A Case of Medically Refractory Epilepsy Treated with Vagal Nerve Stimulation: Initial Experience in Nepal

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ABSTRACT

Seizures are any sort of alteration in the brain's electrical activity that is different from a normal signal and is usually characterized by abnormal body movement, loss of consciousness, frothing, and fainting. Usually, treatment of such conditions is carried out either with anti-epileptic drugs or surgical intervention. However, in some cases, both alternatives fail, and novel techniques of Vagus Nerve Stimulation (VNS) are necessary. In this case report we demonstrate a 24-year-old who had medically refractory seizure treated with VNS. The case was the first of its kind to be concluded in Nepal. This surgical technique is believed to explore a new dimension in the treatment of seizure patients in Nepal.

Keywords: Medically Refractory Epilepsy; Neuro-modulation; Vagal Nerve Stimulation.

INTRODUCTION

Drug resistant epilepsy is characterized by the inability to achieve sustained seizure control despite adequate trials of two well-tolerated, appropriately selected, and correctly administered antiepileptic drug regimens, either as monotherapies or in combination.[1] Various stereotactic targets have been proposed for the treatment of this condition, including the medial regions of the temporal lobes, the caudate nucleus, the cerebellum, the centromedian nucleus of the thalamus, the subthalamic nucleus, and the anterior thalamic nucleus (ATN).[2] Electric modulation of epileptic neural circuits is a palliative option to decrease seizure frequency and improve quality of life.[3] Vagus nerve stimulation (VNS) is indeed used as a treatment option for intractable seizures, particularly in cases of epilepsy that have been resistant to other forms of treatment. A VNS device generates electrical pulses directed to the vagus nerve by adjusting parameters such as output current, pulse width, and frequency. Within the first year of treatment, about 45%-65% of patients experience a reduction in seizures by more than 50%[4] The exact mechanism by which VNS helps control seizures is not fully understood, but it's thought to modulate neuronal excitability and disrupt seizure activity in the brain.[5] The device is typically implanted under the skin in the chest area, with a wire connected to the vagus nerve. It delivers regular, mild electrical pulses to the nerve. While VNS doesn't necessarily stop seizures altogether, it can reduce their frequency and severity in some individuals, leading to improved quality of life.[6,7] It is often considered for people who have not responded well to medications or who are not candidates for surgery. As with any medical procedure, there are potential risks and side effects associated with VNS, including voice changes, throat discomfort, and surgical complications.[8,9] However, many people find that the benefits outweigh these risks, especially when other treatment options have been exhausted. We reported a case of medically refractory epilepsy with vagal nerve stimulation with a failure of corpus callosotomy.

CASE REPORT

A 24-year-old male presented with medically refractory seizures starting at the age of 2.5 years. Though he had no remarkable medical or familial history, seizures were characterized by an abnormal sound, which was followed by GTCS, lasting for about 30 seconds to 10 min, bladder incontinence, and post-ictal confusion. He had undergone emergency corpus callosotomy to treat status epileptics 6 years back, however, the symptoms did not improve significantly. On neurological examination, there was no significant deficit. He was on multiple anti-seizure medications (ASM) such as sodium, valproate, lamotrigine, and carbamazepine. Despite continuous treatment with ASM, there was no improvement, and was eventually referred to our center for further management. During evaluation, no symptoms of febrile seizure, encephalitis, metabolic disease, head trauma, or cerebrospinal (CSF) rhinorrhea were noticed.

Pre-surgical evaluation:

MRI Brain showed the right cerebral hemi atrophy with gliosis and encephalomalatic changes associated with moderately dilated right lateral ventricle and mild Rt. sided midline shift. Minimal lateral periventricular white matter T2/ FLAIR iso to hypointense signal showing SWI change along both high frontal convexities at the vertex. Thinning of the Corpus Callosum (Figure 1) was also noted. On further evaluation, 24-hour video electroencephalography (VEEG) was carried out to define the origin of seizure, however, no clear areas of epileptogenic focus were demarcated. The MRI findings, patient's semiology, and VEEG were not concordant, since the seizures had been increasing in frequency and refractory to an optimal dose of anti-seizure medication, the patient was then planned for vagal nerve stimulation.

