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Vagus nerve stimulation on epilepsy and depression

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Abstract. This review presents an overview of vagus nerve stimulation (VNS) utilization. The vagus nerve (VN) is among the most versatile and important nerves, with the capability to regulate a few bodily functions, and has been playing a vital role as part of therapies for a range of health concerns. VNS is an effective therapeutic method, which has gotten the approval of the Food and Drug Administration (FDA) of the United States. It is a type of neurostimulation method that plays a crucial part in drug-resistant depression and refractory epilepsy. It provides a surgical option for patients suffering from the conditions mentioned above, and is rather effective compared with other surgical approaches, thus improving patients' life quality. Despite side effects, it is considered a decent therapeutic method and is currently used widely clinically. Furthermore, the mechanisms of VNS have not been completely understood. Therefore, further research is necessary, to discover the potential of VNS as an additional therapy for various other medical conditions.

Keywords: Vagus nerve stimulation, vagus nerve, epilepsy, depression

1. Introduction

Serving as the main nerves of the parasympathetic nervous system in the human body, the vagus nerve holds leading significance in the complex network. It provides a major sensory pathway between the body and the brain that is both important for life and relevant for disease. It is also vital in regulating many bodily functions, thus important in maintaining the balance within human organisms. Therefore, the vagus nerve emerges as a point of interest in medical research and clinical applications. Its involvement in controlling various processes adds to our understanding of human biology and provides possibilities for exploring new and versatile therapeutic interventions. Researching the vagus nerve's functioning enriches scientific knowledge and gives new aspects for discovering novel clinical methods, promising better treatments, and improving patient outcomes across diverse medical fields.

A neurostimulator is one of the medical treatments that utilize the function of the vagus nerve. A neurostimulator is generally an implanted medical device surgically placed that sends electrical signals to the nerve systems, usually given to patients who have symptoms resistant to pharmaceutical interventions of some diseases or when other treatments have not provided adequate relief, thus making it a very intriguing subject in terms of clinical application.

Vagus nerve stimulator is a type of neurostimulator. VNS a therapeutic method used to treat various diseases that involves nerve systems, such as epilepsy and depression. In 1997, the US FDA granted approval for the use of VNS in treating refractory epilepsy [1]. Since then, VNS has been continually

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used in the medical field. Now, it is approved for clinical use in patients over 12 years old. In contrast to other neurosurgical procedures that involve surgical removal, VNS presents a surgery with less risk and fewer complications [2].

The most common use of VNS is in treating drug-resistant depression and epilepsy. These conditions have been proven to be related to nerve system dysfunction, which results in the wide utilization of VNS in the therapeutic process. In this review, the utilization of VNS in treating epilepsy, depression and stroke will be discussed.

2. How it works

Known as the tenth cranial nerve, The VN is the longest among the cranial nerves. It possesses the ability to perform a complex range of multifaceted functions. VN constitutes an essential physiological conduit linking the body to the brain, overseeing critical facets of autonomic function such as respiration, cardiac rhythm, hemodynamic regulation, gastrointestinal peristalsis, and orchestrating reflex actions including coughing and swallowing. VN plays a pivotal role in governing fundamental survival-related behaviors such as nutrition, hydration, and sickness responses [3]. It also aids the neuro-endocrine-immune axis in maintaining the physiological balance of the human body [2]. This balance is achieved through both its afferent (sensory) and efferent (motor) pathways.

Vagus is the Latin for “wandering”, which points to the complexity of the connections this nerve branch makes inside the organism of a human anatomy. The vagus nerve consists of sensory fibers carrying signals towards the central nervous system and motor fibers transmitting signals away from it, traveling collectively along a shared route. Each fiber possesses its unique point of origin, destination, and threshold for activation. Both the right and left vagus nerves originate from the brainstem and extend through the neck, upper chest, lower chest, and diaphragm [3]. From there, these nerves proceed to enter the abdominal cavity.

VNS has emerged as a highly significant therapeutic approach in managing and improving diverse medical conditions, thus its wide application in medical practice. VNS is sometimes called a “pacemaker for the brain.” In fact, VNS is currently an US FDA approved clinical therapeutic method that can be used in patients aged 12 years and above who are dealing with drug-resistant epilepsy and depression [4].

