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Therapeutic Outcomes of Vagus Nerve Stimulation in Intractable Childhood Epilepsy

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난치성 간질환아에서 미주신경자극술의 임상결과

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목 적 : 난치성 간질환자의 치료를 위해 미주신경자극술(Vagal Nerve Stimulation)이 1988년 처음으로 시술된 이후, 이 시술은 간질의 새로운 치료법으로서 효과와 안정성이 인정되고 있으나, 소아간질환자에서의 본 시술에 대한 연구는 아직 많이 이루어져 있지 않다. 이에 본 연구는 난치성 간질로 미주신경자극술을 시행받은 12명의 환아를 대상으로 미주신경자극술의 효과와 안정성을 평가하고자 하였다.

방 법 : 1999년 6월부터 2004년 4월까지 연세대학교 세브란스병원과 상계백병원 간질센터에서 미주신경자극술을 시행 받은 환아 12명을 대상으로 임상적 소견, 발작 감소 여부, 뇌파의 변동 및 부작용의 유무 등을 의무기록을 통해 후향적으로 분석하여 미주신경자극술의 효과와 안정성을 평가하였다.

결 과 : 미주신경자극술을 시행 받은 시점의 환자들의 평균연령은 9년 9개월이었다. 평균 추적기간은 21.6개월이었으며, 12명 중 5명은 12개월 이상 추적관찰이 가능하였다. 12명 중 9명은 Lennox-Gastaut증후군 환아였으며, 2명은 이차적 전신화를 동반한 부분 간질이었고, 1명은 시상하부 과오종에 의한 홍소발작 환아였다. 시술 후 3개월 경, 8명에서 기저치에 비하여 50% 이상의 발작 횟수 감소가 보였으며, 이중 2명은 완전한 발작소실을 보였다. 1명은 25%의 발작 감소를 경험하였으며, 3명에서는 시술의 효과가 없었다. 50%의 발작 감소를 보인 환아 중 2명은 12개월과 24개월 후 발작빈도가 75%와 90%까지 감소하였다. 미주신경자극술에 의한 부작용으로는 쉰목소리 1례와 수면중 호흡곤란 1례, 삽입부위 감염 1례와 기계고장이 1례 있었으며, 이들 중 대부분은 자극 강도의 조절로 호전되었고, 삽입부위 감염에서는 수술적 처치가, 기계고장은 기계의 적출이 필요하였다. 발작이 완전히 소실된 2명에서 배경파의 안정과 경기파의 감소 등 뇌파상의 호전이 보였으나, 다른 환아들은 뇌파상 특이 변화가 보이지 않았다.

결 론 : 본 연구에서 분석한 12명의 난치성간질환아에서 미주신경자극술은 비교적 유용한 효과를 보였고, 일시적인 부작용들은 대부분 치료의 중단 없이 조절, 회복될 수 있었다. 따라서 미주신경자극술은 소아기의 난치성 간질환자의 치료에 있어 효과적이고 안전한 보조 치료법으로 생각되며, 향후 난치성 소아 간질 환아에서 적극적인 도입이 필요하리라 사료된다.

Key Words : Vagus nerve stimulation, Intractable childhood epilepsy

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Introduction

Ever since the discovery by Bailey and Bremer in 1938 that vagal nerve stimulation (VNS) in cats induced changes in EEG[1], numerous studies have been made on the effects of the vagal stimulation on brain discharges. In 1985, Jacob Zabara published his findings that vagal stimulation induced suppression and prevention of epilepsy in animal models[2], leading to the first human stimulator trial in 1988 [3], ultimately approved by FDA in 1997. Currently, the vagal nerve stimulation (VNS) is, along with ketogenic diet and epilepsy surgery, one of treatment modalities applicable to patients who are refractory to a standard medical treatment. As of the year of 2002, 16,000 patients have received the VNS implantation, with a quarter of them being younger than 18 years of age[4]. First Korean VNS implantation was performed in 1999. According to the data supplied by Cyberonics Co. (Houston, TX), more than 35 patients received the VNS implantation in Korea by the year of 2003, with 15 of them being younger than 18 years of age[5]. The pediatric patient pool in our hospital is one of the largest in Korea, with a history of the VNS implantation that dates back to 5 years age. The outcomes of the pediatric patients with the VNS implantation have not been well reported in the literature. We hereby report on our experiences with an intention to aid in the implementation of this relatively new technique and to evaluate its efficacy in children.

Materials and Methods

1. Subjects

Twelve patients who visited the Yonsei University Medical Center and Sanggye Paik Hospital from July 1999 to April 2004 to receive VNS implantation were followed up and evaluated. Six patients were male and six were female. Patients were considered candidates for VNS if they were medically intractable to more than three kinds of antiepileptic medications, were ineligible for epileptic surgery due to generalized epileptic focuses or unacceptably high risk of surgery, and failed ketogenic diet due to unsatisfactory response, side-effects, or non-compliance. No discriminations were applied to candidates regarding age or types of seizures. Effectiveness of the treatment was determined by the reduction of seizure frequencies as reported by the parents or guardians.

