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The vagal nerve stimulation outcome, and laryngeal effect: Otolaryngologists roles and perspective

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ABSTRACT

Introduction: Epilepsy is one of the most common neurologic disorders. Vagus nerve stimulation (VNS), first investigated in 1938 and subsequently studied as a potential therapy for epilepsy. The FDA approved the use of VNS in 1997 as an adjunctive non-pharmacologic symptomatic treatment option for refractory epilepsy for adults and adolescents over 12 years.
VNS can cause laryngeal and voice side effects that can be managed by otolaryngologists safely and effectively.
Objectives: This study is to review the outcomes of vagal nerve stimulator (VNS) implantation in terms of the surgical procedures, complications, seizure frequency, and the clinical effect on larynx and vocal folds motion.
Methods: Series of thirty consecutive patients who had VNS implantation between 2007 and 2014 were recruited. Seizure-frequency outcome, surgical complications and device adverse effects of VNS were retrospectively reviewed. Additional evaluation included use of the Voice Handicap Index and Maximum Phonation Time (MPT) were conducted before and after the implantation.
Videolaryngoscopy was used to evaluate the vocal fold mobility before and after the VNS implantation.
Results: Seizure frequency reduction over a minimum of 2 years of follow up demonstrated: 100% in seizure frequency reduction in 1 patient, drastic reduction in seizure frequency (70–90%) in 9 patients, a good reduction in terms of seizure frequency (50%) in 8 patients, a 30% reduction in 5 patients, no response in 6 patients, and 1 patient had increased frequency.
The most commonly reported adverse effects after VNS activation were coughing and voice changes with pitch breaks, as well as mild intermittent shortness of breath in 33% of patients. For those patients secondary supraglottic muscle tension and hyper function with reduced left vocal fold mobility were noticed on videolaryngoscopy, though none had aspiration problems.
Surgical complications included a wound dehiscence in one patient (3%) which was surgically managed, minor intra-operative bleeding 3%; a superficial wound infection in one patient (3%) which was treated conservatively, none of the complications necessitated VNS removal.
Conclusions: VNS appears to be an effective non-pharmacologic adjuvant therapy in patients with medically refractory seizures. With the favorable adverse-effect profile previously described, VNS is generally well tolerated and of a great benefit to such patients.
Laryngeal side effects, of which hoarseness being of the greatest repetition, are the most common after the VNS implantation. VNS can affect the voice and reduced vocal cord motion on the implantation side with secondary supraglottic muscle tension.
Otolaryngologists are not only capable of performing VNS implantation, but can also manage surgical complications, assess laryngeal side effects and treat them as needed.

1. Introduction

Epilepsy, a disorder characterized by recurrent seizures, is thought to be present in 0.5%–2% of the world's population [1]; moreover, seizures are the most common neurologic condition encountered in the pediatric population [2]. Vagus nerve stimulation, first investigated in

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1938 and subsequently studied as a potential therapy for epilepsy [3]. In 1985, Zabara et al. [4,5] reported that electrical stimulation from the vagus nerve produces inhibition of the neural processes, which can alter brain electrical activity and terminate seizures in dogs. Multiple controlled trials [6–8] have been implemented to investigate vagal nerve stimulator (VNS) safety and efficacy for seizure control, in patients with intractable epilepsy, and all of which showed positive results indicating efficacy and safety of VNS. The American Food and Drug Administration (FDA) approved the use of VNS in 1997 as an adjunctive nonpharmacologic symptomatic treatment option for refractory epilepsy for adults and adolescents over 12 years [9]. VNS was later on approved by the FDA for the treatment of severe, recurrent unipolar and bipolar depression in 2005 [10].

Despite the fact that initial approval of VNS in the USA was only for adults and adolescents with partial epilepsy, children and patients with generalized epilepsy have also benefited significantly from VNS implantation [11]. It was realized that many non-seizure parameters (for example, behavior, school performance, and mood) are more improved with earlier seizure control and the minimization of adverse drug effects. This led to a paradigm shift toward an earlier identification of pharmacologically resistant epilepsy and patients who would benefit from surgical intervention. This evolving conceptualization of epilepsy treatment in children has led to an increase in the use of VNS in children younger than 12 years of age [12]. VNS has been found to be well tolerated and effective as add-on therapy for refractory seizures in children of all ages. Response is even more favorable in the younger group (<12 years at implantation) [13].

Physiologically, the vagus nerve is composed of both afferent and efferent fibers. The vagus relays afferent impulses [14] from the thoracic and abdominal visceral organs to the cell bodies of the vagal afferent sensory component in the nodose ganglion, which relays this input to the nucleus tractus solitarius. This nucleus has projections to many higher cerebral centers, including the reticular formation in the medulla, locus ceruleus, parabrachial nucleus, amygdala, hypothalamus, thalamus, and the dorsal motor nucleus of the vagus [15–18]. These central projections represent important neuronal pathways that most likely play a vital role in VNS therapy [19]. The locus ceruleus is the major norepinephrine secreting region of the brain; VNS activates the locus ceruleus and releases norepinephrine, which in turn increases seizure threshold, thus modulating seizure control [20]. The release of norepinephrine also may play a role in mood regulation. In addition, the locus ceruleus and parabrachial nucleus have efferent connections to the amygdala, which controls mood and emotion.

