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The Neuromodulatory Effect of Vagus Nerve Stimulation (VNS) in Drug Resistant Generalized Epilepsy in Saudi Arabia

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Abstract

Background: Vagus nerve stimulation (VNS) is a treatment mainly approved as an adjuvant toantiepileptic drugs for therapy-resistant focal epilepsy. Currently, its use is expanded to include patients with generalized epilepsy. The current study reports the outcomes of VNS for patients with drug resistant generalized epilepsy in Saudi Arabia.

Methods: A retrospective research design was employed with a sample of 18 patients with generalized epilepsy who were treated with VNS at King Fahad Medical City. The reported outcomes included seizure frequency reduction, seizure types that were most responsive and side effects of VNS therapy.

Results and Findings: The mean seizure onset age was 4.11 years (SD= 2.85), ranging from 1-9. The mean age of VNS implantation was 17.76 years (SD= 7.46), ranging from 5-30 years. Three years after the implantation, one of the patients was seizure-free, and 13 patients (72.22%) had at least a 50% reduction in the frequency of seizures compared to baseline. The overall reduction in seizure frequency showed a significant reduction of 54%, t (17)=2.07, (P=0.05). Most patients (n= 14, 77.8%) reported no side effects after VNS implantation. More specifically, seizure types that were most responsive to VNS treatment included tonic (100% > 50% reduction), myoclonic (80% > 50% reduction), and GTC (76.4% > 50% reduction), whereas the astatic and atonic seizure types were least responsive (50% > 50% reduction). The usually reported side effects were wound infection, cough, choking, and hoarseness. The study was conducted in one tertiary epilepsy center. Hence, our sample size was relatively small.

Conclusion: The outcomes of VNS confirm its safety and effectiveness as adjunctive therapy for patients with drug-resistant generalized epilepsy in Saudi Arabia. More research with large samples is still needed to specify the characteristics of patients who respond well to VNS.

Keywords: Neuromodulation; Vagus nerve stimulation; Drug resistant epilepsy; Generalized epilepsy; Saudi Arabia

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Introduction

Epilepsy is one of the most common neurological diseases, affecting 0.5%-1.0% of people worldwide, and one-third of these people experience uncontrolled or drug-resistant epilepsy [1]. In Saudi Arabia, the prevalence rate for active epilepsy was 6.54/1000 people [2]. Drug-resistant epilepsy is manifested by the antiepileptic drug regimens' failure to achieve seizure freedom [3]. Although there are currently many new antiepileptic drugs, a large proportion of patients fail to achieve seizure control in response to antiepileptic drugs [4]. Literature has shown that those with drug-resistant epilepsy are at a higher risk of developing epilepsy-related complications and comorbidities [5].

When antiepileptic drugs fail to achieve seizure control in patients with generalized epilepsy, management modalities are limited.

Alternative strategies include a ketogenic diet [6], palliative surgeries [7], and neuromodulation [8]. Three neuromodulatory therapies were approved to treat epilepsy, including Vagus Nerve Stimulation (VNS), Deep Brain Stimulation, and Responsible Neurostimulation (RNS). VNS is a relatively safe and useful neuromodulatory therapy used as an adjuvant to antiepileptic drugs when antiepileptic drugs alone fail to achieve seizure control [9]. VNS delivers intermittent and continuous electrical stimulation to the vagus nerve using an implantable device connected to a pulse generator [10]. The mechanism underlying the action of VNS to reduce the frequency and duration of seizure is not fully understood. However, VNS appears to play a role in modifying the distribution of cerebral blood flow, increasing the inhibitory neurotransmitters, and reducing the excitatory neurotransmitters [11].

VNS is a treatment mainly approved as an adjuvant to antiepileptic drugs for therapy-resistant focal epilepsy in the late 1990s by the US Food and Drug Administration [12-15]. Data about the efficacy of VNS in drug resistant generalized epilepsy are limited. Previous randomized controlled trials [16,17], retrospective studies [18,19] and meta-analysis [20] have shown that approximately 50% to 80% of patients who receive VNS therapy achieve a ≥ 50% reduction in seizure frequency within the first one or two years of treatment, and improvements may increase over time. However, seizure freedom after VNS therapy rarely occurs. Additionally, the rates and the characteristics of patients who achieve seizure freedom remain poorly understood. To date, researchers believe that it is still impossible to precisely predict the characteristics of patients who respond to VNS and to what extent they may benefit from this treatment. Other gaps in knowledge are related to the types of seizures that may benefit from VNS therapy. On the other hand, using VNS for seizure management was associated with various side effects, including hiccups, cough, hoarseness, and dysphagia [21-24].

