

Letter to the Editor

Vagus nerve stimulation in chronic refractory epilepsy: chasing the cardiologist

Sir,

Epilepsy the second most common chronic neurological disorder after stroke affect 0.5-2% population worldwide. Antiepileptic drugs though remain the corner stone in management of epilepsy in majority of patients but still 30% of patients continues to have seizure or experience unacceptable pharmacological side effect. Electrical stimulation of vagus nerve is an effective and promising neurophysiological treatment for patients with refractory epilepsy who are either unsuitable candidate of surgery or falls in category of surgically refractory epilepsy. Vagus nerve stimulation (VNS) device was first implanted in 1988 however US FDA approved it in 1997. VNS enjoys the reputation of being the second commonest intervention in UK after temporal lobectomy. VNS represents the first approved therapy for brain that clearly modulates large neuronal networks by electric stimulation.¹ Apart from VNS other therapeutic brain stimulation technique include ECT (electro convulsive therapy), DBS (deep brain stimulation), TMS (transcranial magnetic stimulation) and magnetic seizure therapy, etc.

The VNS device and its implantation

VNS device is consisting of four components: the pulse generator, lead, spiral electrodes and magnet. Implantation of VNS device is just like pacemaker or AICD and is always performed on left side to catch the left vagus nerve. Under GA an incision is given in subcutaneous plane below left clavicle with formation of a pocket in pectoralis muscle area and the pulse generator is implanted there. Another incision is made in neck at anterior border of sternocleidomastoid muscle and the spiral electrodes are attached to left vagus subcutaneously. The magnet is generally wearing at wrist like a watch and it allows additional source for stimulation or inhibition of pulse generator. After a week or so the programming is done and the generator is made on and the parameters are adjusted with computerized based programming device.^{2,3}

Anatomical basis of left vagus nerve

The left vagus is a mixed nerve consists of 80% afferent fibers (originating from heart, lung, aorta and gastrointestinal tract) and 20% efferent fibers to parasympathetic innervation to these organs via dorsal motor nuclei. Additionally, voluntary striated muscles of larynx and pharynx are also supplied by vagus nerve via nucleus ambiguus. The vagus nerves are actually asymmetrical in regards to cardiac innervation as cardiac

musculature is mainly supplied by right vagus nerve which has dense projection in atria of heart. The left vagus on the other hand has poor efferent supply to heart and more than 80% of its fibers are afferent in nature thus making more suitable for VNS device.^{4,5}

Indications of VNS

The VNS is indicated as an adjuvant therapy with antiepileptic drugs (AED) for patients more than 12 years of age having uncontrolled primary generalized epilepsy or partial epilepsy with or without secondary generalization.⁶ The age bar for 12 years is practiced as vagus nerve is not completely myelinated before this age. In clinical practice no particular seizure type or epilepsy appears particularly sensitive or resistant to VNS.

Mechanism of action of VNS

The device provides a continuous, lower frequency vagus nerve stimulation in an intermittent manner with a fixed cycle. At low stimulation the 'on period' is 130 sec and 'off period' is 90-120 min with a pulse width of 130 msec. With high stimulation setting the 30 sec 'on period' is followed by only 5 min 'off period' with a pulse width of 500 msec. VNS produces stimulation of vagus nerve nuclei especially nucleus of solitary tract leading to widespread activation of cortical and subcortical pathways like raphe nuclei, locus ceruleus, thalamic and other parts of brain stem. This activation increases seizure threshold accounting for its antiseizure activity. The precise mechanism of action remains to be elucidated.^{7,8}

Contra indications of VNS

Absolute contraindications for VNS implantation are limited to previous left or bilateral cervical vagotomy. A stimulator will not be implanted when there is evidence of progressive intracerebral disease. Other conditions that need special attention are patients with cardiac arrhythmias, respiratory diseases like asthma, pre-existing hoarseness, gastric ulcers, vasovagal syncope and coexisting neurological diseases other than epilepsy.⁹

Side effects of VNS

Innervation of larynx by vagus nerve is responsible for temporary hoarseness, change in voice, cough, shortness of breath, throat paresthesias, etc. Most of these acute side effects are related to initial stimulation and resolve

spontaneously over a period of time without even stopping the stimulator.¹⁰ Because of stimulation of cervical cardiac branches of vagus nerve either directly or by collateral current spread, at times excessive over stimulation produces bradycardia, cardiac arrhythmias or even cardiac asystole.¹¹

Clinical benefits of VNS

Once implanted the VNS carries the following unmatched advantages like:

- Device work 24 hours a day, every day, for many years.
- No strict compliance is required unlike antiepileptics.
- No worry of troublesome drug interactions.
- Does not exacerbate any seizure type unlike antiepileptic.
- Does not affect serum levels of concomitant antiepileptic in use.
- Not having any cognitive or central nervous system side effects rather have a positive neurobiological effect.
- Improves quality of life by improving mood, increases alertness, memory and energy.^{12,13}
- On demand stimulation to control aura or impending seizure by use of magnet. The magnet allows additional stimulation by releasing a preset magnet current to generator by passing or rubbing the magnet over pulse generator for 5-10 sec at times of aura. This benefit is unmatched to any of the antiepileptic drug or surgical intervention.
- Safe option for pregnant women.

