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Review Article

Vagus nerve stimulation: A novel approach for prevention and control of refractory seizures

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Abstract
In order to understand the brain function and to treat various neuropsychiatric illnesses including epilepsy, continued search and discovery of newer antiepileptic drugs has failed to revolutionize the approach in the management of this complex disorder. Moreover, in close to 30% of epilepsy patients, the seizure control is either not satisfactory or it is intractable to pharmacotherapy. Amongst the non-pharmacological treatment options for refractory epilepsy, vagus nerve stimulation occupies a unique position as an adjunctive treatment in prevention and control of partial-onset seizures in adults and adolescents older than 12 years. Though the precise mode of action of VNS is still debatable an honest attempt has been mode here to review all possible literatures available on VNS to establish its role in the management of this complex disorder.

Key words: Neuropsychiatric illness, Intractable Epilepsy, Vagus nerve stimulation, Seizure control

Epilepsy is a group or family of recurrent episodes of paroxysmal cerebral disthymia manifesting in sudden, excessive and disorderly discharge of cerebral neurons, as many as 500 times per second as compared to the normal rate of about 80 times a second.[1] The site from where such electrical discharges originate, determines various symptoms like convulsions if the motor cortex is involved and visual, auditory or olfactory hallucinations if the parietal or occipital cortex play a role.

Causes of epilepsy

A variety of contributing factors have been attributed towards the genesis of epilepsy which includes a genetic component in approx. 40% of the patients, other notable predisposing factors are abnormal neuronal connections in brain, imbalance of neurotransmitters, disruption of cell membranes surrounding neurons and activation of BDNF (Brain derived neurotrophic factor) during epileptogenesis. Certain cerebrovascular disorders like brain tumour, cerebral palsy, meningitis, hydrocephalus, head injury etc. may precipitate epilepsies.[1]

Treatment modalities

Currently available treatment modalities of epilepsy, primarily constitutes Antiepileptic drugs (AEDs) which effectively controls approx. 70-80% of the patients. Among the non-pharmacologic treatment options available for refractory epilepsy, surgery and vagus nerve stimulation (VNS) are in the lime light.[1]

Historical background

Biological psychiatry has a long history of using somatic therapies (physical, non-pharmacological) to treat neuropsychiatric illnesses and to understand brain function; these methods include neurosurgery, electro-convulsive therapy (ECT),[2] transcranial magnetic stimulation (TMS)[3] and vagus nerve stimulation (VNS).[4]

Evidences and regulation

Vagus nerve traditionally has been considered as a parasympathetic efferent nerve which regulates autonomic functions such as heart rate and gastric tone. However, the vagus (cranial nerve X) is actually a mixed nerve composed of about 80% afferent sensory fibres carrying information to the brain from head, neck, thorax and abdomen.[5] Stimulation of vagus nerve is thought to affect some of its connections to areas in the brain that are prone to seizure activity.

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The term vagus nerve stimulation generally refers to stimulation of the left cervical vagus by using a commercial device (Neurocybernetic Prosthesis system- NCP)[6] since incoming sensory connections of the left vagus nerve provide direct projection to many of the brain regions implicated in neuropsychiatric disorders.

On July 16, 1997, the U.S. Food and Drug Administration (USFDA) approved the use of VNS as an adjunctive treatment for refractory partial-onset seizures in adults and adolescents older than 12 years.[7]

Possible mode of action of VNS

The precise mode of action of VNS is not exactly known however, various experimental studies have suggested that VNS increases seizure threshold by causing wide spread release of inhibitory neurotransmitters like GABA and glycine in the brain.[1] A lesion in the locus ceruleaus was found to reduce the anticonvulsant effects of VNS[8] while activation of inhibitory effects in the brain areas (cerebellum, thalamus and cortex) by VNS induced changes in cerebral blood flow was observed by Henry et at.[9] The sensory afferent cell bodies of the vagus reside in the nodosa ganglion and relay information to the nucleus of tractus solitarius (NTS). Walker and colleagues[10] outlined a possible role of the NTS in how VNS reduces seizures by micro injecting either GABA agonist or glutamate antagonist in the NTS; it was observed that increased GABA or decreased glutamate blocked seizures. Ben-Menachem et al[11] measured amino acid and neurotransmitter metabolite concentration in CSF samples of patients on clinical trials of VNS before and 3 months after VNS, and observed much higher levels of free and total GABA after long term VNS. So, both pre-clinical and clinical studies demonstrated definite role of GABA in increasing seizure threshold.

Technical aspect

VNS is delivered through the NCP[11] Pulse generator, an implantable, multiprogrammable, bipolar pulse generator (the size of a pocket watch) that is implanted in the left chest wall under general anaesthesia to deliver electrical signals to the left vagus nerve through a bipolar lead. It delivers biphasic current which continuously cycles between "on" and "off" periods. The electrode in wrapped around the vagus in the neck, near the carotid artery by using a separate incision and is connected to the generator subcutaneously.[12] The generator is set to 0mA initially followed by an increase in the output current. This is adjusted to patient tolerance, using a 30HZ signal frequency, with a 500 microsecond pulse width for 30 seconds of "on" time and 5 minutes of "off" time. Electrical stimuli of not more than 14V are delivered to the vagus nerve which does not usually produce any tissue damage. In addition, each patient is given a magnet, which, when held over the pulse generator, turns off the stimulation, when the magnet is removed, normal programmed stimulation resumes.[12]

Clinical data

Several short and long term studies (double blind, active control and parallel design trails) of VNS have been performed[7] including patients with all types of intractable seizures. Results show a mean decrease in seizure frequency in patients (>12 year of age), more in high frequency stimulation group than the low frequency stimulation groups. The data in children (<12 years of age) is scanty.

Tolerability

Adverse effects commonly reported following VNS were hoarseness of voice, throat and chest pain, cough, nausea, dyspnoea and paresthesia.[7] VNS was not associated with adverse effects such as depression, fatigue, dizziness, insomnia, confusion, cognitive impairment, weight gain or sexual dysfunction, some of which are almost always accompanied by the use of antiepileptic drugs.

Conclusion

VNS builds on a long history of investigating the relationship of autonomic signals on limbic and cortical functions. It is one of the newest methods to physically alter brain function. Studies have demonstrated that VNS is an effective therapy of medically refractory partial- onset seizures with an approximate long-term decrease in mean seizure frequency of 40-50%, and a short-term decrease of 20-30%, in patients older than 12 years of age. VNS can be described as a long-lasting, hassle free and clinically useful anticonvulsant in drug resistant patients of epilepsy. The known anatomical projections of the vagus nerve suggests that VNS might also have other neuropsychiatric applications and can be classified as a new tool for brain research and therapy. Further research is needed to establish the exact mechanisms by which VNS produces different effects on the central nervous system and in turn broaden the clinical indications.

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