Intra-operative Procedure

After administration of general anesthesia, the patient was placed supine on an operating table, head extended, and turned slightly to the right. A 4cm transverse skin incision was made, and dissection was done through the midline to the medial border of the SCM muscle. The platysma muscle was then divided and the fascial plane was dissected along the medial aspect of SCM. The Vagus nerve was identified, which was positioned between the carotid artery and the internal jugular vein. About 3-4 cm of the vagus nerve was exposed. For the pacemaker, another incision was given just 3 cm below the left clavicle, the electrode was tunneled beneath the skin to the site of the first incision. First, the anchor contact grid was placed in the inferior part, and then the positive contact grid was placed (Fig 1). Finally, the negative contact grid was placed in the superior part of the exposed vagus nerve. After implantation of helical electrodes, lead was connected temporarily to the battery for impedance check (Fig 2). Impedance check confirmed the good connection between the electrode and the pulse generator, thus the battery was implanted. The stimulation parameters after the procedure are depicted in table 1.

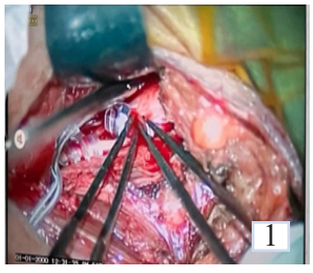

Figure 1: The anchor fixing the contact grid

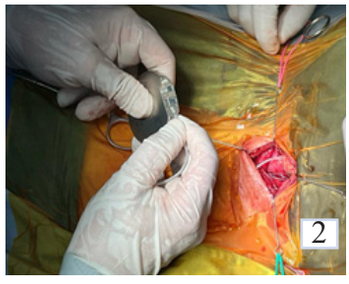

Figure 2: Lead connected to the pulse generator

Table 1: Stimulation Parameters

Time	2nd PoD	1 week	3 week	2 mths	3 mths	6 mths	1 yr
Freq (Hz)	20	20	20	20	20	20	20
On-time	30 sec	30 sec	30 sec	30 sec	30 sec	30 sec	30 sec
Off time	10 min	10 min	10 min	10 min	10 min	10 min	10 min
Current (mA)	0.25	0.375	0.5	0.75	1.00	1.5	2.5
Pulse width	250 µs	250 µs	250 µs	250 µs	250 µs	250 µs	250 µs

DISCUSSION

Vagus nerve stimulation (VNS) therapy has been an important intervention for epilepsy management since its inception. However, its therapeutic potential for epilepsy wasn't explored until much later. In 1988, neurologist James Kiffin Penry and neurosurgeon

William Bell implanted the first patient with VNS Therapy technology at the Wake Forest Bowman Gray School of Medicine in the United States.[10] Since that initial implantation, 10 versions of the VNS Therapy technology have been developed and made available for commercial use. The first clinical trials of VNS therapy for epilepsy began in Europe and the United States. These trials showed promising results, leading to the approval of VNS therapy by the U.S. Food and Drug Administration (FDA) for the treatment of epilepsy in 1997. The FDA approved the first VNS therapy system, manufactured by Cyberonics, Inc. (now LivaNova). This system consisted of a pulse generator implanted under the skin of the chest and connected to the left vagus nerve in the neck via a lead wire. As more patients received VNS therapy, clinicians gained a better understanding of its efficacy and safety profile. Research continued to explore its mechanisms of action and optimize stimulation parameters in 2000.[11]