The purpose of this study is to explore the efficacy of VNS in patients with drug-resistant generalized epilepsy at King Fahad Medical City, Riyadh, Saudi Arabia.

Materials and Methods

Study population

This was a retrospective observational study. Patients with generalized DRE who underwent VNS implantation at KFMC were included. Detailed patient history was obtained from patient files retrospectively. The collected data included current patient age, seizure onset age, age at VNS implantation, epilepsy duration, epilepsy duration before VNS insertion, history of epilepsy surgery, and the brain MRI results. Data about etiological factors, such as genetic, structural, and metabolicwere also obtained. Data were also collected about epilepsy type, seizures types, and comorbidities (relevant to epilepsy). The available data about follow up and outcome data about seizure frequency at baseline (seizure/month) and annually for the first three years of implantation were collected.

VNS insertion

The VNS device was implanted subcutaneously in the upper left side of the chest under general anesthesia ineighteen patients. After a recovery period, the stimulation values were programmed during the outpatient visit within 2 weeks from implantation. The intensity of stimulation started at 0.50mA, was increased by steps of 0.50mA until the stimulation parameters reached the most effective and tolerated intensity. The outcomes were classified into 4 categories: seizure-free (SF); responder with at least 75% reduction in the frequency of seizures from baseline (R 75); responder with seizure frequency reduction at least 50% from baselines (R 50); non-responders which showed < 50% reduction from baseline (NR); or worsening of seizure frequency increased by > 50% from baseline (W). Data about total follow up duration since insertion until the last assessment (36 months) and any adverse events reported (i.e., hoarseness, coughing, throat pain, headache, or others). In the case of VNS discontinuation, data about time and reason for discontinuation were documented. VNS settings and other parameters included model, latest settings, latest VNS parameters: output current mA (OC), frequency Hz (F), pulse width micro sec (PW), on time sec (OT), and off time sec (FT) were included. Three models were used among patients: model 102 (n=1, 5.6%), model 103 (n=11, 61.1%), and model 106 (n=6, 33.3%).

Ethics statement

This study protocol was reviewed and approved by the institutional review board, KFMC research center (IRB00010471).

Statistical analysis

The statistical analysis was done by SPSS version 26. Descriptive statistics were used to present the characteristics of the study participants. A paired t-test was used to compare the difference of the mean scores in seizure frequency over time, and a P-value of < 0.05 was statistically significant.

Results

Demographic and clinical findings

A sample of 18 patients diagnosed with drug-resistant generalized epilepsy who underwent VNS implantation in the Neuroscience Department in King Fahad Medical City completed the study. All patients underwent phase one of pre-surgical assessment by scalp Video electroencephalogram (EEG) monitoring. Scalp-EEG monitoring was performed using the international 10-20 system of electrode placement. MR images using an epilepsy protocol were acquired on a 1.5 T or 3 T and interpreted by a dedicated neuro-radiologist.

More than half of the participants were female (n=10, 55.5%). The patients' mean age was 20.33 years (SD= 6.06), ranging from 8-33. The mean seizure onset age was 4.11 years (SD= 2.85), ranging from 1-9. The mean epilepsy duration was 19.61 years (SD= 8.42), ranging from 2-33. The mean age of VNS implantation was 17.76 years (SD= 7.46), ranging from 5-30 years.

The majority of the study participants (88.9%) did not undergo any prior epilepsy surgery, while one patient had functional hemispherectomy, and one patient had a corpus colostomy (before or after VNS implantation).

Four patients (22.2%) had PME, three patients (16.6%) had LGS, and one patient (5.5%) had Doos syndrome and JME.MRI was non-lesional for all patients; 13 (72.2%) patients had unremarkable MRIs, 4 (22.2%) showed diffuse atrophy, and 1 (5.5%) showed insignificant punctuated subcortical white-matter signal changes. The etiology of epilepsy was unknown in 11 patients (61.1%), genetic in six patients (33.3%), and infection in one patient (5.6%).

Regarding the generalized seizure type, 6 (33.3%) had generalized tonic-clonic (GTC), 6 (33.3%) had myoclonic and GTC, 3 (16.7%) had drop attacks, GTC and myoclonic, 1 (5.6%) had tonic, GTC, and myoclonic, 1 (5.6%) had tonic, and 1 (5.6%) had GTC with apnea. Regarding comorbidities, 9 (50.0%) had cognitive impairment, and 4 (22.2%) had a developmental delay (**Table 1**).

VNS parameters and response rate

VNS parameters at the last visit are shown in **Table 2**. After 3 years of implantation, out of 18 patients, 14 (77.8%) were responders.