Anatomically, branches from the right vagus nerve innervate the sinoatrial node while branches from the left vagus nerve innervate the atrioventricular (AV) node [21]. Right-sided VNS caused more cardiac slowing than left-sided VNS in a canine model [22]. To avoid cardiac slowing, the VNS electrode array is almost always placed surrounding the left vagus nerve.

Technically, a VNS is made of implantable components and two peripheral components. The implantable components are a programmable pulse generator, subcutaneous connecting wire and a bipolar electrode lead. VNS pulse generator is a pacemaker-like device that sends mild intermittent electrical impulses via the connecting wire through the lead to the vagus nerve, which then sends signals to the brain. The peripheral components are a computer-connected programming wand, which is used by neurologists to program the VNS trans-cutaneously, and a strong handheld magnetic piece that is used by the patient or the caregiver to activate the device on demand in case the patient senses a seizure is about to occur. This handheld magnetic piece can also be used to temporarily suspend activity of the VNS in patients in whom the VNS has created significant side-effects.

Functionally, the VNS mechanism of action is not yet well understood, but there are three major theories proposed to explain the effect of the VNS on seizure activity. The first theory states that the VNS might cause stimulation of the nucleus of the solitary tract, resulting in an alteration in the autonomic nervous system and abortion of seizure activity. The second theory suggests that the VNS alters the activity of the brainstem reticular system, thereby enhancing the level of arousal and inhibiting aberrant cortical activity [15]. Finally, the third theory proposes that the VNS causes stimulation of the noradrenergic nuclei leading to disruption of seizure activity [23].

Surgically, the majority of VNS implantation procedures have been performed by neurosurgeons and only (5%) of the procedures have been performed by otolaryngologist although there are reports describing them as well trained for the procedure [24]. This is despite the fact that it would be easier to follow the patients up and track them since the commonest post-operative side effects will need an otolaryngologist to assess them, as the commonest side effect is hoarseness of voice caused by stimulating laryngeal motor fibers, by the electrical impulses generated by the VNS, through the recurrent laryngeal nerve [25]. The VNS can also cause vocal cord dysfunction, which typically presents as an immobile fold in the paramedian or median position, with higher stimulation parameter [26].

The aim of this study is to review our results of VNS implantation at the otolaryngology department of a major international referral university hospital in term of efficacy, complications and side effects.

2. Methodology

Thirty patients (21 males and 9 females) were VNS-implanted over a 7-year period. Complete pre- and post-VNS surgical data were available for all patients, neurological data of seizure frequency, severity and other neurological assessments were obtained, with a minimum post implantation follow up of 2-year duration. The median age at implantation was 14 years (ranging from 3 to 25 years) and the mean duration of epilepsy was 6 years.

All patients were referred by the neurology service to our ENT clinic for implantation due to their intractable epilepsy despite treatment with at least 3 anti-epileptic drugs. The list of vagal nerve stimulator implantees was obtained from the institutional database. Medical records were reviewed for operative note, progress notes, in-hospital stay duration, and seizure frequency diaries of both pre- and post-implantation periods. All devices were implanted on the left side, the surgical procedure involved two incisions for implanting the device (Fig. 1).

The first incision was a left-sided, paramedian, horizontal incision that was made at the level of the cricoid cartilage over the sternocleidomastoid muscle. The platysma was opened and the plane medial to the sternocleidomastoid muscle was created, exposing the carotid sheath. The sheath was opened, the jugular vein was retracted laterally, and the vagus nerve was usually apparent in the groove between the jugular vein and carotid artery. Careful dissection was performed to expose 2–3 cm of the vagus nerve. The second incision was made vertically in the left anterior axillary line. A pocket was created just under the skin of the chest above the fascia of the pectoralis major muscle for the pulse generator (~5 cm in diameter, determined by the size of the model).

The lead was tunneled subcutaneously between the two incisions. The diameter of the vagus nerve was measured with a caliper to determine if a 2 or 3 mm coiled electrode should be used. Then the helical electrode was encircled around the exposed vagal nerve, and the lead was attached to the pulse generator.

Before the incisions were closed, intra-operative electrical impedance testing was done trans-cutaneously by means of a handheld programming wand to ensure the integrity of the implant. At the beginning of the test, the anesthesia team was notified as cardiac arrhythmia and asystole had been reported during such test (0.1%) [11]. After successful testing, the pulse generator was made inactive for a period of 2 weeks post-operatively, allowing wound healing before its clinical use. A mean surgical duration of 80 min was needed for the procedure.

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