Vagal Nerve Stimulation for Refractory Epilepsy: Eight Years of Experience on 183 Iraqi Patients

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Abstract

Background: Vagus nerve stimulation has been broadly known as one of treatment lines for refractory epilepsy, especially in poor applicants for resection surgeries or in whom resection has failed. Its use for different seizure-types control is increasing. **Aims:** We aimed to assess the efficacy of Vagal nerve stimulation (VNS) therapy outcome predictive aspects utilizing subgroup analysis. **Materials and Methods:** From 2008 until 2016, 183/190 refractory epilepsy cases with specific inclusion criteria were selected. All underwent pre- and postimplantation assessment of response utilizing Engel criteria and Chalfont seizure severity scoring system for 2 years. Descriptive and statistical data analysis was accomplished for the data of age at epilepsy start and VNS insertion, seizures nature, device stimulation parameters, and peri-surgical antiepileptic medicines. **Results:** At 12 months follow-up period (29.5%), patients were assigned to a Class I and II outcome (representing very good seizure outcome) especially among patients with G. T. C seizure. 38.8% had a "worthwhile" improvement and consigned as Class III outcome mostly among P. S. G patients. The response was better at 24 months' follow-up period. Patients <10 years of age with pre surgery mean duration of epilepsy of 10 (+5) years and mean age at onset of epilepsy of 7 (+5) years showed better response. Mean seizure frequency reduction was 69.8% (+18). **Conclusions:** Stimulation parameters needed was lower for class I and II with significant reduction of required anti-epileptic drugs (AED). Our study may help to provide response predictive characteristics.

Keywords: Chalfont seizure severity scoring system, Engel criteria, refractory epilepsy, vagal nerve stimulation

Introduction

Stimulation of the vagal nerve (VNS) is an extra cranial method of neurostimulus that settled over 20 years back.[1] Ever since its authorization as a supplementary treatment for drug intractable epileptic attacks (in Europe: 1994, in United states of America: 1997), 10th cranial nerve stimulation (VNS) has been broadly recognized as the third line management option for epilepsy.[2] While several studies have reinforced VNS treatment to decrease the rate of partial onset fits in medically intractable cases, who are bad applicants for surgical resection or in whom resection has been unsuccessful.[3] It is efficacy for other seizure types is recognized.[4] The up-to-date agreement is that one third of patients with epilepsy have significant progress in their fit attacks control with at least 50% decline in seizure frequency, while other one third of cases show a worthwhile decline of seizure rate among 35 and 52% (responder rate). Over time better seizure control was apparent with longstanding follow-up studies.[5] However, it remains unclear those patient criteria predictive of response to VNS therapy besides VNS therapy carry significant added charges, hazards and adversarial effects, additionally definite limits for the use of high-field magnetic resonance imaging (MRI) (3.0 T+) in cases with inserted or partly detached medical devices may exist. Researches have yet to regularly discover relationship concerning patient criteria and VNS treatment responsiveness.[6,7]

Patients and Methods

From January 2008 (when consistent VNS insertions started in our unit) till December 2016, 183/190 epilepsy patients (99 males and 84 females) with implanted VNS system

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were selected. Seven patients were excluded as 3 had severe infection that required removal of device and 3 cases lost contact and follow up and one suicides 1 year after implantation. One epilepsy centers took part in this open study. Pre surgical assessment comprising electroencephalogram monitoring, epilepsy protocol MRI which involved added temporal coronal pictures and T2 weighted or FLAIR sequences were conducted for all patients involved in the study. In our unit, add-on VNS is just done for cases if surgical resection of the epileptogenic focus has been omitted or has been unsuccessful. Follow-up of as a minimum of 2 years following the implantation was the rule in this study. Implantation was performed by the same neurosurgeon following standard procedures. The patients were classified according to the obtained data of age at seizure onset, types of seizures (using the International Classification of Diseases), ages in years at time of and after VNS surgery, parameters of VNS, antiepileptic drugs number given before VNS insertion and at extreme follow-up. Gained consent of the Ethical Board of epilepsy center in neuroscience hospital before starting the study was a rule. In order to evaluate its usefulness accurately as VNS is a surgical action, we concluded that we must subject it to the additional strict Engel criteria which assign patients into one of four groups (Class I No disabling seizures, Class II Rare disabling seizures, Class III Worthwhile improvement, Class IV No worthwhile improvement), and Chalfont seizure severity scoring system. By means of the Engel classification, the effect of seizures on life quality will also be taken into consideration. All the included patients had complete data both at baseline and two follow-up periods at 12 and 24 months (+2 months window).

