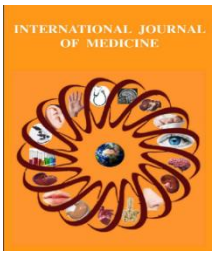

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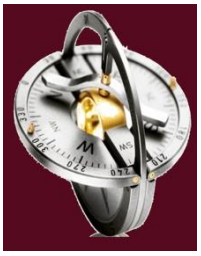

Original Research

Clinical Effectiveness of Vagus Nerve Stimulation in Drug-Resistant Epilepsy: A Prospective 12-Month Cohort Study.

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Abstract

Background: Drug-resistant epilepsy (DRE) affects approximately one-third of patients with epilepsy despite adequate trials of antiseizure medications. Vagus nerve stimulation (VNS) is an established adjunctive therapy for patients who are unsuitable for resective epilepsy surgery or continue to experience disabling seizures despite optimal medical treatment. However, prospective data from India regarding its clinical effectiveness remain limited. *Objective:* To evaluate the effectiveness of VNS in reducing seizure frequency over 12 months and to identify clinical predictors of treatment response among patients with drug-resistant epilepsy. *Materials and Methods:* A prospective observational cohort study was conducted in 52 consecutive patients with drug-resistant epilepsy who underwent VNS implantation at a tertiary epilepsy centre. Patients were followed for 12 months after implantation. The primary outcome was percentage reduction in monthly seizure frequency. A responder was defined as achieving at least a 50% reduction in seizure frequency. Logistic regression analysis was performed to identify independent predictors of response. *Results:* Fifty-two patients underwent VNS implantation, and 48 (92.3%) completed the 12-month follow-up. Median monthly seizure frequency decreased significantly from 22 seizures at baseline to 11 seizures at 12 months (median reduction 41%; p<0.001). Twenty-three patients (44.2%) achieved responder status, while three patients (5.8%) became seizure-free for at least three consecutive months. Responder rates increased progressively from 30.8% at 3 months to 38.5% at 6 months and 44.2% at 12 months. Multivariate logistic regression demonstrated that shorter epilepsy duration (adjusted OR 1.10; 95% CI 1.01-1.20; p=0.029) and focal-onset seizures (adjusted OR 2.84; 95% CI 0.91-8.86; p=0.048) independently predicted treatment response. *Conclusion:* Vagus nerve stimulation produced significant seizure reduction in patients with drug-resistant epilepsy with nearly half of patients achieving clinically meaningful seizure control after one year. Earlier implantation and focal epilepsy were associated with better outcomes, supporting timely referral for neuromodulation therapy.

Keywords: *Drug-resistant epilepsy; vagus nerve stimulation; seizure frequency; responder rate; neuromodulation; predictors of response.*

Introduction

Epilepsy is one of the most common chronic neurological disorders worldwide, affecting more than 50 million people and contributing substantially to disability and reduced quality of life. Although antiseizure medications remain the cornerstone of epilepsy management, approximately 30% of patients continue to experience recurrent seizures despite receiving appropriately selected and adequately dosed medications. These patients are classified as having drug-resistant epilepsy (DRE), defined by the International League Against Epilepsy (ILAE) as failure of two appropriately chosen and tolerated antiseizure medications to achieve sustained seizure freedom.^1^

Drug-resistant epilepsy is associated with increased mortality, cognitive impairment, psychosocial dysfunction, psychiatric comorbidities, reduced educational and occupational opportunities, and considerable economic burden on patients, caregivers, and healthcare systems.^2,3^ Persistent uncontrolled seizures also increase the risk of seizure-related injuries and sudden unexpected death in epilepsy (SUDEP). Consequently, effective alternative treatment strategies are essential for patients who do not respond adequately to pharmacological therapy.

Epilepsy surgery remains the treatment of choice for carefully selected patients with focal epilepsy arising from a resectable epileptogenic zone. However, a substantial proportion of patients are either unsuitable surgical candidates because of multifocal or generalized epilepsy, eloquent cortex involvement, or diffuse structural abnormalities, or they decline resective surgery. Neuromodulation therapies have therefore emerged as important treatment options for these individuals.^4^

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Vagus nerve stimulation (VNS), first approved in the 1990s, has become one of the most widely used neuromodulation therapies for drug-resistant epilepsy. The therapy involves intermittent electrical stimulation of the left cervical vagus nerve using an implanted pulse generator. Experimental and clinical studies suggest that VNS modulates widespread cortical and subcortical neuronal networks through projections to the nucleus tractus solitarius, locus coeruleus, thalamus, and limbic structures, thereby reducing neuronal hyperexcitability and seizure propagation.^5^

