The efficacy of vagus nerve stimulation for epilepsy in Malaysia

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ABSTRACT

Introduction: The first vagus nerve stimulation (VNS) implantation in Malaysia was back in 2000, and the implantation rate increased tremendously since 2019. VNS has been used in patients who had persistent seizures despite epilepsy surgeries or were not candidates for epilepsy surgeries. We aimed to study the efficacy of VNS in Malaysia.

Materials and methods: We conducted a retrospective cross-sectional study on the VNS done in Malaysia. We included DRE patients from all age groups who underwent VNS from 1st January 2000 to 31st December 2022. We analysed the efficacy of VNS for patients with at least one year of implantation.

Results: A total of 62 implantations were performed from 2000 to 2022. Most patients (52.5%) had implantation at <18 years old, 54.0% had focal seizures, 34.4% had Lennox Gastaut Syndrome and 23.0% had developmental epileptic encephalopathy. A total of 22.6%, 42.8%, and 63.3% of patients achieve ≥50% seizure reduction at three months, six months, and one-year post-implantation, respectively. At their last follow-up, 73.5% of patients had ≥50% seizure reduction. The majority of responders were at a current intensity of ≥2mA (98.0%) and 81.6% were at a duty cycle of ≥35%. No significant difference was found between responders and non-responders by age at implantation, duration of epilepsy, and seizure type.

Conclusion: VNS is effective for patients with refractory epilepsy in Malaysia with two-third achieving more than 50% seizure reduction at one year and the last follow-up.

KEYWORDS:
Vagus nerve stimulation, epilepsy, Malaysia

INTRODUCTION

Vagus nerve stimulation (VNS) was first reported to be effective in seizure reduction in three drug-resistant epilepsy (DRE) back in 1990.[1] The current implantable device consists of a battery-powered generator with a fine electrode extending from the device and wrapped around the left cervical vagus nerve. The exact mechanism of VNS has been unknown to date. Its neuromodulating effect was presumably due to neuronal desynchronization, hippocampal plasticity, anti-inflammatory changes and alterations in neurotransmitter levels are all possible mechanisms.[2]

Since the United States Food and Drug Administration (FDA) approved its use in focal DRE in patients more than 12 years old in 1997, VNS has been used in patients who had persistent seizures despite epilepsy surgeries or were not candidates for epilepsy surgeries.[3] In Malaysia, the prevalence of lifetime epilepsy was 7.8 in 1,000 population.[4] An estimated 30% of these patients treated with ASMs were DRE.[5] These patients may benefit from this neuromodulation therapy. The first meta-analysis in 2011 showed an average of 45% seizure reduction after VNS with a higher seizure reduction rate of 51% after more than one year of therapy[6] Patients with generalised epilepsy and children could benefit significantly from VNS.[6] When compared to continued anti-seizure medications (ASMs), patients on VNS were able to achieve ≥50% and ≥75% seizure frequency reduction with the odds ratio (OR) of 2.27 and 3.56, respectively.[7] In other Asian countries, in previous studies, VNS has been shown to

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have similar efficacy in adult and paediatric populations.[8-10] Alongside the seizure frequency reduction, VNS has also been shown to improve self-accessed quality of life (QoL), depression and suicidality over time.[9,11]

The first VNS implantation in Malaysia took place in 2000 but it remained underutilised until 2019 when the implantation rate significantly increased. We aimed to study the efficacy of VNS in Malaysia over these 22 years, to guide the future VNS referral, selection and management in our country.

MATERIALS AND METHODS

We conducted a retrospective cross-sectional study on the VNS done in Malaysia, since 2000, the year the first vagus nerve stimulation generator was implanted. This was a national multicentre collaborative study, on the initiation of the Malaysian Epilepsy Council. This study was approved by the Malaysia National Medical Research Registry (NMRR) (NMRR-21-1379-57891 (IIR)).