Statistical analysis

Subsequent data analysis methods were used to analyze and evaluate the study results:

1. "Descriptive data analysis" using tables "(frequencies, percentages, and cumulative percentages), mean value, standard deviation, 95% confidence interval for population mean values, two extreme values (min. and max.) respondents, graphical presentations (bar charts, stem and leaf charts)"
2. "Statistical analysis" to accept or reject statistical hypothesis using "Chi-square test, binomial test, paired matched (*t*-test)" for testing difference between mean in periods. Table 1 shows descriptive statistics for related variables with comparison significance while Table 2 is the base for patient's distribution according to Chalfont epilepsy severity score according to patient parameters (age, gender and seizure type) before and after VNS implantation and their mean values and *P* value significance. Here it is clear that gender but not age has no significance difference in seizure severity reduction outcome. Age groups of 10 years and 30–40 years were statistically higher in response than other groups and those older than 40 years of age were the least to respond. With regard to seizure type, the group presented with G. T. C and P. S. G were statistically the highest responders. Come next patients of partial complex seizure and multiple groups respectively. In our study the majority of the implanted patients fall in the age group of <10 years of age with a frequency of 45.9%. In relation to the type of epilepsy treated with VNS in our series, patients having focal seizure type with secondary generalization occupied the highest frequency (54.1%), complex partial seizures come next in frequency by (25.1%). It is also obvious that the highest percentage of the study sample were diagnosed since <5 years (43.7%) and the least involves patients with >20 years history of ongoing epilepsy (5.5%). In the subject of duration elapsed for implant, the majority of the study sample were presented in the group of <2 years with a frequency of 41.5%. Most of the patients had no significant complications to be mentioned (81.4%), while the most common post implantation side effect was transient vocal cord paralysis (hoarseness of voice) and neck muscles painful contraction with a frequency of 5.5% and chronic coughing (3.3%). 4 (2.2%) cases required revision for imperfect implant and other 4 cases developed palpitation that required cardiologist intervention. Intraoperative side effects were rare but important in form of vascular injury in 2 cases (1.1%) as shown in Table 1. Table 3 shows the relation of some patient criteria and the response status according to Engel classification. Here, it is obvious that in the very good seizure outcome group and worthwhile improvement groups (Classes I and II and III) the mean age at surgery, mean duration of epilepsy before surgery and mean age of epilepsy onset were all lower as compared to nonimprovement group (class IV). At 24 months follow-up period, it was shown that the joined class I and class II and III groups from all seizure types were set to have significantly ($P < 0.01$) lesser stimulus currents (1.1 mA; range 0.26–2.5) in comparison with joined class IV groups (1.7o mA; range 0–3.5). Seizure outcome were set in subclasses conferring to type of seizure at 12 and 24 months follow-up period according to the Engel classification. 54/183 (29.5%) cases were allocated to a class I and II outcome, these subclasses were joint into a group demonstrating very good seizure consequence with the highest response being among patients of G. T. C seizure type. Another 71 patients (38.8%) showed a worthwhile improvement in controlling fit attacks and/or life quality, and were allocated class III outcomes being most in the group of P. S. G patients. Class IV outcomes included 58/183 Patients (31.7%) who showed no benefit after VNS implantation. At 24 months follow-up period, additional cases were added to class I, II and III from all seizure type subgroups especially among patients with G. T. C and P. S. G. Preceding VNS implantation 36% of patients were on at least 2 medications and the rest were in need for >2. Post-VNS anti-epileptic necessity showed a lessening tendency with 21% started to need one drug and 70% were controlled on 2 combined AED

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Table 1: Descriptive statistics for related variables with comparison significance