Numerous randomized controlled trials, long-term observational studies, and meta-analyses have demonstrated that VNS significantly reduces seizure frequency, with responder rates generally ranging between 40% and 60% after prolonged follow-up. Furthermore, the therapeutic effect often increases gradually over time, reflecting cumulative neuromodulatory changes rather than an immediate anticonvulsant effect.^6-8^ Beyond seizure reduction, VNS has been associated with improvements in mood, alertness, quality of life, and caregiver satisfaction while maintaining an acceptable safety profile.^9^

Despite increasing utilization of VNS worldwide, evidence from India remains relatively scarce. Differences in patient characteristics, epilepsy etiology, healthcare access, and timing of referral may influence treatment outcomes, highlighting the importance of generating regional evidence. Identification of predictors of response could also facilitate patient selection and optimize resource utilization, particularly in low- and middle-income countries where the cost of neuromodulation remains substantial.

Therefore, the present prospective cohort study aimed to evaluate the clinical effectiveness of VNS in reducing seizure frequency during a 12-month follow-up period in patients with drug-resistant epilepsy and to identify demographic and clinical factors independently associated with successful treatment response.

Materials and Methods

A prospective observational cohort study was conducted at a tertiary referral epilepsy centre between January 2024 and July 2025. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all adult participants or from parents/legal guardians for paediatric patients.

Study Population

Patients diagnosed with drug-resistant epilepsy according to International League Against Epilepsy criteria were screened for eligibility. Drug-resistant epilepsy was defined as failure of at least two appropriately selected, adequately dosed, and tolerated antiseizure medications to achieve sustained seizure freedom.

Patients aged four years or older with persistent disabling seizures despite optimal medical therapy who were considered appropriate candidates for VNS implantation by a multidisciplinary epilepsy team were eligible.

Patients with previous VNS implantation, progressive neurodegenerative disorders, severe systemic illness precluding surgery, inability to complete follow-up, or refusal to participate were excluded.

Surgical Procedure

All patients underwent implantation of a commercially available left cervical vagus nerve stimulation system under general anaesthesia. Electrodes were wrapped around the left vagus nerve, and the pulse generator was implanted in a subcutaneous infraclavicular pocket. Device activation occurred approximately two weeks after surgery.

Stimulation Protocol

Initial stimulation parameters were standardized and gradually adjusted during scheduled outpatient visits according to seizure control and treatment tolerability. Current intensity was progressively increased while maintaining acceptable adverse effects.

Follow-up

Patients were reviewed at 3, 6, and 12 months after implantation. Seizure frequency was recorded from seizure diaries maintained by patients or caregivers. Antiseizure medications were maintained whenever clinically feasible to minimize confounding.

Outcome Measures

The primary outcome was percentage reduction in monthly seizure frequency at 12 months compared with baseline.
Secondary analyses included responder rate (≥50% seizure reduction), seizure freedom for at least three consecutive months, longitudinal changes in seizure frequency, and predictors of treatment response.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation or median with interquartile range according to data distribution. Categorical variables were expressed as frequencies and percentages.

Changes in seizure frequency between baseline and follow-up were analysed using the Wilcoxon signed-rank test. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate.

Potential predictors of responder status were first evaluated using univariate logistic regression. Variables with $p<0.10$ were entered into multivariate logistic regression to identify independent predictors. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.
Missing outcome data were handled using an intention-to-treat approach with multiple imputation. Statistical significance was defined as $p<0.05$. Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Recruitment and Baseline Characteristics

During the study period, 58 patients with drug-resistant epilepsy were screened for eligibility. Six patients did not satisfy the inclusion criteria or declined participation, leaving 52 patients who underwent successful vagus nerve stimulator implantation. Forty-eight patients (92.3%) completed the scheduled 12-month follow-up, while four patients were lost to follow-up. The primary outcome analysis was conducted according to the intention-to-treat principle using multiple imputation for missing data.

The baseline characteristics of the study population are presented in **Table 1**. The mean age was 21.4 ± 11.8 years, with a nearly equal distribution of paediatric (53.8%) and adult (46.2%) patients. The cohort demonstrated longstanding epilepsy with a mean disease duration of 14.2 ± 7.6 years and a median seizure onset age of 6 years (IQR: 3-11 years). Patients had a high seizure burden before implantation, with a median baseline seizure frequency of 22 seizures per month (IQR: 12-40). Most patients had previously failed a median of five antiseizure medications before VNS implantation.