Data collection

We included DRE patients from all age groups who underwent VNS from 1st January 2000 to 31st December 2022, Data was collected by the site investigators, who are the treating neurologists or neurosurgeons, using a standard data collection form. The data collected included (1) basic demographic: age and sex, (2) clinical history of epilepsy: age of seizure onset, aetiology, seizure type, prior epilepsy surgery, (3) VNS implantation details: model, implantation date, age at implantation, duration from onset to implantation, seizure control after implantation at three and six months, and one year, mean seizure reduction and their VNS parameter settings at last clinical follow up. Data collection was performed from 1st September 2022 to 31st December 2022. Subjects' names were anonymised in data collection.

Statistical analysis

We defined responders as patients who experienced ≥ 50% seizure frequency reduction post-implantation. The statistical analysis was performed using the Statistical Package for Social Sciences version 28 (SPSS version 28). Pearson's Chi-Square tests were used to compare the clinical factors between patients who achieved ≥ 50% and < 50% seizure reduction. A p-value of < 0.05 was considered statistically significant.

RESULTS

VNS implantation trend in Malaysia

A total of 62 DRE patients underwent VNS implantation in our country over 22 years, from 2000 to 2022. The number of implantations increased tremendously since 2019 from 1-2 cases per year to 10 cases in 2019 and peaked at 20 cases per year in 2020. Despite the COVID pandemic in 2020, there were 17 and 6 implantations in 2021 and 2022, respectively. (Figure 1) The implanted generators were PulseTM (Model 102), Demi-PulseTM (Model 103) and AspireHCTM (Model 105) from 2000 to 2018. Aspire SRTM (Model 106) has been used since the second half of 2018.

Basic demographics and clinical characteristics

The basic demographic and clinic characteristics of the patients who underwent VNS implantation were summarised in Table I. A total of 52.5% and 49.1% of patients had implantation before and after 18 years old, respectively. Most of the patients were diagnosed with epilepsy for up to 15 years before implantation. A total of 90.2% of patients had implantation for at least one year. Of the seven patients who had implantation for more than 10 years, four had generator replacement, two did not and one was lost to follow-up.

A total of 54.0% of patients had focal seizure type while 45.9% had generalised seizure type. The commonest aetiology was Lennox Gastaut Syndrome (LGS) (38.2%). Eighteen patients (29.5%) were treated with a ketogenic diet before implantation and five (8.1%) had previous epilepsy surgeries. (Table I)

Overall VNS efficacy analysis

In the efficacy analysis, we included cases with at least one-year post-implantation at the time of data collection (n=61) and excluded cases who did not undergo generator replacement when the previous batteries were depleted (n=2), patients who were lost to follow-up (n=1) and those with missing data (n=4). The seizure responses at three, six months and one year are shown in Table II. The number of cases with ≥ 50% seizure reduction gradually increased from three months (22.4%) to six months (42.8%) and at one year (63.3%). A total of 73.5% of patients had ≥ 50% seizure reduction, 28.6% of patients had ≥ 75% seizure reduction and 6.1% reported no change in seizure frequency at their last follow-up. Two patients were seizure-free at their last follow-up. (Figure 2)

VNS stimulation parameters and efficacy analysis

Among those with ≥ 50% seizure reduction at one year, almost all (48/49, 98.0%) patients were at an intensity output of ≥2.0mA (2.0-3.25mA). (Table II). A total of 74.1% of responders at 1 year were at the intensity output of 2 to 2.5mA while 22.6% were at the intensity of 2.75 to 3.25mA. Similar findings were seen among responders at their last follow-up. Most patients (75.0%) were at the intensity output of 2 to 2.5mA. Another 22.2% of responders were at an intensity of 2.75 to 3.25mA. Only one responder remained at an intensity output of <2mA due to increased seizure frequency on an intensity higher than 1.75mA. A total of 92.3% of the non-responders at the last follow-up were at an intensity of 2.0 to 2.5mA. Majority (40/49, 81.6%) were at DC of 35% (Table II).