Variables	Groups	Frequency	Cumulative frequency	Percentage	Cumulative percentage
Age groups in years (at surgery)	<10	84	84	45.9	45.9
	10-20	44	128	24	70
	20-30	32	160	17.5	87.4
	30-40	13	173	7.1	94.5
	>40	10	183	5.5	100
Gender	Males	99	99	54.1	54.1
	Females	84	183	45.9	100
Type of epilepsy	Focal				
	PSG	99	99	54.1	54.1
	CP	46	145	25.1	79.2
	Generalized				
	Tonicclonic (GTC)	30	175	16.4	95.6
	Multiple types				
	AS, MS, G.T.C, PCS, MR	8	183	4.4	100
Side effects	Nill	149	149	81.4	81.4
	Intraoperative vascular injury	2	151	1.1	82.5
	Revision of an imperfect implant	4	155	2.2	84.7
	Transient vocal cord paralysis and neck	10	165	5.5	90.1
	Muscles painful contraction	2	167	1.1	91.3
	Permanent hoarsness of voice coughing	6	173	3.3	94.5
	Dysphagia	2	175	1.1	95.6
	Palpitation	4	179	2.2	97.8
	Mild sleep apnoea	1	180	0.55	98.4
	Drooling	1	181	0.55	98.9
	Snoring	2	183	1.1	100
Duration of epilepsy in years	<5	80	80	43.7	43.7
	5-10	64	144	35	78.7
	10-15	29	173	15.8	94.5
	>20	10	183	5.5	100
Duration of implant in years	<2	76	76	41.5	41.5
	2-4	53	129	29	70.5
	4-6	30	159	16.4	86.9
	6-8	24	183	13.1	100
Side effects	Nill	149	149	81.4	81.4
	Defectives	34	183	18.6	100

PSG: Partial with secondary generalization (evolving to a bilateral, convulsive seizure involving tonic, clonic, or tonic-clonic components), CP: Complex partial (with impairment of consciousness or awareness), GTC: Generalized tonic-clonic, AS: Atonic seizure, MS: Myoclonic seizure, PCS: Partial with secondary generalization, MR: Medically refractory one

Discussion

In order to lower the effects of cases assortment bias, we tried to focus on comparisons between subclasses, or between seizure frequency alterations at many management pauses in our study sample. Upon utilizing the Engel classification trying to find predictive aspects for seizure outcome alongside Chalfont sore to assess seizure severity aftermath. Upon reviewing the Engel classification for seizure outcome after VNS, 29.5% of cases showed a very good (class I and II) outcome by VNS and 41% showed a worthwhile (class III) improvement. Utilizing this sort of grouping was very helpful on behalf of a lot of reasons. One of them was to identify those patients who could reach to the very near point of seizure freedom or being almost free putting in consideration factors other than seizure rate only. Going into a detailed analysis by reviewing the response frequency and severity in the sample subgroups according to seizure types, we can see that patients with G. T. C and P. S. G had the highest response among the others and if we compare the above results with those obtained using Chalfont seizure severity score on the same subgroups in the study sample, we can see that there is statistically significant reduction in the severity of seizures in all seizure type subgroups apart from those presented with multiple seizure types. The above results run with a study held by Wheeler *et al*.,[8] but does not go with another study done by Yu *et al*.[9] Vagal nerve stimulation (VNS) is a novel adjunctive therapy for intractable seizures of partial onset with or without secondary generalization.[10] Though it was not dedicated at start for G. T. C ones. The explanation behind higher rate of response among our patients with G. T. C may

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be accepted when understanding the important role played by VNS on brain structures constituting pathogenic mechanisms of generalized epilepsies such as the thalamo-cortical networks. Ongoing thalamic dysfunction in patients with IGE has been revealed by many investigation results, confirming the concept of atypical such circuitry as a cause of fit generation in this epilepsy form.[11] Besides, norepinephrine secretion rises in several brain areas with VNS. Many animal models of generalized epilepsy revealed the pathogenic role played by norepinephrine.[12] Obviously, sufficient clinical and experimental data are available now to propose that VNS might be an efficient treatment option for patients with generalized epilepsy.[13,14] Utilizing adds-on VNS treatment for reducing seizure rate in patients with multiple type seizures was better than not using it. That was especially in patients with syndromic epilepsy. This was reported previously. Our study reported VNS efficacy increment slightly over time as more cases were added to class I and II between the 2 periods of follow up. Many previous studies reported the progressive effectiveness in patients over multiple years of exposure beginning from 6 months up to 12 years post VNS insertion.[15] The ongoing accumulating action of stimulus by itself, and not merely alterations in stimulus settings could be behind better seizure frequency decline with extended VNS treatment.

