Vagal Nerve Stimulation in the Treatment of Epilepsy

Epilepsi Tedavisinde Vagal Sinir Uyarımı

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Up to 10% of patients with epilepsy do not benefit from medical and surgical therapies, this necessitating the use of new effective therapies. Vagus nerve stimulation (VNS) is proposed as an alternative treatment to control medically refractory seizures. In experimental animals, vagal stimulation produces EEG synchronization and desynchronization with different stimulus parameters. Vagal nerve stimulation has been demonstrated to be safe, tolerable, and effective in up to 1000 cases. However, no criteria have been developed yet to indicate which patients will respond to VNS therapy. The best clinical and most effective stimulation variables need to be determined.

Key Words: Electric stimulation therapy/methods/instrumentation; electroencephalography; epilepsy/therapy/classification; vagus nerve/physiology/anatomy&histology physiopathology; seizures/therapy/classification; neural pathways; neural conduction.

Epilepsili hastaların yaklaşık %10 kadarı medikal ve cerrahi tedaviden yarar görmemektedir; bu durum yeni ve etkin tedaviler geliştirilmesini gerektirmektedir. Medikal olarak dirençli epileptik nöbetlerin kontrolünde vagal sinir stimulasyonunun (VSS) alternatif bir tedavi yöntemi olduğu öne sürülmüştür. Hayvanlarda değişik stimulus parametreleri ile vagal stimulasyonun EEG senkronizasyonu ve desenkronizasyonuna yol açtığı gösterilmiştir. Yaklaşık 1000 hasta üzerinde VSS'nin etkin, güvenli ve tolere edilebilir olduğu gösterilmiştir. Ancak hangi hastalarda VSS'nin kullanılacağına dair kriterler henüz tam olarak oluşturulmamıştır. En iyi klinik ve etkin uyarım değişkenlerinin belirlenmesi gerekmektedir.

Anahtar Sözcükler: Elektrik stimulasyonu tedavisi/yöntemler/enstrümantasyon; elektroensefalografi; epilepsi/tedavi/sınıflandırma; vagus siniri;fizyoloji/anatomi ve histoloji/fizyopatoloji; nöbet/tedavi/sınıflandırma; nöral yollar; nöral iletim.

Epilepsy is a common, chronic disorder that has been known since antiquity; yet, its treatment underwent rapid development during the second half of this century. With current antiepileptic drug (AED) therapy, satisfactory seizure control can be obtained in about 70% of patients. There remains a significant percentage of patients with medically intractable seizures. In this group, considerable improvement or even complete seizure control can be achieved when new AEDs become available. Surgical treatment such as resection of cortical seizure focus, offers an option for some patients with a poor prognosis. Despite all medical and surgical measures, there remains a group of patients, possibly up to 10%, in whom seizures

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continue to be disabling.[1] Many of these patients also suffer from some chronic and diverse side effects of long-term, high-dose AED polytherapy. Hence, new effective therapies are of considerable importance. Cerebellar stimulation,[2] thalamic stimulation,[3] and recently vagal nerve stimulation[4] have been proposed to control seizures.

Preliminary studies have suggested that chronic, intermittent stimulation of the vagus nerve may be an alternative treatment for patients with medically refractory seizures.[1,5,6]

Anatomy

The vagus nerve is a mixed nerve carrying somatic and visceral afferents and efferents. The efferents innervate the voluntary striated muscles of the larynx and the pharynx, providing parasympathetic innervation to the heart, lungs, gastrointestinal tract and other visceral organs of the abdomen. The afferents, which account for approximately 80% of the fibers of the nerve, are mostly of the visceral type and originate from receptors in the lungs, aorta, heart, esophagus, gastrointestinal tract and the aortic chemoreceptors.[7] The cell bodies of these afferents are in the nodose ganglion, projecting primarily to the nucleus of the solitary tract (NST); but there are also connections to the medial reticular formation of the medulla, the dorsal motor nucleus of the vagus, the area postrema and the nucleus cuneatus.[8-10] The nucleus of the solitary tract projects to the hypothalamus, amygdala nucleus, dorsal raphe, the nucleus ambiguus, the dorsal motor nucleus of the vagus, parabrachial nucleus and the thalamus, which projects to the insular cortex.[10]

Transmitters mediating the flow of visceral information to the forebrain structures are glutamate, cholecystokinin, GABA and neurotensin.[11]

Because of the widespread projections of the NST, stimulation of vagal afferents may exert profound effects on CNS function. In experimental animals, stimulation of the cervical vagus was observed to produce evoked potentials in the cerebral cortex, the hippocampus, the thalamus and the cerebellum.[10] Stimulation of the vagal afferents tends to depress the monosynaptic reflex of the flexor and extensor hind limb muscles, to reduce the spinothalamic neuron activity in the thoracic cord, and to inhibit nocioceptive reflexes. These vagal-afferent-induced depression of motor and nocioceptive reflexes exerts an effect on the descending reticular system controlling spinal cord function. In a similar way, vagal afferents are able to modulate cortical activity via ascending reticular systems.[1,10]

