RESEARCH ARTICLE

The role of vagal nerve stimulation on psychosocial associated disorders in refractory epilepsy patients

Mohamed Abdul Jalil Al-Tamimi

Abstract

Objective: To determine the effects of vagal nerve stimulation on cognition and epilepsy-associated psychosocial problems in patients with intractable epilepsy, and to assess their relation to seizure decline.

Method: The longitudinal study was conducted at Saad Al-Witry Neurosciences Hospital, Baghdad, Iraq, from December 2015 to December 2020, and comprised refractory epilepsy cases with implanted vagal nerve stimulation devices. They were subjected to pre- and post-implantation epilepsy protocol assessment with added neuropsychological evaluation using the Mini-Mental State Examination system. Each case was followed up for 2 years post-implantation. Descriptive data regarding patient records of age, seizure nature, mental functioning level, and vagal nerve stimulation insertion was noted. Data was analysed using SPSS 21.

Results: Of the 150 patients, 75(50%) each were males and females, with 70(46.7%) aged <10 years at the time of surgery. Overall, 80(53.3%) patients had partial seizures with secondary generalisation, 70(46.7%) had refractory seizure attacks for <5 years, 78(52%) had attack frequency of 2-5 per day. All 150(100%) patients had had vagal nerve stimulation for >2 years. Post-intervention, 80(53.3%) patients had <2 attacks per day. Mini-Mental State Examination score was >25 in 35(23.3%) patients which post-intervention rose to 64(42.7%).

Conclusion: There was evidence of improvement with respect to patient characteristics predictive of vagal nerve stimulation-related cognition and neuropsychological responsiveness in refractory epilepsy.

Key Words: Vagus Nerve, Cognition, Seizures

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Introduction

Early in the last century, neuroscientists first wondered whether it might be likely to influence brain activity and concomitant behaviour by stimulating the vagus, or the 10th cranial nerve (CN-X), in the neck. Many have speculated whether vagal nerve stimulation (VNS) could offer a chance to deal with other neuropsychiatric disorders. It appears obvious to ask whether and to what extent VNS can affect brain function. This has been widely investigated during the last century. Of all the cranial nerves (CNs), the vagus has been the most misunderstood [1]. In the 1880s, it was observed that manual pressure of the carotid artery in the cervical area could suppress seizures. This could be due to crude stimulation of CN-X[2]. Brain electrical activity can also be affected by different methods of paced breathing, which might be arbitrated by VNS, starting from the diaphragm[3, 4]. For years, VNS was established as one of the methods of neuro-stimulation by implanting a left vagal nerve electrode connected to a pulse generator. Clinical trials ultimately led to the approval by the United States Food and Drug Administration (FDA) of an implanted VNS device for the management of refractory epilepsy in 1997[5]. Later, in 2005, the FDA approved its use in chronic drug-resistant depression. Some small open-label studies and case series have labelled the usage of VNS in rapid cycling bipolar disorder, Alzheimer's disease, chronic refractory headaches, and treatment-resistant anxiety disorders, though none of these procedures had FDA approval[6]. Patients with refractory epilepsy are in need of higher dosage, duration and frequency of anti-epileptic drugs (AEDs), which can have a negative impact on cognition and life quality[7,8]. When AED intake is given as a monotherapy at an average therapeutic dose, it may improve cognition through seizure control. On the other hand, higher seizure frequency, period and severity increase the chance of deranged cognition. VNS, as one of the measures that help decrease the frequency or dosage of AED, may thus have an appositive effect on the patient's cognition[9].

No relevant studies in this regard were found in literature from Iraq. The current study was planned to fill the gap by determining the effects of VNS on cognition and epilepsy-associated psychosocial problems in patients with intractable epilepsy, and to assess their relation to seizure decline.

Department of Surgery, Mustansiriyah University, Baghdad, Iraq.

