

# Long-Term Outcome of Vagus Nerve Stimulation for Refractory Epilepsy: A Longitudinal 4 year Follow-up Study in Korea

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## Original Article

Journal of Epilepsy Research  
pISSN 2233-6249 / eISSN 2233-6257

Received February 27, 2013  
Accepted May 22, 2013

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**Background and Purpose:** We evaluated the long-term outcome of patients with refractory epilepsy who were treated with vagus nerve stimulation (VNS).

**Methods:** This investigation is designed as an uncontrolled, open-label, retrospective and long-term study. From June 1999 to October 2009, 20 patients were suitable for inclusion criteria: 4-year follow-up and documented seizure frequency before and after implantation. Seizure frequency was collected by clinical recording and interview. Primary outcome measures were the reduction in mean seizure frequency and responder rate (seizure frequency reduction of >50%).

**Results:** In 20 patients (M:F=16:4), mean age at the time of implantation was 22.3 years (range 8-44) and mean disease duration was 13.9 years (range 1-37). Mean maximum stimulation output current was 1.90 mA (range 0.25-3.5). Overall mean seizure frequency reduction rate was 61.8% at 4 year follow-up comparison with baseline ( $p<0.001$ ). Proportion of responder (> 50% seizure frequency reduction) of yearly follow-up were 40 % at 1 yr, 50% at 2 yrs, 45% at 3 yrs, and 60% at 4 yrs. There was no difference of stimulation parameter between the responders and non-responders.

**Conclusions:** Long-term outcome of VNS suggests that VNS is an effective treatment option that can be alternative to surgery in patients with refractory epilepsy. (2013;3:16-20)

**Key words:** Vagus nerve stimulation, Refractory epilepsy, Epilepsy, Outcome

## Introduction

Antiepileptic drugs (AED) can be effective for seizure control in patients with epilepsy, but still about 30 % of them are suffering from medically refractory epilepsy.<sup>1</sup> If AEDs fail to control seizures, alternative treatment options, such as epilepsy surgery or ketogenic diet, can be considered. However, still some number of patients is not good candidates for surgical treatment: for these patients, vagus nerve stimulation (VNS) or deep brain stimulation (DBS) can be recommended.<sup>2,3</sup> VNS was firstly tested on human subjects by Penry and Dean in 1988 and underwent E01-E05 large scale clinical trials in 1996.<sup>4</sup> VNS is now considered as effective and safe therapy for patients with drug-resistant epilepsy, and over 60,000 patients worldwide have underwent implantation surgery until 2011. In

Korea, VNS therapy was approved in July 1999 and its fee began to be covered by insurance for those who were not candidates for focal resective surgery in 2005. As a result, 389 domestic patients are using VNS to control their seizures until 2012.

There are several studies in the western countries that evaluated clinical efficacy of VNS. Although some VNS studies have been performed in Korea after Korean VNS research group reported 18-month follow-up study of 14 patients in 2001, there is no long-term retrospective study on the same patients.<sup>5,6</sup> Schachter claimed that VNS should last more than two years to objectively evaluate clinical efficacy of the therapy.<sup>7</sup> In this regard, we present a long-term (4 years) retrospective study on patients with VNS in order to provide information on the utility of VNS therapy for patients who are not candidates for epilepsy surgery.

## Methods

### Patients

This is a retrospective study through medical record and interview on the epilepsy patients who have been implanted vagus nerve stimulator for more than 4 years. From July of 1999 to May of 2007, 22 patients underwent VNS implantation surgery in Samsung Medical Center and 20 of them were available for four-year follow-up. Two patients failed to collect seizure data. One patient was lost to follow-up, the other patient discontinued VNS treatment within 1 year after VNS implantation because of lack of efficacy and had anterior temporal lobectomy three years later after that. All of these patients went through careful presurgical evaluation such as simultaneous video-EEG monitoring and magnetic resonance imaging (MRI). All of them were drug-resistant, showing at least 1 unprovoked seizure per month even with more than two AEDs. Clinical profiles are summarized in Table 1.

Approval for this study was obtained from the institutional review board at Samsung Medical Center. We obtained written informed consent for participation in the trial from each patient or his/her legal representative.

### Vagus nerve stimulation

We used pulse generators manufactured by Cyberonics (Houston, TX, USA), specifically NeuroCybernetic Prosthesis (NCP) 100 and 101 models, for VNS therapy. There was no difference of stimulation method between two models except battery life-time. The implantation procedure was performed under general anesthesia and required two incisions in left neck and chest. Bipolar helical lead was carefully placed around the left vagus nerve. The connectors of the lead were tunneled from neck to chest incision site under skin, and connected to the pulse generator. After checking impedance of electrodes and confirmation of fully functional generator circuitry, the implantation surgery was finished with suturing incision sites.