Responders versus non-responders to VNS

We did not find any statistically significant association between sex, age at the time of implantation, seizure type, duration of epilepsy and VNS parameters using rapid cycling and mean seizure reduction at the last follow-up. (Table III)

DISCUSSION

VNS implantation trend in Malaysia

Our study showed an upward trend in the number of implantations over these 22 years, with an obvious increase in cases since 2019. This positive trend was due to several factors, such as better knowledge among the neurologists for

Table I: Basic demographic, clinical characteristics, and aetiologies of epilepsies of implanted cases (N=61)[a]

Demographic profile	Number of cases (%)
Sex	
Male	37 (60.7)
Female	24 (39.3)
Age at implantation (years)	
Age < 18	34 (52.5)
Age ≥ 18	27 (49.1)
Duration of epilepsy at the time of implantation (years)	
< 5	13 (21.3)
5.1-10.0	14 (23.0)
10.1-15.0	14 (23.0)
15.1- 20.0	11 (18.0)
>20.0	9 (14.8)
Duration on VNS (years)	
Less than 1 year	6 (9.7)
≥ 1 year[b]	55 (90.2)
Median duration on VNS	2.4 (IQR 1.5, 3.5)
Seizure type	
Focal	33 (54.0)
Generalised	28 (45.9)
Aetiology	
Developmental epileptic encephalopathy	
Lennox Gastaut Syndrome (LGS)	19 (31.7)
Other DEE[c]	15 (25.0)
Focal epilepsy	
Structural abnormalitiesd	11 (18.3)
Temporal lobe epilepsy (Unilateral and bilateral)	6 (10.0)
Tuberous sclerosis	1 (1.7)
Malformation of cortical development	3 (5.0)
Post encephalitis	5 (8.3)
Previous treatment	
Ketogenic diet before implantation	18 (29.5)
Previous surgery[e]	5 (8.1)

[a]One missing data, [b]Seven had implantation for more than 10 years, [c]Infantile epileptic encephalopathy, Doose syndrome, Dravet syndrome, infantile spasms, [d]Structural abnormalities: schizencephaly, colpocephaly, gliosis at the eloquent cortex, previous abscess at frontal lobe, [e]One each had an anterior temporal lobectomy and corpus callosotomy, three with missing data

Table II: VNS parameters in cases with implantation duration of more than 1 year (N=49)

	Seizure reduction at 1 year (N=49), n (%)		Proportion of responders (N=49), n (%)	
	≥ 50% (n=31)	< 50% (n=18)	Responders (n=36)	Non-responders (n=13)
Intensity output (mA)				
< 2	1 (3.2)	1 (5.6)	1 (2.8)	0
2.0-2.5	23 (74.1)	15 (83.3)	27 (75.0)	12 (92.3)
2.75-3.25	7 (22.6)	2 (11.1)	8 (22.2)	1 (7.6)
Duty cycle (%)				
16	4 (12.9)	2 (11.1)	3 (8.3)	3 (23.1)
25	2 (6.5)	1 (5.6)	2 (5.6)	1 (7.7)
35	20 (64.5)	12 (66.7)	24 (66.7)	8 (61.5)
≥ 36	5 (16.1)	3 (16.7)	7(19.4)	1 (7.7)

Table III: Comparison of factors associated with seizure reduction at last follow-up (N=49)

	The proportion of responders (N=49), n (%)		p-value
	Responders (n=36)	Non-responders (n=13)	
Sex			
Male	21 (58.3)	8 (61.5)	0.841
Age at time of implantation (years)			
< 18	13 (36.1)	8 (61.5)	0.112
≥ 18	23 (63.9)	5 (38.5)	
Seizure type			
Focal	18 (50.0)	7 (53.8)	0.812
Generalised	18 (50.0)	6 (46.2)	
Duration of epilepsy pre-implantation (years)			
< 5	6 (16.7)	6 (46.2)	0.172
5.1-10.0	7 (19.4)	1 (7.7)	
10.1-15.0	10 (27.8)	2 (15.4)	
15.1- 20.0	8 (22.2)	1 (7.7)	
>20	5 (13.9)	3 (23.1)	
VNS parameters			
Rapid cycling[a]	30 (83.3)	10 (76.9)	0.683

[a] Rapid cycling with off time ≤1.1 minutes and duty cycle < 50%.

