Original Article

Vagus Nerve Stimulation for Pediatric and Adult Patients with Pharmaco-resistant Epilepsy

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Abstract

Background: Over past two decades, vagus nerve stimulation (VNS) has been widely used and reported to alleviate seizure frequency worldwide, however, so far, only hundreds of patients with pharmaco-resistant epilepsy (PRE) have been treated with VNS in mainland China. The study aimed to evaluate the effectiveness of VNS for Chinese patients with PRE and compare its relationship with age cohort and gender.
Methods: We retrospectively assessed the clinical outcome of 94 patients with PRE, who were treated with VNS at Beijing Fengtai Hospital and Beijing Tiantan Hospital between November 2008 and April 2014 from our database of 106 consecutive patients. The clinical data analysis was retrospectively examined.
Results: Seizure frequency significantly decreased with VNS therapy after intermittent stimulation of the vagus nerve. At last follow-up, we found McHugh classifications of Class I in 33 patients (35.1%), Class II in 27 patients (28.7%), Class III in 20 patients (21.3%), Class IV in 3 patients (3.2%), and Class V in 11 patients (11.7%). Notably, 8 (8.5%) patients were seizure-free while ≥50% seizure frequency reduction occurred in as many as 60 patients (63.8%). Furthermore, with regard to the modified Engel classification, 12 patients (12.8%) were classified as Class I, 11 patients (11.7%) were classified as Class II, 37 patients (39.4%) were classified as Class III, 34 patients (36.2%) were classified as Class IV. We also found that the factors of gender or age are not associated with clinical outcome.
Conclusions: This comparative study confirmed that VNS is a safe, well-tolerated, and effective treatment for Chinese PRE patients. VNS reduced the seizure frequency regardless of age or gender of studied patients.

Key words: Epilepsy Surgery; Pharmaco-resistant Epilepsy; Vagus Nerve Stimulation

Introduction

Epilepsy is a common and occasionally serious disease that affects both children and adults world-wide.[1] According to World Health Organization reports, over 50 million patients world-wide suffer from epilepsy, 85% of whom are in developing countries. About 70–80% of patients with epilepsy can be successfully treated with single or combined antiepileptic drugs (AEDs) though 20–30% of patients suffer from pharmaco-resistant epilepsy (PRE).[2]

Vagus nerve stimulation (VNS) is a new nonpharmacological treatment for PRE. Traditional surgery was designed to remove the epileptogenic zone to cure the disease or reduce the frequency of seizures. However, in quite a few cases with PRE, the epileptogenic zones are multifocal or difficult to localize despite the use of both invasive and noninvasive monitoring methods. Because the mechanism of VNS therapy is different from pharmacotherapy and traditional surgery, and it can be

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.166023

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Received: 10-11-2014 **Edited by:** De Wang and Peng Lyu
How to cite this article: Meng FG, Jia FM, Ren XH, Ge Y, Wang KL, Ma YS, Ge M, Zhang K, Hu WH, Zhang X, Hu W, Zhang JG. Vagus Nerve Stimulation for Pediatric and Adult Patients with Pharmaco-resistant Epilepsy. Chin Med J 2015;128:2599-604.

used to reduce seizure burden by stimulating the vagus nerve instead of localizing the epileptogenic focus. Moreover, it has been found that VNS improves attention, cognition, behavior, mood, and quality of life (QOL) besides of reducing seizure burden.[3-7] Therefore, VNS therapy provides an alternative method for patients with PRE, especially for those with multifocal or unlocalized epileptogenic foci.

Although VNS has been proven to be effective in multiple centers over past two decades,[8-15] only hundreds of patients in mainland China have been surgically treated with VNS up to date, moreover, the clinical outcomes and optimal modulation parameters are still unknown. Therefore, in this study, 106 consecutive patients with VNS implantation at Beijing Fengtai Hospital and Beijing Tiantan Hospital from November 2008 to April 2014 were reviewed and evaluated for its efficacy and safety in Chinese patients with PRE.