2. Application of Device

VNS device was supplied by NeuroCybernetic Prosthesis (NCP). Four patients were implanted with NCP Model 100, and the rest were implanted with Model 101. No significant differences existed between the two devices except battery lifespan - Model 101 can last for 10 years, as opposed to Model 100, which had a battery life of 5 years only. Device parameters were set in accordance with the guidelines set by FDA and the device manual supplied by the Cyberonics company, with settings adjusted to each patient's individual requirements. After implantation, initial parameters were set as follows; output current at 0.25 mA, frequency of 30 Hz, pulse width of 500

μsec, and duty cycle of 30 seconds "on" and 5 minutes "off" time. Parents or guardians were supplied with device magnets to manipulate the device in cases of seizures or extreme side effects, and the magnet parameters were set with output current 0.25 mA higher than baseline in order to facilitate habituation at higher currents, and hence improve tolerability. Patients were followed up every 2 weeks post-surgically to evaluate the efficacy and the presence of any adverse effects and to adjust the device parameters. Output currents were increased by 0.25 mA at every visit until clear reduction in seizure frequency was achieved or an output current of 3.5 mA was reached. Duty cycle ratio was increased to more than 25% (30 seconds ON, less than 1.8 minutes OFF) in patients who did not show any visible reduction in seizure activities 3 months post-surgically. Duty cycle was returned back to the initial setting if the patient failed to respond to higher cycles after 3 months in order to conserve the battery. Pulse width was decreased to 250 μsec in cases of intolerance to initial settings. Stimulation was usually started 2 weeks post-surgically, but in uncomplicated cases with no special difficulties present after the implantation, stimulation was initiated one day post-surgically (Fig. 1).

3. Data Collection

Reduction in seizure frequencies, seizure characters, and side-effects were obtained verbally from parents or guardians at every clinical visits, and were analyzed at three months, twelve months and twenty four months post surgically.

Results

Twelve cases were analyzed, which was composed of six male and six female patients. The mean age (±SD) at the initiation of VNS were 9 years 9 months (±60.5 months) (2

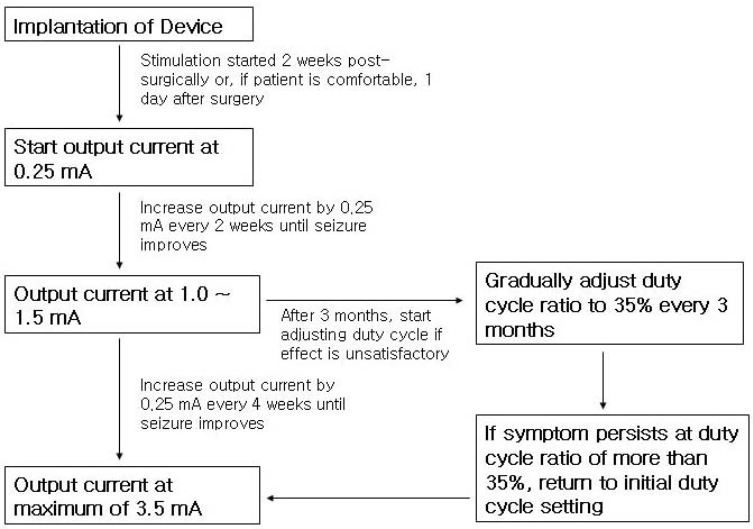

Fig. 1. Recommended protocol of VNS parameter settings (Data from Heck C, Helmers SL, Degiorgio CM. Neurology 2002;59(Suppl 4):31-7).

years 9 months-17 years 10 months), and the mean duration of seizure (±SD) before implantation was 8 years 7 months (±68.6 months) (1 year 8 months-17 years 10 months). Mean follow-up period after implantation was 21.6 months (±23.3 months) (3 months-4 years 9 months). In five patients, follow-up period exceeded 12 months, while in seven patients, it was less than 12 months. Types of seizure included 9 with Lennox-Gastaut syndrome, two patients with partial seizure with secondary generalization, and one patient with gelastic seizure originating from hypothalamic harmatoma. All cases of Lennox-Gastaut syndrome received ketogenic diet and failed due to either unsatisfactory effect or patient intolerance. Two cases of partial seizure with secondary generalization were inappropriate candidates for surgery due to the presence of multiple seizure foci over both hemispheres, and one case of hypothalamic harmatoma did not receive resection of mass due to parental refusal to operate owing to the risks associated with surgery, which they deemed unacceptable (Table 1). Efficacy of the treatment was evaluated at 3 months, 12 months and 24 months after implantation. Among the five patients who were followed up for more than 12 months, two patients with Lennox-Gastaut syndrome and one patient with partial seizure of cryptogenic origin showed a 50% decrease in seizure frequency after 3 months. At 12 and 24 months, patient with partial seizure showed a 90% reduction in seizure frequency, while one case of Lennox-Gastaut syndrome originating from previous encephalitis showed a reduction of 75% at 12 and 24 months, and one case of Lennox-Gastaut syndrome of cryptogenic etiology showed maintenance of reduced seizure frequency at 50% of baseline. One case of gelastic seizure from hypothalamic harmatoma and a case of cryptogenic Lennox-Gastaut syndrome failed to respond to VNS after 24 months of treatment. However, brief reduction of seizure severity was observable after magnetic stimulation of the device in gelastic seizure. Magnetic stimulation was useless in other four cases. In seven patients, follow-