One patient was seizure-free. Thirteen patients (72.2) had at least a 50% reduction in the frequency of seizures compared to baseline, including 9 (5.00%) with at least a 75% reduction in seizure frequency. The overall reduction in seizure frequency was estimated employing paired t-tests and showed a significant reduction of 54%, t (17)=2.07, (p=0.05).

These outcomes show slight improvement over the outcomes obtained from 1 and 2 years post-implantation (**Table 3**).In this study, seizure syndromes that were most responsive to VNS treatment included progressive myoclonic epilepsies (PME, 100% > 50% reduction) and Lennox–Gastaut syndrome (LGS, 66% > 50% reduction). There was one patient with Doos syndrome, but he did not respond to VNS treatment. More specifically, seizure types that were most responsive to VNS treatment included tonic (100% > 50% reduction), myoclonic (80% > 50% reduction), and GTC (76.4% > 50% reduction), whereas the astatic and atonic seizure types were least responsive (50% > 50% reduction).

Adverse events and complications

Most patients (n=14, 77.8%) reported no adverse events after VNS implantation. One patient each developed wound infection (5.6%), cough (5.6%), and choking (5.6%), and 3 patients developed hoarseness. VNS discontinuation was reported in 1 patient (5.6%) due to infection (**Table 4**).

Discussion

Drug-resistant epilepsy is currently regarded as a worldwide health concern as it affects a significant proportion of patients with epilepsy, requires complex treatment, and imposes a substantial financial burden and health costs. This study is a novel report of VNS therapy efficacy in Saudi Arabia as few studies have been conducted to assess the efficacy of VNS in patients with drug resistant generalized epilepsy including genetic/idiopathic

Table 1 The sample characteristics.

Characteristics		Frequency	%	Mean	SD
Age		-	-	20.33	6.06
Seizure Onset Age		-	-	4.11	2.85
Age Insertion VNS		-	-	17.76	7.46
Epilepsy Duration		-	-	19.61	8.42
Gender	Female	10	55.50%	-	-
	Male	8	44.40%	-	-
Prior Epilepsy Surgery	No	16	88.9	-	-
	Functional Hemispherectomy	1	5.6	-	-
	Corpus Colostomy	1	5.6	-	-
Etiology	Unknown	11	61.1	-	-
	Genetic	6	33.3	-	-
	Infection	1	5.6	-	-
Generalized Seizure Type	GTC	6	33.3	-	-
	Myoclonic, GTC	6	33.3	-	-
	Drop Attacks, GTC, Myoclonic	3	16.7	-	-
	Tonic, GTC, Myoclonic	1	5.6	-	-
	Tonic	1	5.6	-	-
	GTC, Apnea	1	5.6	-	-
Comorbidity	Developmental Delay	4	22.2	-	-
	Cognitive Impairment	9	50	-	-
	None	5	27.8	-	-

Table 2 VNS parameters and response rate.

Parameters	Min	Max	Mean	SD
Output current (mA)	0.75	2.75	2.08	0.52
Frequency (Hz)	20	30	25.31	4.98
Pulse Width (Mic S)	250	500	316.66	114.43
On time (Sec)	14	30	27.87	4.8
Off time (Min)	1.1	8	3.15	1.95

or symptomatic generalized epilepsy. For example, Marti et al. [24] assessed the responses of 46 patients with generalized drug-resistant epilepsy to the VNS treatment. Their results showed that 41.7% (n=12) of patients with Lennox–Gastaut Syndrome (LGS) and 64.7% (n=11) of patients with genetic generalized epilepsy (GGE) had an overall seizure reduction of 50% or more. The authors concluded that VNS should be considered a treatment option in patients diagnosed with generalized drug-resistant epilepsy. In this study, after VNS implantation, 14patients (77.8%) had at least a 50% reduction in the frequency of seizures compared to baseline with 1 patient (5.6%) achieving seizure freedom. Such percentages are notably consistent with the previous studies that reported more than 50% seizure reduction in about 50% to 80% of patients [25-27]. Furthermore, this outcome supports studies that emphasize the efficacy of VNS not only in treating focal epilepsy, but also in reducing the frequency of other types of seizures, such as generalized epilepsy [28].

Despite the seizure reduction noted in this study, none of our patients discontinued the AEDs, emphasizing that VNS is an

Table 3 The outcomes of VNS implantation.