Methods

Study population

Totally, we identified 106 refractory epilepsy patients who undergone VNS operations at Beijing Tiantan Hospital and Beijing Fengtai Hospital between November 2008 and April 2014. The clinical characteristic of all studied patients was prospectively entered into our epilepsy VNS database. Specifically, our database included general patient condition, demographic information (age, sex), physical and neurological exams, mean weekly seizure frequency, treatment history, antiepileptic medication use, seizure duration, video-electroencephalography (V-EEG) monitoring, and magnetic resonance images (MRI). Each patient underwent a standard preoperative evaluation by our epilepsy team. Patients were followed up for at least 6 months after VNS implantation. Among the 106 patients, 11 cases were lost and 1 died. Eventually, 94 patients were followed up. Among these studied patients, 65 are males and 29 are females with age ranging from 2 to 50 years (mean ± standard deviation [SD] =16.0 ± 10.2). The medical history range was 2–18 years.

The seizure types manifested as partial seizures and generalized tonic-clonic seizures. All patients were treated with at least two AEDs prior to VNS. V-EEG showed multi-site abnormal discharges from one or both hemispheres. MRI scanning was performed to exclude brain tumor. MRI revealed that some patients had normal brain structure, while the other had brain atrophy, ventricle expansion, temporal lobe narrowing, or other structural abnormalities.

Inclusion and exclusion criteria for the VNS candidates were listed previously.[10,11] Briefly, the inclusion criteria are AEDs failure, AEDs toxicity, intolerable AEDs side effects, or multifocal or diffuse seizure onset not amenable to surgical resection. The exclusion criteria are progressive neurological diseases, severe mental disorders, arrhythmia, peptic ulcer, brain tumor, or poor health condition.

Surgery and stimulation

The surgical techniques for implantation of the VNS device were detailed previously in the literature.[10,11,16] Specifically, the VNS Therapy System (Cyberonics, Houston, TX, USA) was used in this study. The *in vitro* control device included a parameter-controlled instrument and magnet. The implantation operation was performed under general anesthesia.

The stimulator was switched on at approximately 2–3 weeks postoperatively. Long-term follow-up and adjustments of VNS parameters were conducted by epileptologist team.

Outcome

The evaluation of VNS efficacy was performed based on the VNS-specific outcome scale proposed by McHugh *et al*. in 2007 and modified Engel description.[10,17] In McHugh classification, patients are divided into five classes according to the percentage of seizure reduction (Classes I-V), and the first three classes are further subdivided into two distinct sub-groups in relation to the improvement in ictal or postictal activity ([A] Improved ictal or postictal severity, and [B] No improvement in ictal or postictal severity): Class I means an 80–100% reduction, Class II means a 50–79% reduction, Class III means a <50% reduction in seizure frequency, Class IV means benefit only when magnet is used, and Class V means no improvement. In modified Engel description, Class I means seizure-free or rare, nondisabling simple partial seizures, Class II means >90% reduction in seizure frequency or rare complex partial seizures, Class III means 50–90% reduction in seizure frequency, Class IV means <50% reduction in seizure frequency.

The patients were followed up either at our outpatient clinic or by telephone interview. The information regarding seizure frequency, severity, and types were collected.

Statistical analysis

Data are expressed as means ± standard deviation (SD). All statistical analyses were performed using SPSS version 21.0 (SPSS, Chicago, IL, USA). A bilateral $P < 0.05$ was considered statistically significant.

Results

Study population

Table 1 presents an overview of the clinical and demographic characteristics of the 94 patients.

Vagus nerve stimulation parameter modulation

The parameters were modulated according to efficacy and patient tolerance. The initial standard was: Stimulation for 30 s followed by a stimulation-free period of 5 min, a frequency of 20–30 Hz, a pulse width of 250–500 μs, and an output current of 0.25 mA. The output current was increased every 2–3 weeks in 0.25 mA increments to a maximum of efficacy with minimal side effects. The output current parameter of the magnet was one level higher than the cycle stimulation, but the frequency, pulse width, and the time for ON and OFF were not changed.

Seizure control outcomes and follow-up

The mean duration of follow-up was 42.3 months (range: 6–65 months). All patients were alive at last follow-up except 1 patient died. Univariate analysis did not identify any demographic or clinical variables that predicted a better response to VNS.