Efficacy of VNS

The optimal efficacy in regards to seizure control is generally attained in few months to 1-2 years and the positive effect improves over time unlike antiepileptics. It accounts for more than 50% reduction in seizure frequency in one third, 30-50% reduction in another one third and the remaining show no response.¹⁴ With VNS producing its optimal effect, gradually the need of antiepileptics decreases to minimum. The VNS is unique to produce an overall positive neurobiological effect and is likely to be used as a treatment for chronic resistant depression, chronic pain syndrome and even Alzheimer disease.

Cost-benefit considerations

VNS is a costly treatment with the usual cost being 10,000-12,000 USD (around 8-9 lacs INR). There is a significant decrease in epilepsy related direct medical cost after VNS implantation. It is estimated that the cost of the device can be paid back after 3 years or so.¹⁵ The life of pulse generator battery is 7-8 years depending upon whether low stimulation or high stimulation setting is used.

Electrical stimulation of vagus nerve is an effective and promising neurophysiological modality for refractory epilepsy patients who are either unsuitable candidate of surgery or fall in category of surgically refractory epilepsy. VNS provides a lower frequency stimulation in an intermittent manner to the vagus. The vagal nerve nuclei especially solitary nuclei produce wide spread activation of subcortical & cortical pathways thus increasing their seizure threshold and accounting for its antiepileptic activity. The implanted device carries lots of advantages as it work round the clock, every day for many years without affecting serum levels of antiepileptic drug in use. It has no cognitive or central nervous system adverse effects. The device is known for its positive neurobiological effects like increasing alertness, energy, improving mood and memory hence improving the overall quality of life. Although the efficacy of device is variable and it increases over time unlike that of antiepileptic drugs. One third of patient show more than 50% reduction in seizure frequency, the next one 3rd shows 30-50% reduction while in the remaining the seizure frequency remain unaltered.

VNS is an efficacious but palliative treatment for patients with refractory epilepsy. Its value to neurobiological research extends beyond current applications for neurologic and psychiatric disorders. The development of VNS for the treatment of epilepsy has demonstrated well the translation of concepts gained through laboratory research in to clinical therapeutics.

Ansh Chaudhary^{1*}, Bhupendra Chaudhary²

¹Department of Paediatrics, Bharati Vidyapeeth Medical College and Research Centre, Pune, Maharashtra, India

²Department of Neurology, Jaswant Rai Speciality Hospital, Meerut, Uttar Pradesh, India

***Correspondence to**

Dr. Ansh Chaudhary,

E-mail: doctorabpl567@gmail.com

REFERENCES

1. Schachter SC, Saper CB. Vagus nerve stimulation. *Epilepsia*. 1998;39(7):677-86.
2. Reid SA. Surgical technique for the implantation of the neurocybernetic prosthesis. *Epilepsia*, 1990;31(2):38-9.
3. Landy HJ, Ramsay RE, Slater J, Casiano RR, Morgan, R. Vagus nerve stimulation for complex partial seizures: surgical technique, safety and efficacy. *J Neurosurg*. 1993;78:26-31.
4. Murphy JV. Left vagal nerve stimulation in children with 'medically refractory epilepsy. *J Pediatr*. 1999;134:563-6.
5. Hornig GW, Murphy JV, Schallert G, Tilton C. Left vagus nerve stimulation in children with refractory epilepsy: an update. *South Med J*. 1997;90:484-8.
6. Ben-Menachem E, Manon-Espaillet R, Ristanovic R. Vagus nerve stimulation for treatment of partial

- seizures: A controlled study of effect on seizures. *Epilepsia.* 1994;35:616-26.
7. Naritoku D. K. Vagus nerve stimulation: mechanisms of action. *Epilepsia*, 1998, 39 (2): 12.
 8. Kram SE, Clark KB, Smith DC, Browning RA. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia.* 1998;39(7):709-14.
 9. Morris GL, Meuller WM. The Vagus Nerve Stimulation Study Group E-01-E05. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. *Neurology.* 1999;53:1731-5.
 10. Sackeim HA, Rush AJ, George MS. Vagus Nerve Stimulation (VNS) for treatment resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacol.* 2001;25:713-28.
 11. Asconapé JJ, Moore DD, Zipes DP, Hartmann LM, Duffell WH. Bradycardia and asystole with the use of vagus nerve stimulation for the treatment of epilepsy: a rare complication of intraoperative device testing. *Epilepsia.* 1999;40:1452-4.
 12. Eiger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res.* 2000;42:203-10.
 13. Helmstaedter C, Hoppe C, Elger CE. Memory alterations during acute high-intensity vagus nerve stimulation. *Epilepsy Res.* 2001;47:37-42.
 14. Vonck K, Boon P, D'Have M, Vandekerckhove T, O'Connor S., De Reuck J. Long-term results of vagus nerve stimulation in refractory epilepsy. *Seizure.* 1999.
 15. Bon P, Vonck K, D'Havé, M., O'Connor, S., Vandekerckhove, T. and De Reuck, J. Cost-benefit of vagus nerve stimulation for refractory epilepsy. *Acta Neurologica Belgica* 1999;99:275-80.

Cite this article as: Chaudhary A, Chaudhary B. Vagus nerve stimulation in chronic refractory epilepsy: chasing the cardiologist. *Int J Adv Med* 2021;8:732-4.