Correspondence: Mohamed Abdul Jalil Al-Tamimi

Email: mhmdtamimi20202@gmail.com

Patients and Methods

The longitudinal, descriptive study was conducted at Saad Al-Witry Neurosciences Hospital, Baghdad, Iraq, from December 2015 when VNS implantations, were introduced at the health facility, to December 2020. The sample comprised all patients with confirmed refractory epilepsy who were referred to the hospital. Those included were patients who had been diagnosed with refractory epilepsy on the basis of neurology reports with failure of medical treatment, having >2 attacks per day despite changing drug combination regimens and on >1 drug at a time, having abnormal neuropsychological associated symptoms, and referred for VNS system implantation with no contraindications on assessment. All the included patients had complete data available both at baseline and at follow-up periods for 24 months with a +2 months window. Pre-surgical assessment, including an electroencephalogram (EEG), epilepsy protocol magnetic resonance imaging (MRI) scan with additional temporal coronal study, and T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI sequences, was done for all the enrolled cases. Implantation was performed under standard protocol. The patients were classified according to the obtained data of age at seizure onset, types of seizures (using the International Classification of Diseases [ICD]) 10 ages in years at the time of and after VNS surgery, mentality level (using the Mini-Mental State Examination [MMSE][11], which is a 30-point questionnaire to measure cognitive impairment, including registration, attention, calculation, recall, language, ability to follow simple commands, and orientation, and parameters of VNS.

Data was analysed using SPSS 21. Data was expressed as frequencies, percentages and cumulative percentages. A paired t-test was conducted ($p < 0.05$) to assess if there was a statistical difference between the pre- and post-intervention groups.

Results

Of the 150 patients, 75(50%) each were males and females, with 70(46.7%) aged <10 years at the time of surgery. Overall, 80(53.3%) patients had partial seizures with secondary generalisation (PSG), 70(46.7%) had refractory seizure attacks for <5 years, 78(52%) had attack frequency of 2-5 per day. All 150(100%) patients had had vagal nerve stimulation for >2 years (Table 1).

Vagus nerve stimulation (VNS) resulted in a statistically significant ($p<0.05$) reduction in attack frequency. Post-intervention, a greater proportion of patients (80%, n=53.3%) experienced less than two attacks per day compared to none receiving monotherapy pre-operatively. Additionally, VNS therapy led to a significant decrease in the number of concomitant antiepileptic drugs (AEDs) prescribed. Notably, no patients were on monotherapy before VNS implantation, whereas 20 patients (13.3%) achieved seizure control with a single AED following VNS treatment. (Table 2).

In 40(26.6%) cases, patients or their caregivers reported social behaviour improvement, 24(16%) reported alleviated mood, 26(17.3%) patients showed alertness, and 20(13.3%) reported better school performance, while 40(26.6%) reported no change.

MMSE score was >25 in 35(23.3%) patients which post-intervention rose to 64(42.7%). Also, 31(20.7%) patients showed a median improvement of 1.5 points, 10(6.7%) showed 2.5 points, and 2(1.3%) showed a >2.5 point increment (Table 3).

Table-1: Descriptive statistics.

Variables	Groups	Frequency	Cum.	Frequency %	Cum %
Age groups In years (at surgery)					
	<10	70	70	46.7	46.7
	10-20	45	115	30	76.7
	20-30	35	150	23.3	100
Gender					
	Males	75	75	50	50
	Females	75	150	50	100
Type of epilepsy					
Focal	PSG	80	80	53.3	80
	C.P.	25	105	16.7	70
Generalised	Tonic clonic (GTC.)	30	135	20	90
Multiple types	AS, MS, GTC, PCS, MR	15	150	10	100
Duration of epilepsy in years					
	2-5	70	70	46.7	46.7
	5-10	55	125	36.7	83.3
	10-15	15	140	10	93.3
	>20	10	150	6.7	100
Duration of implant in years					
	2-4	40	40	26.7	26.7
	4-6	78	118	52	78.7
	6-8	32	150	21.3	100

PSG: Partial with secondary generalisation, CP: Complex partial, GTC: Generalised tonic-clonic, Cum: Cumulative.