With regard to the McHugh classification [Table 2], 33 (35.1%) patients were classified as Class I, 27 (28.7%) as Class II, 20 (21.3%) as Class III, 3 (3.2%) as Class IV, and 11 (11.7%) as Class V [Table 2]. It should be noted that 8 (8.5%) patients were seizure-free while as many as 60 patients (63.8%) had ≥50% seizure frequency reduction.

In terms of the modified Engel classification [Table 2], 12 patients (12.8%) were classified as Class I, 11 patients (11.7%) were classified as Class II, 37 patients (39.4%) were classified as Class III, 34 patients (36.2%) were classified as Class IV. Moreover, the difference in seizure reduction between patients with ≥12 (12–50) years of age and patients with <12 (2–11) years of age, or patients with ≥18 (18–50) years of age and patients with <18 (2–17) years of age was not significant, which indicates that VNS therapy resulted in a significant reduction in seizure frequency, which is not associated with age or gender of these patients [Table 3].

Complications

No infection, bleeding, or permanent neurological deficits were reported during the peri-operative period. Nineteen (17.9%) patients complained of transient hoarseness, cough, or pharynx pain when the generator was switched on, and most of these side effects resolved over time or modulation of the stimulation parameters. One patient was re-operated due to a poor connection between the wire and generator. Two stimulators were removed because of the poor effectiveness. There were no serious complications with the permanent neurological deficit.

Table 1: Clinical data of patients with pharmaco-resistant epilepsy

Variable	*n* (%)
Sex	
Male	65 (69.1)
Female	29 (30.9)
Age at VNS implantation (years)	
Median	16.0
Range	2–50
Age (years)	
2–11	28 (29.8)
12–50	66 (70.2)
2–17	55 (58.5)
18–50	39 (41.5)

VNS: Vagus nerve stimulation.

Discussion

Efficacy of vagus nerve stimulation

Totally, 94 patients were followed after VNS implantation with a mean follow-up duration of 32.3 months (range: 6–65 months). In the current study, we found the tendency of increasing effective rate with the extension of stimulation [Table 4]. A ≥50% improvement can be found in 10 (47.6%) out of the 21 patients in the first year of VNS, which increased to 24 (61.5%) out of the 39 patients in the first 2.5 years, to 38 (67.9%) out of the 56 patients at the 3.5 years, to 60 (63.8%) out of the 94 patients at the end of the follow-up. The data confirm the idea that the tendency of increasing effective rate with the extended duration of stimulation. It can be assumed that the factor associated with seizure reduction was the duration of follow-up.

The seizure frequency was significantly reduced from baseline after the implantation of VNS. In one VNS study[10] that had a mean follow-up time of 4.94 years for 436 treatment-resistant epilepsy patients, mean seizure frequency decreased significantly following implantation (mean reduction = 55.8%). Seizure control of ≥90% was achieved in 90 patients (22.5%) with ≥75% seizure control in 162 patients (40.5%), ≥50% in 255 patients (63.75%), and <50% in 145 patients (36.25%). Permanent injury to the vagus nerve occurred in 2.8% of patients. The increase in VNS efficacy over time was reported by others centers.[11,18] A meta-analysis of VNS efficacy in epilepsy, which included 74 clinical studies with a total of 3321 patients suffering from intractable epilepsy, found that seizure frequency was reduced by an average of 45%, with a 36% reduction in seizures at 3–12 months after surgery and a 51% reduction after >1 year of therapy.[19]

Although VNS is an effective and relatively safe adjunctive therapy in patients with medically refractory epilepsy not amenable to resection, it is important to recognize that complete seizure freedom is rarely achieved by VNS. Moreover, as many as a quarter of patients do not get any benefit from this therapy.[19] In our group, only 8 (8.5%) patients became seizure-free.