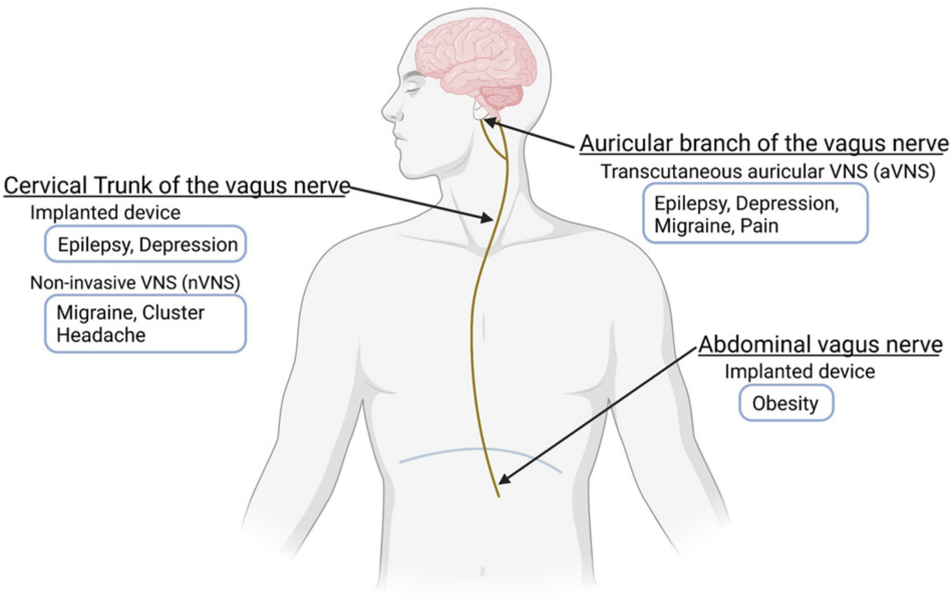

Figure 1. Clinical uses of VNS approved by US FDA [5].

VNS involves a variety of techniques that stimulate VN. At present, despite ongoing research, VNS is only applied to the left cervical vagal trunk. Therefore, in practical terms, for all studies performed on humans, VNS refers to the stimulation of the left cervical vagus nerve. This trunk contains fibers from the recurrent laryngeal, cardiopulmonary, and subdiaphragmatic vagal branches [3]. The stimulation is typically achieved using the NeuroCybernetic Prosthesis (NCP) System, which is a commercially available device [6]. The NCP System is an implantable, multiprogrammable pulse generator, specifically designed for use in VNS therapy. Its function is to deliver a continuous flow of electrical impulses to the vagus nerve, aiming to lessen the frequency and severity of epileptic seizures. These electrical signals are dispensed according to a pre-established schedule or can be adjusted by the patient using an external magnet. The implantation procedure involves placement of the device within a subcutaneous pocket, typically positioned beneath the clavicle, akin to the placement procedure employed for pacemakers. The stimulation signal is transmitted from the implant to VN via a lead affixed to an electrode. This electrode displays a multi-turn silicone helix configuration. A platinum band is located on the innermost coil of one of the helices [7].

VNS has been proved to be safe and efficient on most pediatric patients, and there are no recognized risks to the pregnant patients. It is also safe and compatible with other treatments such as psychotic drugs and electroconvulsive therapy (ECT) [2]. It has favorable outcomes in various aspects; this versatility and compatibility with other treatment approaches contribute to its status as a widely used therapeutic option in the clinical management of various medical conditions.

3. Current Applications of VNS

3.1. Epilepsy

VNS is still considered a novel therapeutic approach in treating multiple neurological diseases, including depression, epilepsy, tinnitus, and schizophrenia.

Epilepsy is a chronic noncommunicable condition which results in repeated, unprovoked seizures in the brain. The World Health Organization (WHO) states that an estimated number of 50 million people in the world are struggling with epilepsy. It has been proved that it is due to the sudden abnormal discharge of the cerebral nerve, which also leads to the temporary impairment of the cerebral function, which is the definition of a spontaneous recurrent seizure. Numerous researches have proved the effectiveness of VNS as an indirect neuromodulatory intervention, using electrically induced currents. VNS is often administered to patients who do not qualify for surgery operations or those with a history of seizures that are refractory to surgery and whose condition cannot be alleviated by standard medication [6]. According to The International League Against Epilepsy, for one-third of people with epilepsy, seizures do not cease to happen despite the use of traditional medications, it has been defined that these patients have drug-resistant epilepsy (DRE), and up to 40% of people with epilepsy are diagnosed with DRE, particularly those with focal epilepsy. According to Boluk C et al.'s study on VNS on epilepsy, VNS therapy is a safe and efficient treatment approach for various forms of epilepsy, including focal, generalized, and combined types [8]. Although it's only giving a low percentage of seizure freedom, VNS is a nice alternative choice of therapeutic approach for patients who cannot treat epilepsy through surgery. Therefore, using VNS in treating DRE and refractory epilepsy becomes important.

Two types of VNS devices are used in clinical treatment: Invasive vagus nerve stimulation (iVNS) and transcutaneous vagus nerve stimulation (tVNS). iVNS requires surgery to put the device into patients' bodies, while tVNS is a rather non-invasive approach, and are easier to remove when needed. Implantable VNS devices are currently widely used as the therapeutic method for DRE patients who are also do not qualify for surgical treatment of epilepsy. The device consists of implantable components, such as the pulse generator and lead wire. Additionally, it comes with external remote controls. These controls allow the patient to manage the stimulation or initiate an electrical pulse. Winter Y et al. carried out a study on the combined effects of iVNS and anti-seizure drugs (ASMs). Despite the need for further validation of the data acquired, a suggestion was made. The combination of iVNS and ASMs, specifically SV2A modulators or slow-release sodium channel inhibitors, appears to improve seizure control [9]. However, while the clinical efficacy of VNS is remarkable, the exact mechanism of VNS in treating epilepsy remains a mystery. Several potential mechanisms have been proposed. These include Neuroelectrophysiology, Neurotransmitters, and Inflammation.