Parameters		1st year		2nd year		3rd year	
		Frequency	Percent	Frequency	Percent	Frequency	Percent
Response To VNS	Non-Respondent	6	33.3	5	27.8	4	22.2
	Responders	12	66.6	13	72.2	14	77.8
	R50	4	22.2	3	16.7	4	22.2
	R75	7	38.3	9	50	9	50
	SF	1	5.6	1	5.6	1	5.6

R50: At least a 50% reduction in the frequency of seizures compared to baseline
R75: At least a 75% reduction in the frequency of seizures compared to baseline
SF: Seizure free

Table 4 The adverse events of VNS implantation.

Adverse Events*	No Side Effects	14	77.8
	Hoarseness	3	16.6
	Cough	1	5.6
	Wound Infection	1	5.6
	Choking	1	5.6

*Some participants reported more than one adverse event

adjuvant to antiepileptic drugs that enhances seizure control among patients who are treated with AEDs. Adaptation of an AED regimen based on the patient response to VNS therapy is essential, which may influence seizure control. Four patients had less than 50% reduction in the frequency of seizure, all of them had GTC, 2 were children (ages 8 and 12), 2 had epilepsy surgeries, and 2 had idiopathic generalized epilepsy.

The characteristics of patients who do not achieve significant seizure reduction in response to VNS therapy and their role in influencing the response to treatment is still poorly understood. Some studies tried to identify responders based on the type of epilepsy. One study reported a better response to VNS in drop attacks [29], which is supported by this study that included 3 patients with drop attacks, and all of them were responders to the VNS treatment. However, these 3 patients in the current study were also suffering from other types of seizure episodes, indicating that it is difficult to conclude that there is a favorable response to VNS in a specific seizure type.

In this study, the average reduction in seizure frequency was 54%. This outcome is closely related to a previous study that reported 57.2% [30]. In the current study, the overall percentage of responders to VNS treatment was about 72%. This percentage is somewhat better than that reported by previous research [31,32], which found that 23% to 60% of patients with intractable epilepsy were responders to VNS treatment (showed > 50% reduction in seizure). The outcomes of the current study are consistent with those of the previous research regarding LGS response to VNS [33] that reported a 60% reduction in Gafter VNS therapy; however, the current study showed more improvement in GTC (76.4% > 50% reduction) compared with that in previous research, which showed that only 25% - 57% of patients with GTC had > 50% reduction. However, our outcomes revealed no improvement in the patient with Doos syndrome who received VNS treatment, which contradicts a previous study. In this study, patients with atonic seizures were the least responsive to VNS treatment (50% > 50% reduction). However, previous research shows a percent improvement of about 80% in this seizure type [34].

Our study also revealed that myoclonic seizure had a good response to VNS treatment (80% > 50% reduction), which is also consistent with that reported earlier (75% > 50% reduction) [34]. The tonic seizure was the type most responsive to VNS treatment (100% > 50% reduction). This result is considered a high percentage compared with previous findings showing a 73.3% reduction in tonic seizure [32]. More research with large samples is still needed to specify the characteristics of patients who respond well to VNS since the small sample size in the current study probably limited our ability to do in-depth analysis in this regard.

The study outcomes were reported for the first 3 years after VNS implantation, which is a relatively adequate time to show the VNS efficacy. Previous research has shown that reduction in seizures' frequency cannot be noted immediately following VNS implantation, but it occurs steadily over the years [35]. Elliott et al. [36] described the first 2 years after VNS implantation as a "ramp-up period" and emphasized that the process of seizure control increases slowly and gradually over the following years before stabilizing eventually. In contrast, AEDs usually initiate their action rapidly with a possible reduction of efficacy in some patients over time due to tolerance.

The adverse events of VNS therapy in this study included wound infection, hoarseness, cough, and choking. However, about 78% of the patients reported no side effects. Previous research indicated that laryngeal and cardiovascular side effects are possible complications of VNS implantation surgical procedures [21-23]. These complications could be minimized by modifying the surgical

technique utilizing evidence-based surgical protocols during the VNS implantation surgery [37]. Also, the transient side effects of VNS can be usually reduced by lowering the output current during actual stimulation. Therefore, VNS can be considered a safe therapy, since most of its side effects are transient and can be reduced by some well-documented interventions.

Conclusion and Limitations

The current study has some limitations. The retrospective research design used in this study is associated with selection bias and lack of control. The small sample size is another limitation that affects the generalizability of findings. However, this study makes an essential contribution to knowledge, being a novel study among those about VNS therapy efficacy in patients with generalized epilepsy in Saudi Arabia. This study shows the potential of widespread application of VNS therapy to treat generalized epilepsy.

The outcome of our patients from King Fahad Medical City in this retrospective study confirms that using VNS therapy is safe and effective for patients with drug-resistant generalized epilepsy. However, using VNS therapy cannot replace AEDs.

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