EEG Effects of VNS

Antiepileptic properties of VNS are based on the modulation of electroencephalographic (EEG) activity and sleep states. The effects of electrical stimulation of the vagus nerve in preventing seizures was first suggested by Zabara.[4] In animals, VNS can induce EEG synchronization, desynchronization, rapid eye movement (REM) sleep or slow wave sleep (SWS) with different stimulus parameters. In canines, VNS (3-100 mA, 0.2-2.0 ms, 20-150 Hz) interrupts or abolishes strychnine-induced generalized seizures and pentylentetrazol-induced tremors.[12] In cats, VNS (50 Hz) decreases the frequency of focal cortical spikes produced by topical strychnine and blocks sleep spindle occurrence during SWS.[13] Stimulation of NST results in EEG synchronization and desynchronization at low (1-16 Hz) and high (>30 Hz) frequencies, respectively.[14]

In cats, stimulation of low intensity (1-2 V) decreases strychnine-induced focal spikes, but an increase in frequency can be produced by increasing the voltage of stimulation to 4-10 V.[15]

In rats, VNS (0.2-1.2 mA, 0.5 ms, 20-50 Hz) applied ipsilateral to the cortical focus for 1-20 seconds decreased, and in some cases abolished, penicillin-induced spikes for up to 3 minutes after stimulation; mean spike frequency was decreased by 33%. No increases in interictal spike activity were noted even at high intensity stimulations.[16]

Lockard and Congdon[17] observed the abolishment of alumina-induced focal and secondarily generalized seizures in two of four monkeys with VNS (5 mA, 0.5 ms, 50-250 Hz). In the remaining animals, the interseizure interval was lengthened and the interval between seizures became relatively invariant. No consistent effects on interictal spikes were observed.

Vagal nerve stimulation produced EEG desynchronization at frequencies above 70 Hz and intensities greater than 3 V; whereas EEG synchronization was observed at frequencies above 70 Hz and intensities less than 3 V. EEG synchronization was associated with rapidly conducted vagal stimulation of greater than 15 m/s, and desynchronization with a conduction veloc-

ity of 1-15 m/s.[18,19] EEG synchronization or desynchronization by VNS was bilaterally symmetric. On the other hand, bilateral VNS produced no measurably greater effect than did unilateral stimulation. Moreover, right or left VNS was found to be equally effective in controlling seizures.[12]

In spite of remarkable effects of VNS in experimental preparations, Hammond et al.[20] observed no noticeable effect of VNS at various frequencies and amplitudes on EEG activity, whether the patient was under general anesthesia, awake or asleep. However, they suggested that VNS may interrupt ongoing ictal EEG activity.

Neuro-Cybernetic Prosthesis (NCP) System

The NCP system (Cyberonics, Inc, Houston, TX)[6] includes a pulse generator implanted surgically in the patient's chest under the skin, bipolar stimulating electrodes that conduct the signal from generator to the vagus nerve, a programming wand which conveys changes in stimulation parameters to the pulse generator, and software that allows parameter adjustments and controls communication between the signal generator and the programming wand. The generator delivers intermittent pulses in accordance with its programming. Patients or observers may use an external magnet to activate the generator and deliver additional pulses. Initial stimulation parameters include 1 mA current output, 50 Hz frequency, 250 seconds pulse width, 60 seconds on, 60 minutes off, 24 hours a day. Later, pulse width may be increased to 500 seconds or more, current output and signal on-time increased as tolerated, and signal off-time decreased.[6]

Mechanisms of VNS

The mechanism by which VNS decreases seizure frequency is unknown. It has been suggested that VNS utilizes specific projections from NST to limbic structures to inhibit partial seizures.[10] Naritoku et al.[21] observed VNS-induced increases in the latency of thalamocortical somatosensory evoked potentials. They suggested that VNS alters the neuronal networks outside the brainstem vagus system. Fos immuno-reactivity studies support this hypothesis. Fos is a nuclear protein which results from expression of early immediate genes in highly active neurones. Vagal nerve stimulation causes a specific fos immunolabeling in the superior colliculus, amygdala, limbic neocortex, lateral posterior thalamus and the hypothalamus. This suggests that antiepileptic effect may be mediated in these areas.[22] Another mechanism is activation of the brain stem noradrenergic nuclei, locus ceruleus and sector A5 which also denotes fos immunolabelity.[22]

With VNS, aspartate levels, an excitatory aminoacid which has proconvulsant effect through the activation of the neuronal N-methyl-D-aspartate receptor, decrease significantly.[23] Levels of 5-hydroxyindolacetic acid and homovanilic acid and gamma-amino butyric acid (GABA) increase.[19,24,25] An increased level of GABA and glycine may account for the massive inhibitory effect of VNS on both tonic and clonic seizures. Glycine pathways are involved in regulating the mean level of brain excitability and GABA pathways are involved in preventing the spread of activity which produces tonic clonic convulsions. The specific GABA and glycine pathways, activated by VNS, are not known; but VNS involves vagal afferents that enter the NST. The NST contains both GABAergic and glycinergic synapses and has a widespread projection through CNS. As a result, VNS may prevent the initiation and spread of seizure activity in many areas of the brain.[19] The epileptogenic focus is described as an "isolated and anarchic" state devoid of control inputs; and intermittent VNS may interrupt the activity of that focus. Vagal nerve stimulation at random rather than at regular intervals may have a better antiepileptic effect.[26]

Clinical Trials

Neuro-Cybernetic Prosthesis system was first implanted by Penry and Dean[27] who applied VNS in four patients. They observed complete seizure control in two, a 40% reduction of seizure frequency in one, and no change in seizure frequency in the other. Then came subsequent studies.