Over the years, there have been advancements in VNS technology, including the development of smaller and more sophisticated pulse generators, improved lead designs, and the introduction of responsive or closed-loop stimulation systems that adjust stimulation in response to brain activity. VNS therapy is now an established treatment option for patients with epilepsy, particularly those who have not responded well to medication or other forms of treatment. It's also being explored for other neurological and psychiatric disorders, such as depression and migraine.[12] Several mechanisms have been proposed to explain how VNS reduces epileptic seizures.[10,13] Among these are mechanisms involving intracranial modulation of neurotransmitter release and anti-inflammatory effects. Electrical stimulation may trigger action potentials in a greater number of nerve fibers within the vagus nerve, thereby enhancing the seizure reduction effect. The mechanisms by which vagus nerve stimulation (VNS) reduces epileptic seizures are not entirely understood, but several hypotheses have been proposed based on research findings. VNS is believed to modulate the release of various neurotransmitters in the brain, including gamma-aminobutyric acid (GABA), serotonin, norepinephrine, and acetylcholine.[14] These neurotransmitters play crucial roles in regulating neuronal excitability and seizure activity. VNS may influence the activity and connectivity of brain networks involved in seizure generation and propagation. By altering the synchronization of neuronal firing patterns, VNS may disrupt epileptic activity and promote more normal brain making it less likely for epileptic discharges to spread and manifest as clinical seizures. This effect is thought to occur through changes in neuronal excitability and synaptic plasticity within seizure-prone brain regions. VNS has been shown to exert anti-inflammatory effects in the brain, possibly by inhibiting the release of pro-inflammatory cytokines and other immune mediators.[15] Chronic inflammation is thought to contribute to epileptogenesis and seizure recurrence, so reducing inflammation could help mitigate seizure activity. VNS may have neuroprotective properties, safeguarding neurons from the damaging effects of prolonged seizures or excite-toxicity. [16] By promoting neuronal survival and preserving structural integrity in epileptic brain regions, VNS could help prevent seizure recurrence. The vagus nerve is a major component of the autonomic nervous system, which regulates physiological functions such as heart rate, blood pressure, and stress response. VNS may exert its antiepileptic effects indirectly by modulating autonomic function, thereby influencing brain activity and seizure susceptibility.[17] VNS has been shown to promote neuroplasticity and synaptic remodeling in the brain. By inducing structural and functional changes in neuronal circuits, VNS may help restore aberrant network dynamics associated with epilepsy and promote adaptive responses to pathological conditions.

These mechanisms are not mutually exclusive, and the antiepileptic effects of VNS likely result from a combination of these factors. Further research is needed to elucidate the precise mechanisms underlying VNS therapy and optimize its therapeutic efficacy for patients with epilepsy and other neurological disorders. Indications for VNS in epilepsy are wide ranging, A meta-analysis of 74 clinical studies involving 3,321 patients demonstrated a 51% reduction in seizure frequency after one year of VNS therapy. The analysis revealed that children experienced better outcomes compared to adults. The most significant benefits were observed in patients with posttraumatic epilepsy, showing a 79% reduction in seizures, and those with tuberous sclerosis, with a 68% reduction. Additionally, generalized epilepsy had a higher reduction rate (58%) compared to focal seizures (43%).[18]

Current dosing guidelines for VNS parameters are divided into two phases: Phase 1 and Phase 2. In Phase 1, the focus is on gradually increasing the output current to achieve a therapeutic effect, while ensuring the patient can tolerate the adjustments, which consists of stable signal frequency, pulse width, ON and OFF time with steady increase in output current every 1-2 weeks.

Phase 2 involves gradually increasing the duty cycle over time and evaluating clinical outcomes every 3 to 6 months. The duty cycle is calculated using the formula: ON time + 4 seconds / (ON time + OFF time), where both ON and OFF times are measured in seconds. In our patient, we followed a similar protocol with steady increase in output current during phase 1, followed by slowly increasing the duty cycle in the current phase. However there are studies that demonstrate that higher stimulation parameters might be more effective in certain age groups. The study by Tamura et al included 74 patients who underwent VNS implantation, categorized into children and adolescents/adults. [19] The study found that approximately 40% of adolescents and adults experienced a significant reduction in seizures when subjected to higher stimulation parameters, exceeding 2.25 mA of output current and a 25% duty cycle. In nearly all cases, this resulted in a 50% or greater reduction in seizures. In contrast, the response rate in children was notably lower, at 26.7%, despite the use of higher stimulation settings. The study concluded that while high-stimulation VNS is particularly effective for adolescents and adults with intractable epilepsy, it may be less effective for children with extremely refractory epilepsy and high seizure frequency.

CONCLUSION

VNS surgery has progressed from being an experimental procedure to becoming a well-established therapy for epilepsy, offering hope to many patients who haven't found relief through other means. Ongoing research aims to further refine its use and understand its full potential in the management of epilepsy and other conditions.