Table 2: Seizure control outcomes by modified Engel and McHugh outcome classification following VNS therapy in the 70 patients with complete follow-up

Class	McHugh description	*n* (%)	Modified Engel description	*n* (%)
I	80–100% reduction in seizure frequency	33 (35.1)	Seizure-free, rare, nondisabling simple partial seizures	12 (12.8)
II	50–79% reduction in seizure frequency	27 (28.7)	>90% reduction in seizure frequency, rare complex partial seizures	11 (11.7)
III	<50% reduction in seizure frequency	20 (21.3)	50–90% reduction in seizure frequency	37 (39.4)
IV	Magnet benefit only	3 (3.2)	<50% reduction in seizure frequency	34 (36.2)
V	No improvement	11 (11.7)	–	–

VNS: Vagus nerve stimulation.

Relationship of the efficacy between age and sex

Different age-associated results have been reported by different centers. It has been reported that the response to VNS was even more favorable in younger groups (<12 years of age at implantation).[20] While a separated analysis of patients younger than 16 years of age showed lower efficacy rates of VNS in comparison to the whole group in another study.[12] De Herdt *et al*. reported that mean seizure frequency reduction was seen in 41.1% of the children (16 years or younger, mean: 10 years, range: 4–16 years) and 52.7% in the adult group (>16 years old, mean: 34 years, range: 17–59 years), respectively. A Belgian multicenter study revealed that seizure frequency decrease of 50% or more was seen in 43.0%, compared to 62.4% in the adult group.[21] Colicchio *et al*. found that the age of implantation <18 years ($P = 0.0242$, log-rank test) was associated with better response to VNS.[22] Englot *et al*. also found that children (age <18 years) experienced a significantly higher rate of response ($P < 0.05$) than adults after 1 year of therapy.[23] However, a fair amount of reports showed that the age of the patients is not associated with VNS benefit[1,10,16,24,25] [Table 5].

Although VNS is only approved by the Food and Drug Administration for the treatment of refractory partial epilepsy in patients older than 12 years in 1997, currently, it has been used in patients ≤12 years old. Thompson *et al*.[16] studied 146 patients and found that VNS can reduce both seizure frequency and AEDs use in the majority of pediatric patients regardless of sex, age, or seizure type. The patients were followed up for a mean of 41 months after VNS implantation. Furthermore, there were no significant differences in seizure frequency reduction, seizure duration, postictal period, medication use, overall clinical improvement, or improvement in QOL between different age groups (≥ or <12 years old) or epilepsy types. Elliott *et al*. also found that children younger than 12 years had a similar response to that of older children with similar complications.[1] This result has been confirmed by other research centers.[24,25] Our results showed 71.4% patients of younger than 12 (2–11) got a seizure reduction ≥50% (Class I and II), as compared the rate of 60.6% in patients ≥12 (12–50). In addition, we also found 61.8% patients who are younger than 18 (2–17) and 66.7% patients with age ≥18 (18–50) years got a ≥50% seizure reduction. However, the differences were not statistically significant. Furthermore, there was no significant difference between males and females [Table 3].

Parameter modification

The correct modification of the stimulation parameters is important for the efficacy of VNS. In this group, stimulation parameters were modified several times according to efficacy and tolerance. The order of parameter adjustment was output current, pulse width, frequency, stimulation time, and spacing interval. The output current was adjusted according to patient tolerance without adverse effects, beginning at 0.25 mA and increasing gradually to a maximum of 3.5 mA. The general adjustment parameters were a frequency of 20–30 Hz, a pulse width of 250–500 μs, and stimulation for 30 s followed by a stimulation-free period of 5 min. Output current is the most important factor in the initial period of parameter modification. The initial output current should be 0.25 mA, which should be then increased by 0.25 mA every 2–3 weeks. Epilepsy could be controlled gradually when the current was larger than 1.0 mA. In general, if the output current is smaller than 1.0 mA, VNS cannot achieve curative effects despite prolonged stimulation time.

