagus nerve) in its extracranial cervical segment. Even if the pathophysiology of VNS in the treatment of refractory epilepsy is not yet clearly understood, the procedure has shown its efficacy in terms of quality of life improvement since the end of the 1990's in many types of epilepsy. The United States Food and Drug Administration (FDA) have approved the technique in 1997 as an adjunct to pharmacotherapy for adults and adolescents (more than 12 years). The VNS device has been developed by Cyberonics, Inc (Houston, TX).

In this review, we describe the state of the art of VNS including technical considerations, possible mechanisms of action, main clinical studies and future trends.

2. Technical considerations

Initially, the FDA approved the use of the VNS system as an adjunctive therapy in adults and adolescents with partial onset seizures, but lately extended the use of the VNS device for children and in seizures other than partial onset. The placement of the device is performed either by neurosurgeons or ENT surgeons after rigorous selection of patients by specialized neurologists. The surgical procedure is simple but requires special skills to identify the vagus nerve in the neck and carries complications and potentially lethal risks (Santos 2004).

2.1 Vagus nerve anatomy and VNS device

The vagus nerve or tenth cranial nerve is composed for up to 80% of its fibers by afferent ones originating from the viscera while 20% of its fibers are efferent and dedicated to the innervation of the larynx but also to the parasympathetic management of the heart, lungs and digestive tract. During VNS, the procedure will involve the mid paralaryngeal skeleton portion of the vagus nerve just behind the carotid sheath between and posterior to the common carotid artery and internal jugular vein. It is important to avoid using the device on the vagus nerve before the birth of its cardiac superior and inferior branches.

The VNS device consists in a generator and a lead. This generator delivers an intermittent electrical stimulation with precise and adjustable characteristics including output current, pulse width, frequency and stimulation on and off time. These parameters are adjusted postoperatively depending on therapeutic response and clinical tolerance. Initially the output current is usually set to zero mA for the first 2 to 3 postoperative weeks. Normalized parameters have been found to be the more effective at the beginning of the adjustments and have been found to be the more valuable in double-blind controlled studies: 500 μ s pulse width, 30 Hz signal frequency, 30 seconds on-time and 5 minutes off-time. Further incremental increases in output current may be necessary depending on therapeutic effects. A hand-held magnet is given to patients with VNS (or to their caregivers) to activate directly the generator trans-cutaneously in case of auras or partial fits in order to reduce the incidence of severe seizures.

2.2 Surgical procedure

Many variations of VNS placement techniques have been described until now. In the majority of cases, the left vagus nerve has been used because of potentially higher risks of bradycardia and cardiac rhythm anomalies with the right vagus nerve. There is no clear evidence for this last data, resulting in the placement of VNS devices on either side.

Preoperative consent must be obtained and signed either by the patient or his guardian, after explaining attending risks and benefits of the procedure. The patient should be informed of the scarring lines in the neck and the preaxillary region as well as the voice changes possibilities during the stimulation cycles of the device. The patient and/or guardian should also be informed of the limited duration of the battery that will have to be replaced within a 7 to 10 years period depending on parameters set.

Under general anaesthesia and orotracheal intubation, the patient is placed supine with the head turned to the right side for a left-sided VNS placement. A 3 cm transverse incision is performed at the level of the cricothyroid membrane parallel to the anterior edge of the sternocleidomastoid muscle. This latter is dissected medially until one reaches the common carotid artery and the internal jugular vein. The vagus nerve is usually found on the posterior wall of the carotid sheath. Nearly 25 to 35 mm of the nerve are carefully dissected without any tearing or injury to the nerve. The vagus nerve adventitia and vasa nervorum must be preserved. The choice of the lead model is adapted to the nerve diameter before being delicately placed around the vagus nerve. An ipsilateral infraclavicular subcutaneous pocket is dissected to receive the generator, while the lead connector is tunneled subcutaneously and connected to the helical electrodes. Proper placement of helical lead (distal to superior laryngeal nerve and cardiac cervical branches) and electrodes orientation is mandatory before preoperative testing of the device. The surgical and anaesthetic teams must be aware of the potentially serious cardiac rhythm anomalies that may occur during VNS testing including cardiac arrest (2-3%). Various complications and side effects are actually very well documented (Table 1) (Spuck et al. 2010).