### VNS setting

Stimulation was turned on 2-4 weeks after surgery when surgical wounds were healed and show no sign of infection. The generator is connected to a handheld computer by programming wand. The initial setting was output current 0.25 mA, frequency 30Hz, pulse width 500  $\mu$ s, on-time 30 sec, off time 5 min as "standard stimulation protocol". During follow-up visit in the outpatient clinic, the output current was gradually increased with 0.25-0.5 mA per visit. There was

individual difference on the rate of output current increments based on individual tolerance and the degree of seizure frequency reduction. In general, output currents were ramped up at every visit per a month or two: seventeen reached "optimal" current within a year, but the others increased output current even after a year. When a patient complained about adverse event related to stimulation, the pulse width was reduced to 250  $\mu$ s or output current was temporarily reduced with/without shortened signal off time to 3 minutes. We tried rapid cycle protocol, which reduces off time period below 180 seconds, on a single patient but returned to the standard cycle as there was no significant difference in seizure control. All of patients continued to take AEDs without any further restrictions.

### Outcome measure

The objective of this study is to evaluate the change in seizure frequency depending on the progressing time of implantation of VNS. Mean seizure frequency (per month) during three months prior to VNS implantation surgery was considered as 'baseline'. Seizure frequency data were collected through retrospectively reviewing medical records. Auras were not counted. To evaluate the efficacy of VNS, we have divided into four groups in terms of seizure frequency reduction: 1) seizure frequency reduction more than 75%, 2) between 50 and 75%, 3) between 25 and 50%, and 4) less than 25%, no change or worsening. We considered first and second groups, who show more than 50% seizure frequency reduction as responder group, while others as non-responder group.

All analyses were performed using SPSS software for windows (version 18.0, SPSS Inc, Chicago, IL, USA). The Wilcoxon signed rank test was performed for the statistical analysis of the changes in seizure frequency yearly follow-up visit in comparison with baseline. The Friedman test was performed to evaluate overall response with time.  $p < 0.05$  was considered to be statistically significant in all statistical tests used.

## Results

### Patients characteristics

Out of 20 patients, 16 were male. Mean age at the onset of seizures was  $8.4 \pm 9.9$  years (range: 0-41) and mean duration of disease was  $13.9 \pm 9.6$  years (range: 1-37). Mean age at the implantation surgery was  $22.3 \pm 9.6$  years (range: 8-44). Seventeen patients were diagnosed as partial epilepsy (bilateral or multifocal), two as generalized epilepsy and one as Lennox-Gastaut syndrome. Past medical

history of these patients includes infection in the central nervous system (n=7), perinatal problem (n=4), tuberous sclerosis (n=2), febrile convulsion (n=1), and tumor (n=1). Sixty-five percent (n=13) of patients showed abnormalities in MRI scans: brain atrophy was found in seven patients, hippocampal sclerosis in two, tuberous sclerosis in two, benign tumor in one, and cortical dysplasia in one.

Before VNS implantation, the mean number of AEDs was  $4.3 \pm 1.4$  (range: 2-7). This number was slightly increased to  $5.0 \pm 1.85$  at 4 years after VNS implantation (range: 1-8) although it was not statistically significant. The number of AEDs decreased in one patient, increased in thirteen and remained constantly in six. Only one patient had VNS implantation 9 years after anterior temporal lobectomy with tumor resection (Table 1).

### Overall seizure frequency

Mean seizure frequency (excluding aura) before surgery was  $40.9 \pm 71.0$  times/month. After one year of VNS insertion, the num-

ber reduced to  $19.0 \pm 27.9$  times/month. Although the degree of reduction decreased as time progressed, but it showed clear trend of decrease in seizure frequency over time. Most importantly, change in seizure frequency was statistically significant (Table 2).

### Predictors of seizure frequency reduction

Fig. 1 illustrates the progress of seizure frequency reduction when patients were divided into four groups according to the degree of reduction. The responder group, who showed more than 50% of seizure frequency reduction, increased from 8 (40%) at the first year to 12 (60%) at the fourth year. In the responder group, baseline seizure frequency was lower than that of non-responders, but the difference was not significant. When we divided responder and non-responder groups according to the criteria of 50% seizure frequency reduction, no clinical factors such as seizure frequency before surgery, seizure onset age and duration of epilepsy, predicted seizure outcome.