In this study, 94 consecutive patients with VNS implantation between November 2008 and April 2014 were studied, and

Table 3: Clinical parameters associated with seizure control outcome

Parameter	Seizure control outcome, *n* (%)		χ^2	*P*
	I-II	III-V		
Age (years)				
2–11	20 (71.4)	8 (28.6)	0.997	0.357
12–50	40 (60.6)	26 (39.4)		
2–17	34 (61.8)	21 (38.2)	0.232	0.669
18–50	26 (66.7)	13 (33.3)		
Sex				
Male	43 (66.2)	22 (33.8)	0.493	0.495
Female	17 (58.6)	12 (41.4)		

Table 4: The effect of VNS with the duration of stimulation (McHugh classification)

Duration	Seizure control outcome (*n*)				Total (*n*)	≥50% improvement (%)
	I	II	III	IV+V		
1.0 year	3	7	9	2	21	47.6
2.5 years	13	11	11	4	39	61.5
3.5 years	22	16	13	5	56	67.9
At the end of follow-up	33	27	20	14	94	63.8

VNS: Vagus nerve stimulation.

Table 5: Different reports in age of the patients associated with seizure outcome

Authors	Number of patients	Age (*n*)		*P*	Difference of outcome
		<12	≥12		
Alexopoulos *et al.*[20]	46	21	25*	†	<12 is better
Elliott *et al.*[1]	141	86	55*	†	N/A
Elliott *et al.*[10]	436	86	350	0.66	N/A
Thompson *et al.*[16]	146	108	38	0.746	N/A
Arhan *et al.*[24]	24	15	9	0.178	N/A
Coykendall *et al.*[25]	28	21	7	‡	N/A
Meng *et al.*	94	28	66	0.357	N/A
Kuba *et al.*[12]	90	15 (<16)	75 (≥16)	†	≥16 is better
De Herdt *et al.*[21]	138	21 (≤16)	117 (>16)	†	>16 is better
Colicchio *et al.*[22]	53	8 (<18)	45 (≥18)	0.024	<18 is better
Meng *et al.*	94	65 (<18)	29 (≥18)	0.495	N/A

*The VNS device was implanted between the ages of 12 and 18 years. †*P* value is not listed in paper; ‡*P*=0.20, 0.64 and 0.62, respectively, at 3 months, 1-year, and 2 years. N/A: No significant difference can be found between the two groups; VNS: Vagus nerve stimulation.

the efficacy and safety of the VNS therapy were analyzed. After the stimulation of the vagus nerve for 6–65 months, the McHugh classifications and modified Engel classification were reviewed. We found that neither age nor sex of patients was correlated with the VNS efficacy. Overall, patients were tolerated the procedures, and there were no serious complications with the permanent neurological deficit. The VNS efficacy was correlated with parameter modulation and duration of stimulation.

In summary, we report that VNS therapy can reduce the seizure frequency regardless of age cohort or sex. VNS is also safe, well-tolerated, and effective treatment for PRE in Chinese patients though some patients (11.7%) do not receive any benefit from this therapy. In this group, 8 patients (8.5%) were seizure-free, and 50% or greater reduction in the seizure was achieved in 63.8% (60/94) of patients. The efficacy of VNS therapy in Chinese patient is similar to the other reports from other countries.

Study limitations, as China is a developing country, many expensive medical consumables are not covered by medical insurance. Apparently, VNS is a new brain stimulation technique and costly, and has not been covered by medical insurance in China. Usually, it costs 30,000 US $ per patient. Patient and family member have to pay it from their own pocket. Compared with international, multi-center, large studies with long-term follow-up, the number of patients studied here is not relatively large, and the time of follow-up (the longest follow-up is no more than 6 years at end of study) is not very long. However, this study is the maximum quantity of Chinese patients in VNS study with the longest follow-up in mainland China.

The male to female ratio of our studied patients was 65/29. This may be due to the higher socioeconomic status of males in mainland China. It is really difficult to follow-up the patients in China because the patients in this study come from all over the country, 11 cases were not able to be followed up for long-term.

Financial support and sponsorship

This research was supported partly by Beijing Health System Advanced Health Technology Talent Cultivation Plan (No. 2011-3-032), the Basic-clinical collaborative research projects of Beijing Capital Medical University (No. 1140170045-14JL52), Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (No. ZY201305) and China National Clinical Research Center for Neurological Diseases (No. NCRC-ND).

Conflicts of interest

There are no conflicts of interest.

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