Complications	Infection (3-8%) requiring generally device explantation Vocal cord paralysis 0,7% (transient or permanent) that can be avoided with careful dissection of the nerve and rigorous choice of the size of the lead Hematoma, seroma Nausea and vomiting Paresthesia Bradycardia Cardiac arrest (1/400 to 1/800) Device malfunction Lead fracture Pneumothorax Facial paralysis Horner's syndrome
Stimulation cycle related side effects	Coughing Laryngismus Voice alteration Local strap sensation Neck muscle contractures and spasms Dyspnea Dyspepsia Dysphagia Local pain

Table 1. Complications and adverse effects of VNS

3. Rationale of VNS in refractory epilepsy

Pathophysiology and mechanisms of action of VNS in refractory epilepsy are still subject to discussions and debates (Barnes et al. 2003). As already said, vagus nerve is composed of 80 % of afferent fibers and 20 % of efferent ones. The afferent fibers of the vagus nerve are known to originate from nodose and jugular ganglia to innervate both nuclei tractus solitarius and projecting to different regions involved in epileptic activity. This afferent contingent of fibers is mainly composed of small diameter unmyelinated fibers (C) but also large diameter myelinated ones (A and B). It is hypothesized that the chronic and intermittent stimulation of these afferent fibers of vagus nerve are involved in the anti-epileptic effect of VNS, while the exact mechanism is still unclear. Initially, C fibers were thought to be responsible of this effect in animals, but human studies did not comfort this hypothesis. Elsewhere, it has been demonstrated that various thalamic nuclei contain thalamocortical relay neurons with large projections on cerebral cortex. VNS may therefore induce changes in the metabolism of these thalamic nuclei by the mean of trans-synaptic neurotransmission modulation, as shown by PET scan. This latter demonstrated an increase of the blood flow in both thalami secondary to VNS that correlates with anti-epileptic effect.

Many studies of neurochemical concentrations of aminoacids and neurotransmitters in CSF and brain samples during VNS have shown variations of ethanolamine in specific locations such as locus coeruleus, a region directly involved in seizure propagation. VNS is also involved in long stimulation of NTS, parabrachial nucleus, paraventricular nucleus of the hypothalamus, ventral bed nucleus of the stria terminalis, dorsal raphe nucleus and cingulate cortex. CSF aspartate level, an excitatory neurotransmitter, has also been shown to decrease significantly in chronic VNS.

On an electrical point of view, EEG studies have proven cortical synchronization or desynchronization depending on stimulation frequency and intensity, explaining the importance of rigorous stimulation parameters in VNS (Marrosu 2005).

4. Clinical outcome

Significant clinical data supports that chronic and intermittent VNS is actually considered as a valuable treatment of refractory epilepsy (Table 2). It is mandatory to present this therapeutic modality to patients and their family not as a curative treatment but as an adjunct to antiepileptic drugs. Additionally to the significant decrease of epilepsy frequency and severity according to Engel postoperative assessment (Table 3), VNS reduces antiepileptic drugs toxicity but also the frequency of epilepsy-related hospitalization which is a great financial issue. Efficacy and clinical tolerance of VNS may require a long period of parameters adjustments. After promising preliminary results of pilot studies in the 1990's, multicenter double-blinded randomized trials in adults with refractory epilepsy confirmed the efficacy of VNS in terms of reduction of frequency, severity and duration of seizures. It is now admitted that this efficacy may require several months or even years of VNS to be obvious. Patients are considered as responders to VNS if they experience more than 50 % of reduction in seizure frequency.