Table-2: Change in number of drugs used and seizure frequency pre- and post-vagal nerve stimulation (VNS).

No. of drugs	No. of patient's pre-VNS	Frequency %	No. of patients post VNS	Frequency %	P-value
1	0	0	20	13.3	0.02
2	68	45.3	90	60	0.01
3	45	30	35	23.3	0.04
4	37	24.7	5	3.3	0.001
No. of attacks/day pre-VNS	**No. of patients**	**Frequency %**	**No. of attacks/day post-VNS**	**No. of patients**	**Frequency %**	**P-value**
2-5	78	52	<2	80	53.3	0.07
5-10	47	31.3	2-5	65	43.3	0.04
>10	25	16.7	5-10	5	3.3	0.001

Table-3: Median difference between MMSE values at baseline and after 24 months of follow-up.

	No. of patients Pre implantation	%	No. of patients post implantation	%	No. of patients post VNS implantation	Median MMSE points improvement
MMSE>25	35	3.3	64	42.7	31/150	1.5
MMSE 20-25	85	56.7	69	46	10/150	2.5
MMSE10-20	30	20	17	11.3	2/150	2.5-5
Neuropsychological symptomatic response			**No. of patients post implantation**		**Frequency %**	
Social behaviour improvement			40/150		26.6	
Mood improvement			24/150		16	
Alertness improvement			26/150		17.3	
Improved school performance			20/150		13.3	
No reported change			40/150		26.6	

MMSE: Mini-mental state examination.

Discussion

Most of the patients in the current study had a decrease in their attack frequency per day compared to the pre-VNS period, with a resultant decrease in the number of drug combinations needed, especially among PSG patients, in whom drug frequency declined to the extent that most patients started to be controlled on one or two drugs. It is well documented that AEDs, especially when used in combination with higher doses, can have adverse effects on life quality and the patient's neuropsychology. This fact can be somehow attributed to the patient's better cognition post-VNS, which reflects itself on many patient parameters, including social behaviour, mood, alertness and improved school performance[7]. A study[12] stated that significant epilepsy has psychological consequences, with increased levels of anxiety, depression, and poor self-esteem compared to people without this condition, and that the decline of their seizure frequency could have a positive effect on these parameters.

In the current study, most patients had better overall MMSE post-VNS, with 20.7% having a median rise 1.5 points, and 6.7% having 2.5 points. Only 1.3% patients showed a 25 point median rise. This was in line with an earlier study[10]. The same effect was noted in their study which attributed the positive effect to neurochemical processes affecting norepinephrine concentrations[9]. Numerous similar studies have stated that mood improvement may be an additional benefit of using VNS for epilepsy patients[13,14]. The improved mood and cognitive abilities put VNS as one of the treatment options for chronic depression. Seizure rate decline together with several centro-encephalic nuclei controls were involved even though they have not been well clarified so far.[15,16] Erhan et al.[17] stated that VNS can reduce cortical activation induced by depression through a reduction of alpha power. Unconnected to seizure frequency decline, Sylvia et al.[18] found a positive impact of VNS on mood in general, while others stated no additional benefit to cognition with VNS implantation.[19] The current study showed that neuropsychological parameters of the affect could be ascribed to both seizure frequency decline together with drug dose and combination.

Limitation: The current study has limitations as the ability to assess the sample error was constrained by the non-probability sampling method used. As such, caution should be exercised when extrapolating the results.

Conclusion

There was evidence of improvement with respect to patient characteristics predictive of VNS-related cognition and neuropsychological responsiveness in refractory epilepsy. It may still be uncertain if the improvement could be related to drug modifications and not merely to continued VNS. However, VNS seemed to be rewarding in the improvement of neuropsychological symptoms and cognitive functions for patients with intractable epilepsy.

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