**Table 1.** Clinical characteristics of the patients

No	Age* (yr)	Sex	sz onset (yr)	disease duration (yr)	MRI	History	Epilepsy	sz type	Sz freq before VNS (/mon)	Sz freq 4yr after VNS (/mon)	AEDs before VNS	AEDs after VNS	Prev op
1	8	M	4	4	TS		R frontal	CPS	30	30	4	4	No
2	12	M	2	10	TS		multifocal	CPS	40	5	2	3	No
3	14	M	2	12	atrophy		multifocal	CPS, 2GTC	6	3	2	4	No
4	14	M	6	8	HS	CNSI	B FT	CPS, 2GTC	4	1	4	7	No
5	14	M	7	7	normal		B frontal	CPS, 2GTC	2	0	4	5	No
6	14	M	10	4	normal	CNSI	B FT	SPS	10	3.5	6	7	No
7	15	F	4	11	atrophy	CNSI	multifocal	CPS, 2GTC	60	20	4	6	No
8	16	M	1	15	Atrophy	Perinatal	GE	tonic	100	60	5	6	No
9	18	M	2	16	normal		LGS	ab, GTC	19	25	5	8	No
10	21	M	7	14	atrophy	Perinatal	L temporal	CPS, 2GTC	4.5	0.6	5	4	No
11	22	M	1	21	normal	FC	B FT	CPS, 2GTC	10	4	3	3	No
12	23	M	22	1	normal	CNSI	B FT	CPS, 2GTC	3	0	2	1	No
13	24	F	17	7	normal	CNSI	B temporal	CPS	1	0	4	6	No
14	26	M	0	26	CD		L parietal	SPS, CPS	90	2	3	3	No
15	27	M	12	15	Tumor		R temporal	CPS, 2GTC	2	0.7	7	7	Yes
16	31	M	8	23	atrophy	Perinatal	L TP	SPS	120	60	6	4	No
17	31	F	18	13	HS	CNSI	B temporal	CPS	3.8	1.3	6	7	No
18	35	M	4	31	Atrophy		B frontal	CPS, 2GTC	3	1	5	7	No
19	37	F	0	37	normal	Perinatal	GE	tonic	300	0	4	4	No
20	44	M	41	3	atrophy	CNSI	B temporal	CPS	9.8	5	5	5	No

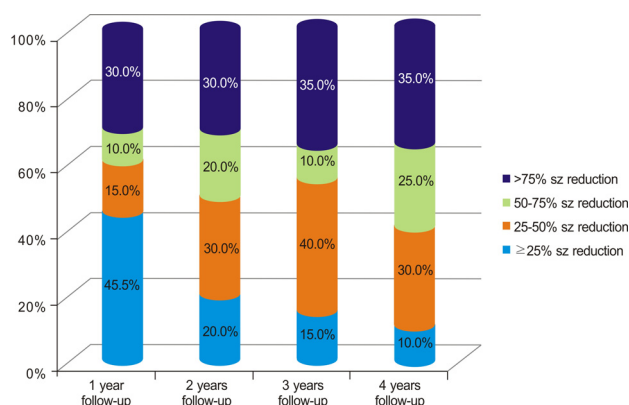
sz, seizure; freq, frequency; HS, hippocampal sclerosis; CD, cortical dysplasia; TS, tuberous sclerosis; CNSI, central nervous system infection such as encephalitis; Peinatal, perinatal insults; FC, febrile convulsion; R, right; L, left; B, bilateral; FT, frontotemporal; TP, temporoparietal; GE, generalized epilepsy; LGS, Lennox-Gastaut syndrome; ab, absence; SPS, simple partial seizure; CPS, complex partial seizure; 2GTC, secondarily generalized tonic-clonic seizure; Number of antiepileptic drugs, Prev. op: epileptic surgery history before VNS implantation.

\*at VNS implantation.

**Table 2.** Range, average seizure frequency and mean seizure frequency reduction rate

	Before-VNS (Baseline)	1 yr F/U	2 yr F/U	3 yr F/U	4 yr F/U	* <i>p</i> -value
Mean±SD (/mon)	40.9±71.0	19.0±27.9	15.8±23.0	14.1±22.2	11.1±18.9	<0.001
Range of sz (freq/mo)	1-300	0-90	0-60	0-60.8	0-60	
Comparison with baseline						
<i>p</i> -value	-	0.02 <sup>†</sup>	<0.01 <sup>†</sup>	<0.01 <sup>†</sup>	<0.01 <sup>†</sup>	
Comparison with 1 yr F/U						
<i>p</i> -value	-	-	0.17	0.03 <sup>†</sup>	0.05	
Comparison with 2 yr F/U						
<i>p</i> -value	-	-	-	0.09	0.07	
Comparison with 3 yr F/U						
<i>p</i> -value	-	-	-	-	0.11	

Statistical analysis: Wilcoxon signed-rank test with Bonferroni correction. SD, standard deviation; sz, seizure; freq, frequency; mo, month. \**p*<0.05. <sup>†</sup>Analysis by Friedman test.