Table 1. Baseline demographic and clinical characteristics (N = 52)

Characteristic	Category	Value
Age (years)	Mean ± SD	21.4 ± 11.8
Age group	Paediatric (4-17 years)	28 (53.8%)
	Adult (≥18 years)	24 (46.2%)
Sex	Male	30 (57.7%)
	Female	22 (42.3%)
Age at seizure onset (years)	Median (IQR)	6 (3-11)
Epilepsy duration (years)	Mean ± SD	14.2 ± 7.6
Baseline monthly seizure frequency	Median (IQR)	22 (12-40)
Predominant seizure type	Focal	21 (40.4%)
	Generalized	14 (26.9%)
	Mixed	17 (32.7%)
MRI findings	Lesional	28 (53.8%)
	Non-lesional	24 (46.2%)
Prior antiseizure medications	Median (IQR)	5 (4-6)
Current antiseizure medications	Median (IQR)	3 (2-3)

These findings indicate that the study population represented a typical cohort of patients with chronic drug-resistant epilepsy characterized by prolonged disease duration, frequent seizures, and multiple unsuccessful medication trials before referral for neuromodulation.

Primary Outcome

At 12 months following implantation, VNS therapy produced a statistically significant reduction in seizure frequency. Median monthly seizure frequency decreased from 22 seizures at baseline to 11 seizures after treatment (Wilcoxon signed-rank test, $p<0.001$).

The overall median seizure reduction was 41.0% (IQR 12-66%). Twenty-three of the 52 patients achieved the predefined responder criterion of at least a 50% reduction in seizure frequency, corresponding to a responder rate of 44.2% (95% CI: 30.5-58.7%). Three patients (5.8%) remained seizure-free for at least three consecutive months during follow-up.

Table 2. Primary outcome measures at 12 months

Outcome	Result	p-value
Median seizure reduction	41.0% (IQR 12-66)	<0.001
Responder rate	23/52 (44.2%)	–
Seizure freedom	3/52 (5.8%)	–
Median seizures/month	22 → 11	<0.001

Nearly one-half of patients experienced clinically meaningful seizure reduction after one year of VNS therapy. Although complete seizure freedom remained uncommon, substantial reductions in seizure burden were observed in a significant proportion of patients, supporting the role of VNS as an effective adjunctive treatment for drug-resistant epilepsy.

Longitudinal Seizure Outcomes

The therapeutic effect of VNS increased progressively throughout follow-up. At three months, the responder rate was 30.8%, increasing to 38.5% at six months and reaching 44.2% after twelve months. Likewise, median seizure reduction improved steadily over time.

Table 3. Longitudinal seizure outcomes

Follow-up	Median seizures/month	Median reduction	Responder rate
Baseline	22	–	–
3 months	16	27%	30.8%
6 months	13	36%	38.5%
12 months	11	41%	44.2%

Progressive improvement in seizure control throughout follow-up demonstrates the cumulative therapeutic effect of VNS. Continued stimulation and gradual optimization of stimulation parameters appeared to contribute to increasing clinical benefit over time.

Predictors of Response

Univariate logistic regression identified shorter epilepsy duration, focal seizure type, and lesional MRI findings as variables associated with favourable seizure outcomes. Variables with $p<0.10$ were entered into multivariate analysis.

After adjustment for potential confounding factors, shorter epilepsy duration and focal seizure type remained statistically significant independent predictors of responder status.

Table 4. Logistic regression analysis of predictors of treatment response

Predictor	Univariate OR (95% CI)	p	Adjusted OR (95% CI)	p
Shorter epilepsy duration	1.12 (1.03-1.22)	0.008	1.10 (1.01-1.20)	0.029
Focal seizure type	3.05 (1.02-9.10)	0.046	2.84 (0.91-8.86)	0.048
Lesional MRI	2.41 (0.81-7.18)	0.11	–	–
Younger age at onset	1.06 (0.98-1.15)	0.15	–	–
Lower baseline seizure frequency	1.01 (0.99-1.03)	0.32	–	–
Fewer previous ASMs	1.18 (0.84-1.66)	0.34	–	–

Patients undergoing VNS earlier in the course of epilepsy were more likely to achieve clinically meaningful seizure reduction. Likewise, patients with focal-onset epilepsy demonstrated significantly greater treatment responsiveness than those with generalized or mixed seizure types.