3.2. Depression

Depressive disorder, also referred to as depression or Major Depressive Disorder (MDD), is a prevalent mental health condition. It is characterized by enduring feelings of sadness and a lack of interest in previously enjoyable activities. According to WHO, it affects a large proportion of the population, with an estimated prevalence of 3.8%. Many treatment approach have been carried out for patients with depression, with electroconvulsive therapy (ECT) being the method that has the highest remission rates. However, it is notable that ECT has significant side effects such as negatively affecting the short-term memory of the patients who had gone through ECT, and it requires repeating therapeutic process, which may impact the patients' other aspect of life [10].

One of the notable positive side effects observed in patients treating epilepsy with VNS is mood improvement [11]. VNS is now extensively applied in treating depression, particularly with the use of transcutaneous auricular vagus nerve stimulation (taVNS). taVNS serves as a comparatively better noninvasive alternative therapy for patients suffering from MDD [12]. Bajbouj et al. led a study wherein 53.1% of patients with chronic, treatment-resistant depression showed a positive response to VNS therapy. This positive response was marked by a 50% reduction in their Hamilton Rating Scale for Depression (HRSD28) score [13]. While antidepressants are known to enhance neurotransmitter release and modulate the sensitivity of inhibitory receptors, VNS seems to work differently. VNS operates by modifying the resting firing rate of noradrenergic and serotonergic neurons. Increasingly, evidence is suggesting a potential impact of VNS on the dopaminergic system [14].

3.3. Stroke

Stroke stands as a prominent contributor to global disability, with an approximate percentage of 60% individuals suffering from lingering upper limb impairments that can persist up to six months following the onset of a stroke [15], which can cause inconvenience or even trouble for the patients in their daily life.

In 2014, VNS was included in an exercise recovery program for a rat stroke model to examine if a combination of VNS and rehabilitation methods would contribute to the recovery of motor function [16]. The study's outcomes proved the hypothesis as the researchers observed a notable improvement in post-stroke recovery, specifically in cases where VNS was consistently synchronized with successful upper forelimb movements, compared to rehabilitation alone.

A study was conducted by Liu YL et al., focusing on the impact of VNS on ischemic stroke. The research identified that VNS suppressed Toll-like receptor 4/nuclear factor kappa-B expression by activating the α7 nicotinic acetylcholine receptor and influenced microglial polarization after the stroke event. It is suggested that this mechanism plays a part throughout the therapy process of ischemic stroke [17]. In a separate clinical trial led by Dawson J et al., a significant clinical outcome was observed after 90 days of in-clinic therapy. The FMA-UE score was achieved in 47% of the patients in the VNS group, compared to the 24% of patients in the control group [18]. Studies and researches surrounding the prospective role of VNS in enhancing motor recovery post-stroke is emerging, supported by numerous evidence from both preclinical and clinical studies.

3.4. Other applications and side effects

Due to the versatile nature of VN, and the efficiency and wide usage of VNS, VNS are also used in treating other diseases, such as gastrointestinal diseases, inflammatory disorders, and other disorders related to the regulation of VN.

Among patients using VNS, the most frequently encountered negative side effects include a range of conditions such as coughing, dysphonia (alterations in voice quality), surgical site infections, and hoarseness. While relatively common, these side effects are essential to monitor and address in the clinical management of individuals receiving VNS therapy, as they can impact the patients' overall well-being and treatment experience.

4. Conclusion

In conclusion, VNS is proven effective and safe for patients with epilepsy, depression, stroke and a number of other conditions by numerous studies and clinical trials, with minor side effects that are not life-threatening. It has been over a decade after VNS was approved by US FDA and put into clinical use, yet it is still a relatively novel treatment method.

VNS has become a notably influential therapeutic method for treating a wide range of medical conditions, it has been a rather widely used approach to give a vast amount of patients proper treatment and enhanced their life quality, leading to its extensive integration into medical practice, it has a promising future and is potential in the aspect of treating other diseases related to the VN. There are also numerous ongoing research revolving around VNS, discovering other potential uses of it, including using VNS to intervene the treatment of inflammatory diseases, helping patients with obesity by helping regulating appetite and metabolism, traumatic head injuries etc. It is a versatile treatment method clinically and has notably high potential.

However, the exact operational mechanism of VNS is still unclear. There is still much to explore and needs further research into its mechanisms. More in-depth study is important, as it will enhance our understanding of how VNS impacts the vagus nerves and other neural systems, leading to more potential applications for VNS.

Also, the side effects are also a concern and even barrier for patients with special needs, and can negatively impact patients' life. It is possible to reduce the risk or unwanted effect by combining another treatment method, surgical or pharmaceutical. Therefore, studies surrounding minimizing the side effects are also necessary, and are certainly a point of interest.

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