**Figure 1.** Proportional change of seizure frequency reduction during the follow up period. The number of responder (patient with >50% seizure frequency reduction after VNS therapy) increased from 8 (40%) at the first year to 14 (60%) at the fourth year follow-up. sz, seizure.

## Adverse event

Seven patients (35%) complaint minor adverse event. Intermittent hoarseness during active stimulation were present in 4 patients, throat discomfort in 3 patients, swallowing difficulty in one patient, cough in one patient. As time passed, most side effects were decreased or disappeared.

## Discussion

The present study investigated the long-term effect of VNS and demonstrated that the VNS therapy is effective in seizure control in medically intractable epilepsy patients. Mean reduction in seizure frequency decreased over time, 25.9% after a year, 27.2% after two

years, 55.2% after three years and 65.8% after four years. The responder rate group, who showed more than 50% seizure frequency reduction, was also increased over longer period after VNS implantation (40% (n=8) after a year, 50% (n=10) after two years, 45.5% (n=9) after three years, and 70% (n=14) after four years). Although the number of responders decreased from second to third year, it increased again after four years. Our results in Korean epilepsy patients showed lower responder rate at first year follow-up but higher rate after four years and were concordant to previous studies in other countries. One study reported responder rate of 54% after one year and 61% after two years.<sup>8</sup> Another study showed the change in mean seizure frequency from 28% after one year to 78% after 5 years.<sup>9</sup> Other studies demonstrated similar findings that the efficacy of VNS therapy in seizure control increases over time.<sup>10,11</sup> There exists no long-term follow-up study on the effect of VNS therapy in Korea, but one study reported the treatment effect over 18 months: it showed that 29% after three months, 43% after 12 months, and 43% after 18 months experienced more than 50% reduction in seizure frequency.<sup>5</sup>

There was no statistical difference in the number of AEDs before and after the VNS therapy. So our result may show VNS effects on seizure frequency independent to the changes of AEDs. This result is consistent with a previous study, which observed 138 patients with VNS therapy for more than one year.<sup>12</sup> This study revealed that mean seizure frequency was decreased to 51% of baseline without significant changes of AED numbers. Another study reported that mean seizure frequency decreased to 58% of baseline after one year, even when the number or dosage level of AEDs were persistently kept.<sup>13</sup>

These studies support the view that seizure frequency reduction by VNS therapy can be attributed to VNS itself rather than the effect of AED changes.

All of our patients included in this study started VNS therapy with 'standard' cycle (frequency: 30 Hz, pulse width: 500 msec, duty cycle: 30 sec on/3-5 min off). One of them changed to 'rapid' cycle (frequency: 20 Hz, duty cycle: 7sec on / 30 sec off) temporarily but returned to 'standard' cycle due to no further effect of seizure control. So we did not analyze the efficacy of rapid cycle. In general, rapid cycling has been studied in patients who have not responded to standard cycle of VNS, and in almost all cases rapid cycle did not lead to long-term efficacy.<sup>12,14</sup> One study reported that 'standard' cycle was more effective in seizure control.<sup>14</sup> It was difficult to explore certain parameters that may have predictive value in seizure control efficacy of VNS due to small sample size in our study.

Various clinical parameters have been used for evaluating the treatment efficacy of VNS therapy. Many of studies adopted diverse parameters such as seizure frequency reduction, decrease in the number or dosage of AEDs, and/or improvement in quality of life. Recently it has been suggested that other parameters, such as improvement in ictal or post-ictal severity and reactivity to magnetics, could be used as VNS therapy outcome measures.<sup>15</sup>

In spite of a small sample size, the present study demonstrates improving seizure control efficacy of VNS therapy over time, as revealed by increasing mean seizure frequency reduction rate. Therefore, VNS may be a safe and effective alternative for those who are refractory to AEDs and not suitable for epilepsy surgery. There are some limitations in our study. The number and dose of AEDs were not kept the same over the entire follow-up period although there was no significant difference. Due to the small number of subjects, VNS outcome were not evaluated according to different types of seizures. It is necessary to conduct a follow-up study with larger number of patients for longer period.

## Acknowledgements

This study was supported by a grant (No. A110097) from the Korean Health Technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea.

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