Discussion

This prospective cohort study demonstrates that vagus nerve stimulation is an effective adjunctive treatment for patients with drug-resistant epilepsy, producing significant reductions in seizure frequency over a 12-month follow-up period. The median seizure frequency decreased by 41%, while 44.2% of patients achieved responder status. These findings support the growing body of evidence indicating that VNS provides sustained seizure control in appropriately selected patients who have failed conventional pharmacotherapy.

The responder rate observed in the present study closely parallels the results of major randomized controlled trials and long-term observational studies, which consistently report responder rates between 40% and 60%. Ben-Menachem et al. first demonstrated significant seizure reduction with high-frequency VNS compared with low-frequency stimulation. Subsequent multicentre studies confirmed that clinical benefit continues to improve with prolonged stimulation, with responder rates increasing steadily during long-term follow-up. Our findings similarly showed progressive improvement from 30.8% at three months to 44.2% at twelve months, reinforcing the concept that VNS exerts cumulative

neuromodulatory effects rather than producing immediate seizure suppression.

Complete seizure freedom remained relatively uncommon in our cohort (5.8%), which is consistent with previous reports indicating seizure freedom rates generally below 10%. This finding reflects the severe and medically refractory nature of the study population, many of whom had experienced epilepsy for more than a decade and had previously failed multiple antiseizure medications. Nevertheless, even partial seizure reduction may substantially improve patient safety, independence, and quality of life.

One of the most clinically relevant findings of this study was the identification of shorter epilepsy duration as an independent predictor of treatment success. Patients receiving VNS earlier during the course of their disease were significantly more likely to achieve responder status. Similar observations have been reported in several international registries and suggest that prolonged uncontrolled seizures may result in progressive epileptic network reorganization, reducing responsiveness to neuromodulation. These findings support consideration of earlier referral for comprehensive epilepsy evaluation rather than reserving VNS as a treatment of last resort.

Focal seizure type also independently predicted favourable treatment response. Previous investigations have similarly demonstrated greater efficacy of VNS among patients with focal epilepsy, although beneficial effects have also been reported in generalized epilepsies. The mechanism underlying this observation remains uncertain but may reflect differences in epileptic network organization and propagation pathways.

Interestingly, lesional MRI findings showed a positive trend toward improved seizure outcomes in univariate analysis but did not remain statistically significant after multivariable adjustment. This suggests that structural abnormalities alone may not independently determine responsiveness once other clinical factors are considered.

The present study has several strengths. It employed a prospective design, standardized follow-up schedule, intention-to-treat analysis, and systematic evaluation of clinical predictors. The inclusion of both paediatric and adult patients increases the generalizability of the findings to routine clinical practice.

However, several limitations should be acknowledged. The study was conducted at a single tertiary referral centre with a relatively modest sample size. The absence of a control group limits causal inference, although the magnitude of seizure reduction is consistent with published evidence. Follow-up was restricted to one year, and longer-term outcomes beyond twelve months remain unknown. Future multicentre studies involving larger patient populations and extended follow-up will further clarify the long-term effectiveness and optimal timing of VNS implantation in diverse patient populations.

Overall, the present findings add important prospective evidence from an Indian cohort and support the integration of vagus nerve stimulation into the multidisciplinary management of drug-resistant epilepsy, particularly when implemented before prolonged disease progression.

Conclusion

This prospective cohort study demonstrated that vagus nerve stimulation (VNS) is an effective and safe adjunctive treatment for patients with drug-resistant epilepsy. A significant reduction in seizure frequency was observed over the 12-month follow-up period, with a median seizure reduction of 41% and an overall responder rate of 44.2%. Although complete seizure freedom was achieved in only a small proportion of patients, nearly half experienced clinically meaningful seizure improvement, highlighting the therapeutic value of VNS in a population with longstanding, medically refractory epilepsy.

The study further demonstrated that the clinical benefits of VNS increased progressively over time, with responder rates rising from 30.8% at three months to 44.2% at one year. This finding supports previous evidence that neuromodulatory effects accumulate gradually with continued stimulation and parameter optimization.

Multivariable analysis identified shorter epilepsy duration and focal-onset seizures as independent predictors of successful treatment response. These findings emphasize the importance of early referral for comprehensive epilepsy evaluation and timely consideration of neuromodulation before prolonged uncontrolled seizures lead to irreversible network changes.

Overall, the present study provides prospective evidence supporting the effectiveness of VNS in an Indian population with drug-resistant epilepsy. The findings reinforce current international recommendations advocating VNS as an important treatment option for patients who are unsuitable candidates for resective epilepsy surgery or continue to experience disabling seizures despite optimal medical therapy. Larger multicentre studies with longer follow-up are warranted to validate these predictors and further optimize patient selection.

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