REFERENCES

1. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069–77. [FullText] [PubMed] [DOI]

2. Sitnikov AR, Grigoryan YA, Mishnyakova LP. Bilateral stereotactic lesions and chronic stimulation of the anterior thalamic nuclei for treatment of pharmacoresistant epilepsy. Surg Neurol Int. 2018;9(1). [FullText] [PubMed] [DOI]

3. Arle JE, Carlson KW, Mei L. Investigation of mechanisms of vagus nerve stimulation for seizure using finite element modeling. Epilepsy Res. 2016 Oct;126:109–18. [FullText] [PubMed] [DOI]

4. Toffa DH, Touma L, El Meskine T, Bouthillier A, Nguyen DK. Learnings from 30 years of reported efficacy and safety of vagus nerve stimulation (VNS) for epilepsy treatment: A critical review. Seizure. 2020 Dec;83:104–23. 5. [FullText] [PubMed] [DOI]

5. Fan JJ, Shan W, Wu JP, Wang Q. Research progress of vagus nerve stimulation in the treatment of epilepsy. CNS Neurosci Ther. 2019 Nov;25(11):1222. [PubMed] [DOI]

6. Iimura Y, Suzuki H, Mitsuhashi T, Ueda T, Nishioka K, Horikoshi K, et al. Effect of vagus nerve stimulation against generalized seizure and status epilepticus recurrence. Front Neurol. 2023;14:1258854. [PubMed] [DOI]

7. Kavčič A, Kajdič N, Rener-Primec Z, Krajnc N, Žgur T. Efficacy and tolerability of vagus nerve stimulation therapy (VNS) in Slovenian epilepsy patients: younger age and shorter duration of epilepsy might result in better outcome. Acta Clin Croat. 2019;58(2):255.[PubMed] [DOI]

8. Révész D, Rydenhag B, Ben-Menachem E. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. J Neurosurg Pediatr. 2016 Jul;18(1):97–104. [FullText] [PubMed] [DOI]

9. Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. J Clin Neurophysiol. 2001;18(5):415–8. [FullText] [PubMed] [DOI]

10. Penry JK, Dean JC. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. Epilepsia. 1990;31 Suppl 2:S40–3. [FullText] [PubMed] [DOI]

11. Ogbonnaya S, Kaliaperumal C. Vagal nerve stimulator: Evolving trends. J Nat Sci Biol Med. 2013 Jan;4(1):8. [FullText] [PubMed] [DOI]

12. Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Biol Psychiatry. 2000 Feb;47(4):276–86. [FullText] [PubMed] [DOI]

13. Ben-Menachem E, Hamberger A, Hedner T, Hammond EJ, Uthman BM, Slater J, et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. Epilepsy Res. 1995;20(3):221–7. [FullText] [PubMed] [DOI]

14. Manta S, Dong J, Debonnel G, Blier P. Enhancement of the function of rat serotonin and norepinephrine neurons by sustained vagus nerve stimulation. J Psychiatry Neurosci. 2009;34(4):272. [PubMed]

15. Bonaz B. Anti-inflammatory effects of vagal nerve stimulation with a special attention to intestinal barrier dysfunction. Neurogastroenterol Motil. 2022 Oct;34(10).

[FullText] [PubMed] [DOI]

16. Jin Z, Dong J, Wang Y, Liu Y. Exploring the potential of vagus nerve stimulation in treating brain diseases: a review of immunologic benefits and neuroprotective efficacy. Eur J Med Res. 2023 Dec;28(1). [FullText] [PubMed] [DOI]

17. Constantinescu V, Matei D, constantinescu I, cuciureanu DI. Heart Rate Variability and Vagus Nerve Stimulation in Epilepsy Patients. Transl Neurosci. 2019 Jan;10(1):223. [FullText] [PubMed] [DOI]

18. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: A meta-analysis of efficacy and predictors of response - A review. J Neurosurg. 2011;115(6):1248–55. [FullText] [PubMed] [DOI]

19. Tamura K, Sasaki R, Sakakibara T, Dahal R, Takeshima Y, Matsuda R, et al. Additional Effect of High-output Current and/or High-duty Cycle in Vagus Nerve Stimulation for Adolescent/Adult Intractable Epilepsy. Neurol Med Chir (Tokyo). 2023;63(7):273–82. [FullText] [PubMed] [DOI]