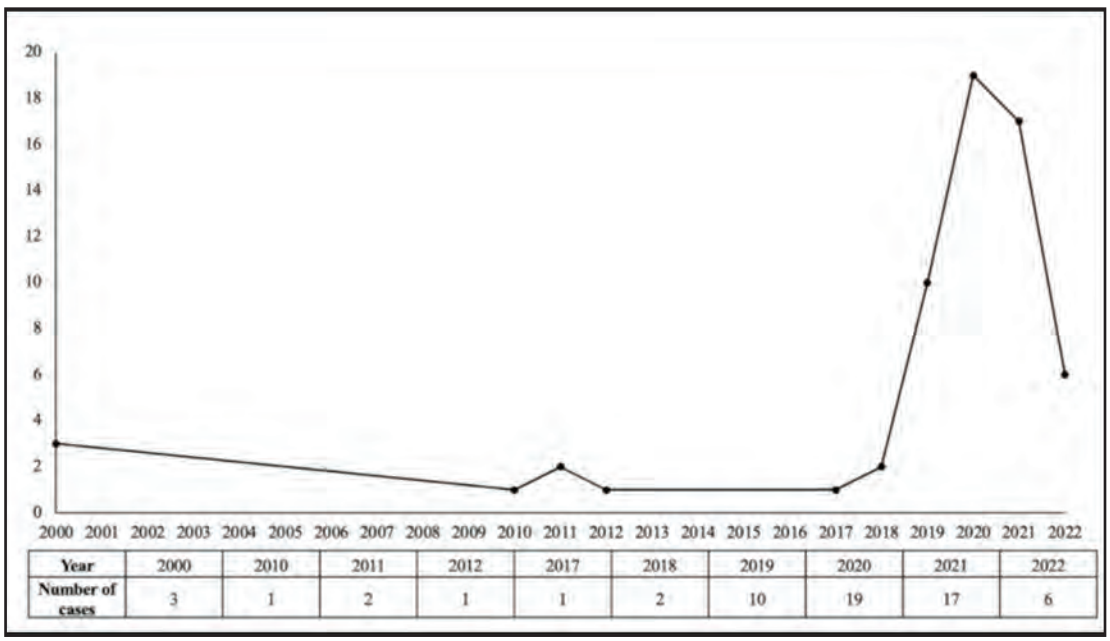

Fig. 1: Number of cases of vagus nerve stimulation implantation over 22 years in Malaysia (N=62)

VNS referral for cases not suitable for resection surgery and a greater number of neurosurgeons who were willing to perform the implantations. In addition, the VNS generator price reduction from USD 22,800 in 2018 to USD 16, 320 in 2019, government subsidization via the National Medical Aid Fund (Tabung Bantuan Perubatan, TBP), public donation for the VNS generators and an increasing number of patients with private insurance were also contributing factors to our increased implantations over the years.

Overall VNS efficacy

The overall VNS efficacy in our cohort was comparable with the efficacy data. VNS efficacy gradually improved over time – 22.4% at 3 months, 42.8% at 6 months and 63.3% at one-year follow-up.[6] Our VNS efficacy at the last follow-up was also similar to the previous meta-analysis in which there were more than half of the patients achieved > 50% seizure reduction.[6] The two paediatric patients who were seizure-free after VNS implantation were Dravet syndrome-like carrying PCDH-19 variant and infantile spasms. VNS were expected to have satisfactory responses in children with DRE of monogenic aetiology especially Dravet syndrome, and tuberous sclerosis complex.[12]

VNS stimulation parameters

Some centres use rapid titration protocol to ensure target intensity output of at least 1.75mA is reached within 3 months post-implantation. Other parameters were adjusted