Table 2: Distribution of Chalfont scale before and after device implantation regarding gender, age and seizure type

	Mean Chalfont scale before	Mean Chalfont scale after	*P*
Gender			
Male (99)	100.95	64.57	<0.0001*
Female (84)	94.92	54.50	<0.0001*
Age group (years)			
<10	109.68	72.40	<0.0001*
10-19	94.33	51.27	<0.004*
20-29	88.18	52.79	<0.005*
30-39	85.64	48.86	<0.0001*
≥40	88.50	55.25	<0.035*
Seizure type			
Focal with secondary generalization	96.45	57.54	<0.019*
Focal with loss of awareness	93.20	57.96	<0.025*
Generalized tonic clonic	105.77	62.10	<0.0001*
Multiple seizure type	119.75	93.13	<0.0345*

*Statistically significant=*P* <0.05

In addition to above our study sample showed that patients of age group <10 years of age with lower mean age at onset of seizures had better response than other age groups even though they were higher in frequency among implanted patients. This was similarly revealed in a study held by Yu *et al*., Colicchio *et al*., Alexopoulos *et al*. and Rychlicki *et al*.,[9,14,16,17] which demonstrated that the preadolescent patients (0–12 years) had better clinical outcomes than older patients, with the youngest children (<6 years) experiencing superior outcomes. The explanation behind these results might be due to higher seizure frequency in this age group or their seizure type. Our studied sample showed also that VNS responsiveness has (−) negative correlation with epilepsy duration, that is to say less seizures on VNS with lower pre surgery mean duration of epilepsy (especially of 10 [+5] years). On reviewing older studies there is a diversity of results with some which did not report a correlation,[18,19] others even reported (+) positive correlation.[6] However; some studies reported similar correlation to our one.[20]

Though ideal stimulus parameters could differ for every case, patients with class I, II and III seizure outcomes needed a considerably lower VNS output current. It is still uncertain if the ongoing better results gained with extended VNS use could the result of drug modifications and not merely to continued VNS. Besides, it has been stated that no precise AED seem to show additive anti-seizure properties with vagal nerve stimulation and that most of patients continued on a persistently

Table 3: Relation of some patient criteria with response status according to Engel classification and seizure outcome according to the Engel classification set in subclasses conferring to seizure kind at 12 and 24 months follow up

Patient features		Class I, II and III		Class IV	
Mean age at surgery		15 (±7) years		30 (±10) years	
Mean period of epilepsy before surgery		10 (±5) years		20 (±5) years	
Mean age at onset of epilepsy		7 (±5) years		20 (±4) years	
Mean seizure rate decline		69.8% (±18)		4.2% (±13)	
Stimulation mean output current		1.2 mA; range 0.25-2.5		1.75 mA; range 0-3.5	
Seizure type	***n* (%)**	**Class I + II Class**		**Class III**		**Class IV**	
		12 months, *n* (%)	**24 months, *n* (%)**	**12 months, *n* (%)**	**24 months, *n* (%)**	**12 months, *n* (%)**	**24 months, *n* (%)**
PSG	99 (54.1)	28 (28.3)	28 (28.3)	41 (41.4)	43 (43.4)	30 (30.3)	28 (28.3)
CP	46 (25)	11 (23.9)	11 (23.9)	18 (39.1)	18 (39.1)	17 (37)	17 (37)
GTC	30 (16.4)	14 (46.7)	14 (46.7)	9 (30)	11 (36.7)	7 (23.3)	5 (16.7)
Multiple seizure types	8 (4.4)	1 (12.5)	1 (12.5)	3 (37.5)	3 (37.5)	4 (50)	4 (50)

PSG: Partial with secondary generalization, CP: Complex partial, GTC: Generalized tonic-clonic

high number of AEDs.[21,22] However, our patients showed significant reduction used AED numbers after VNS and this definitely will decrease burden of side effects on our patients. No statistically significant side effects were recorded in our study sample and their frequency and nature seemed to be similar to what has been recorded previously.

Conclusion

It is obvious that this study presented VNS as an effective supplementary treatment for refractory epilepsy in our center at Neuroscience hospital and can help to provide some evidence on the patient characteristics predictive of VNS responsiveness which are elusive.

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Conflicts of interest

There are no conflicts of interest.

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