Holder et al.[28] studied the effects of VNS in medically refractory patients with partial seizures in a randomized, blinded, and parallel study. After a three-month baseline period, they randomized the patients to high and low stimulation groups. In 37 patients in the high stimulation group, they observed a 33.3% reduction in mean seizure frequency whereas a mean reduction of 8.4% was documented in the low stimulation group. They observed no significant change in seizure duration and intensity. Uthman et al.[6] carried out a single blind pilot study

with 14 patients who had medically refractory partial (simple, complex or both) seizures. Each patient was required to have a documented seizure history of at least one-year; more than six seizures per month and a seizure-free period of no longer than two weeks. The mean reduction in seizure frequency after 14-35 months of VNS was 46.6%; 35.7% of 14 patients had a 50% or greater reduction in seizure frequency. Two patients became seizure-free for over a year.

Another study conducted was a multi-center, randomized, controlled trial involving 114 patients. Selection criteria included medically intractable seizures with a frequency of more than six per month, predominantly of partial types (simple, complex or secondarily generalized) and age over 12 years. After 12 weeks of baseline assessment, patients were randomized to receive 14 weeks of high (0.25-3.0 mA, 20-50 Hz, 500 μs, 30-90 s on, 5-10 min off) or low (0.25-2.75 mA, 1-2 Hz, 130 μs, 30 s on, 60-180 min off) levels of stimulation. Decrease in seizure frequency in the high stimulation group was 24.5% versus 6.1%. In the former group, a 50% or more decrease in seizure frequency was obtained in 31%.[5]

The therapeutic effect of VNS is cumulative and increases with longer periods of stimulation.[1,26] In long-term follow-up (18 months) of 50 patients of the above study, a 50% decrease in seizure frequency was observed in 52%, compared with 31% following three months of stimulation in the high stimulation group.[29]

Vagal nerve stimulation appears to have good antiepileptic efficacy not only in partial seizures but also in refractory primary generalized and symptomatic generalized epilepsies.[30,31] Labar[30] observed a 41% of seizure reduction in symptomatic generalized epilepsy.

Encouraging results in VNS has been achieved also in children. Of twelve children, over 90% reduction in seizure frequency and general improvement in overall functions were noted in 42%.[32] After 30 months follow-up of 19 children by the same authors, VNS resulted in seizure reduction of 50% or more in 53% of patients, with 32% presenting with more than 90% reduction.[33] Further reports on children also suggest VNS efficacy in pediatric age group,[34,35] all of which include VNS in both partial and generalized seizure disorders. Among affected children, those with Lennox-Gastaut syndrome and those who had failed to benefit from corpus callosotomy gave the best responses to VNS.[33]

Currently, decisions to continue or discontinue VNS at any point are arbitrary, depending on the patients' and physicians' discretion. Studies show that chronic VNS has a statistically significant effect in decreasing seizures, its effect being constant over time. To determine continuation or discontinuation of VNS, Clarke et al.[36] suggest the evaluation of consecutive seizure-free days as a significant outcome measure.

Side Effects

Side effects reported by patients are mainly hoarseness during stimulation and tingling at the site of stimulation. Others include muscle movement in the neck, hiccup, cough, sleep disturbances, persistent hoarseness, nausea, vomiting and dyspnea. Serious complications were reported only in two cases: left vocal cord paralysis and non-fatal myocardial infarction.[5,6] Occurrence of postoperative infection is rare.[16] No significant adverse effects on visceral functions, cognitive motor control, and balance have been reported.[5,6,37-41] A total of 15 patients died in the course of VNS therapy. The estimated crude total mortality rate was 11.2/1000 person-years and the standardized mortality ratios for NCP system were 5.3. Mortality rates and standardized mortality ratios were found comparable with studies of patients with intractable epilepsy who were not treated with NCP system.[42]

Conclusion

Vagal nerve stimulation is an emerging therapeutic modality currently under study for the treatment of medically intractable patients. However, no criteria have been established to indicate which patients will respond to VNS. Vagal nerve stimulation can be considered in patients who are not suitable for epilepsy surgery or failed to improve after surgery, those with disabling partial or generalized seizures unresponsive to AED, or in those who exhibit intolerable side effects from AEDs on one hand and are not candidates for surgery on the other. Though imposing a greater financial burden on the patient, long-term benefits of VNS are said to be comparable with those of surgery or AED treatment and its possible side effects. Vagal nerve stimulation proved to be safe, tolerable and effective.

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