Series	N	Follow-up (months)	Mean age (years)	Change in seizure frequency from baseline
Salinsky et al (1996)	100	10-12	33,3	-32 %
Handforth et al (1998)	94	3-4	32	-27,9 %
Scherrmann et al (2001)	95	16	34,9	-30 %
Labar (2004)	269	12	32	-58 %
Saneto et al (2006)	43	18	8	-84 %
De Herdt et al (2007)	138	44	30	-51 %
Amar et al (2008)	3822	24	26	-66,7 %
Sherman et al (2008)	34	12	12,3	-51,2 %
Elliot et al (2011)	65	124,8	30	-76,3 %

Table 2. Selected published data on the efficacy of VNS in refractory epilepsy

In long-term follow-up studies, VNS has proven to have an excellent tolerability with continuation rates reaching 70 % at three years. These studies confirmed also the existence of an incremental and cumulative seizure suppression effect of VNS over time as a possible result of the optimization of parameters adjustments and/or antiepileptic medications changes.

Another benefit of VNS is the marked improvement of the overall quality of life in these patients, probably mediated by the reduction of antiepileptic drugs toxicity and treatment costs or epilepsy-related hospitalization reduction.

In the paediatric population, studies are less common even if they showed obviously better results of VNS on refractory epilepsy than adults, with reduction of 50 to 90% in seizure frequency at one-year follow-up. VNS have also shown evident efficacy in Lennox-Gastaud syndrome and tuberous sclerosis complex.

Class I No disabling seizures	A – Completely seizure-free since surgery B – Non-disabling simple partial seizures only C – Some disabling seizures after surgery but free of disabling seizures for at least 2 years D – Generalized convulsion with antiepileptic drug withdrawal only
Class II Rare disabling seizures	A – Initially free of disabling seizures but has rare disabling seizures now B – Rare disabling seizures since surgery C – More than rare disabling seizures since surgery but rare seizures for at least 2 years D – Nocturnal seizures only
Class III Worthwhile improvement	A – Worthwhile seizure reduction B – Prolonged seizure-free intervals but less than 2 years
Class IV No worthwhile improvement	A – Significant seizure reduction B – No appreciable change in seizure frequency C – Seizures are more frequent or worse

Table 3. Engel classification of postoperative outcome

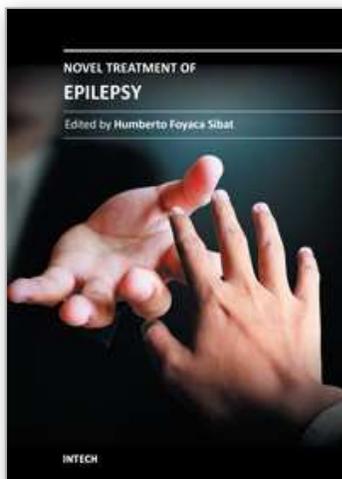
5. Conclusion

Chronic and intermittent vagus nerve stimulation is actually considered as a safe and very effective complementary treatment for patients with refractory epilepsy. Initially indicated exclusively in adults, the technique is currently diffusing in paediatric patients. A cumulative incremental effectiveness of VNS has been demonstrated with an increasing efficacy over the years of stimulation. VNS is also considered as a very valuable technique for the improvement of the overall quality of life in patients with refractory epilepsy. VNS is moreover being used in a variety of other pathologies including major depression, Alzheimer disease, congestive heart failure or even bowel inflammatory disorders.

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Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological evidence for an increasing prevalence of epilepsy throughout the world, and evidence of increasing morbidity and mortality in many countries as a consequence of higher incidence of infectious diseases, head injury and stroke. We decided to edit this book because we identified another way to approach this problem, covering aspects of the treatment of epilepsy based on the most recent technological results *in vitro* from developed countries, and the basic treatment of epilepsy at the primary care level in rural areas of South Africa. Therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis, as a leading cause of epilepsy in developing countries. Many experts from the field of epilepsy worked hard on this publication to provide valuable updated information about the treatment of epilepsy and other related problems.

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