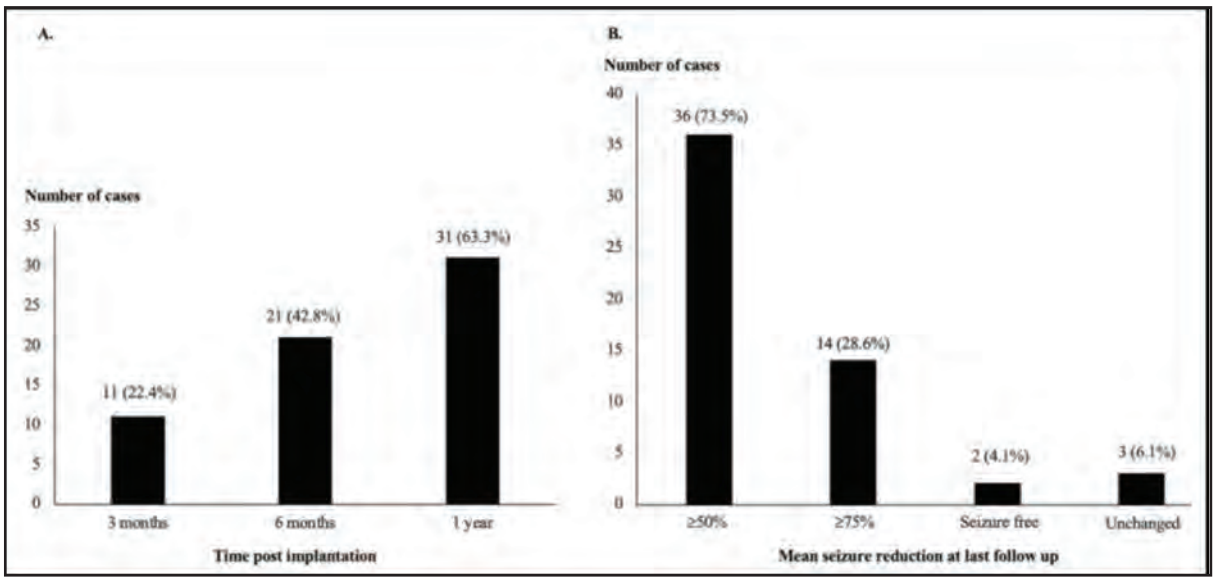

Fig. 2: (A) Time-dependent responders (N=49) and (B) mean seizure reduction rate at last follow-up among patients included for efficacy analysis (N= 49)

to allow better tolerability to this rapid titration (signal frequency 20Hz, pulse width of 250 microseconds) until the target intensity was reached. Rapid titration has been proven to yield faster onset of clinical benefit especially in the paediatric population compared to the conservative titration protocol.[13] This would explain why most of our responders were at the optimal intensity output of ≥2mA.

Challenges of VNS in Malaysia

One of the challenges in the utilization of VNS was the cost of the generator. Although the price reduction has resulted in an increased implantation rate, many patients still require partial subsidisation from the national funds or reimbursement from private insurance to cover the cost. Other patient-related challenges were adherence to the frequent follow-ups during rapid titration in the first three months post-implantation. Since titration could only be done by neurologists in tertiary centres where the implantation was done, the weekly to 2-weekly clinic visits could pose logistic difficulties for some patients, therefore resulting in a suboptimal response from VNS.

Delay in referrals to VNS implantation is another challenge leading to the low implantation rate before 2019. Most patients had VNS surgery done 5 to 10 years after onset of epilepsy. This has also been highlighted in the recent CORE-VNS study, where delays for VNS surgery are common, after multiple trials of ASMs and even failure of epilepsy surgeries, with a median time from diagnosis to first implantation of 10.33 years.[14]

LIMITATIONS

Due to the small sample size, we could not detect a significant difference between responders and non-responders at one year and their last follow-ups to determine the outcome predictors. Future longitudinal studies would be useful to report other findings such as adverse events from implantation and during VNS parameters adjustment, quality of life and long-term efficacy from VNS.

CONCLUSION

Most patients who underwent VNS Malaysia were able to achieve more than 50% seizure reduction at one year and the last follow-up.

CONFLICT OF INTEREST DISCLOSURE

All authors have no conflict of interest to disclose.

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