Table 1. Clinical Data of Twelve Patients with VNS Implantation

Patient	Age at surgery	Duration of F/U	Epilepsy classification	Etiology
1	87	57	P2G	Cryptogenic
2	92	38	LGS	Encephalitis
3	214	57	LGS	Cryptogenic
4	177	53	Gelastic	Hypothalamic harmatoma
5	76	26	LGS	Cryptogenic
6	139	3	LGS	Pacygyria
7	85	8	LGS	Cryptogenic
8	33	4	IS → LGS	Tuberous Sclerosis
9	40	4	LGS	Cryptogenic
10	152	3	LGS	Cryptogenic
11	207	3	P2G	Cryptogenic
12	101	3	LGS	R/O Metabolic disorder

Datas are in months, P2G : Partial Sz c 2^{o} Generalization, LGS : Lennox-Gastaut Syndrome, IS : Infantile spasm

up duration was 3 months. Patient group was composed of six Lennox-Gastaut syndromes and one partial seizure patient with secondary generalization. One Lennox-Gastaut patient exhibited pachygyria in brain MRI, one case had Lennox-Gastaut syndrome that evolved from infantile spasm with concomitant tuberous sclerosis, one case had suspected metabolic disorder, and the rest of the Lennox-Gastaut cases were cryptogenic in origin. One case of partial seizure was cryptogenic in origin. One case of cryptogenic Lennox-Gastaut syndrome and one case of tuberous sclerosis showed total ablation of seizure activity 3 months after implantation. One case of Lennox-Gastaut syndrome with pachygyria and one case of cryptogenic origin showed 50% reduction in seizure frequency after 3 months, while one case of partial seizure also showed a 50% reduction of seizures. Another cryptogenic Lennox-Gastaut syndrome patient showed a 25% decrease in seizure activity, and one patient with suspected metabolic disease failed to respond to the treatment (Fig. 2). In cases that are non-responsive to the treatment, output current was increased to over 3.0 mA, and changes in duty cycles were made as dictated by the protocols or according to the patient's tolerability. However, alterations in duty cycle was clearly effective in only one case of Lennox-Gastaut syndrome, who showed complete ablation of seizure after 3 months. In cases where seizure reduction of over 75% were achieved, range of output current varied from 0.75 mA to 3.25 mA, but in most cases, high output current over 2.0 mA were necessary to reduce seizure frequencies. Duty cycles were adjusted in cases of inadequate effectiveness, but they were mostly ineffective, necessiating a change back to previous duty cycles (Table 2). Antiepileptic medications were unchanged in most patients, except two in whom reduction in seizure frequency was maintained by single and double antiepileptic drug therapy. Complications were observed in four patients. On case developed hoarseness after 12 months at output current of 2.25 mA, and again after 21 months at output current of 2.0 mA. In each episodes, symptoms were controlled after output current was reduced by 0.25 mA. This particular patient also developed wound infection of the operation site that was unresponsive to antibiotics treatment, but infection was healed after revision of the wound site. Another case reported excessive salivation at 3 months, but this particular symptom subsided after clinical observation. One patient complained of a sense of mild dyspnea during sleep, but his symptom improved after follow-up without any changes in the device settings. Only one case of generator malfunction was present after 44 months, and removal of device was necessary in this case. No adverse side-effects such as bradycardia or arrhythmia were observed during implantation and test run of the device

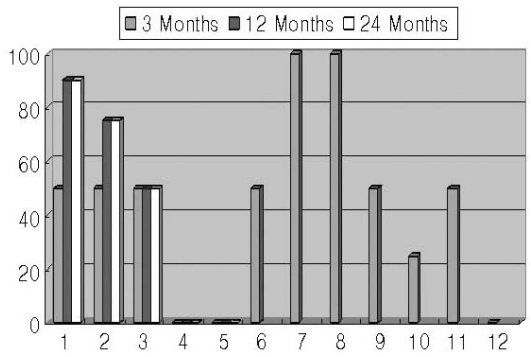

Fig. 2. Seizure frequency reduction compared to baseline for each patients at 3, 12 and 24 months after VNS implantation.

Table 2. VNS Parameter Settings at the Time of Data Acquisition

Patient	Output current	Duty cycle alteration
1	2.75 mA	
2	3.25 mA	
3	3.25 mA	Off time set to 5 min at 3 years 6 months → No effect
4	3.5 mA	On time set to 60 sec, Off time set to 3 minutes after 3 months → No effect
5	3.0 mA	On time set to 60 min, Off time set to 3 min after 3 months → No effect
6	1.25 mA	
7	2.0 mA	Off time set to 3 min after 2 months
8	0.75 mA	Off time set to 5 min from the beginning
9	1.25 mA	On time set to 60 sec, Off time set to 5 min after 1 months
10	0.5 mA	
11	0.75 mA	
12	0.75 mA	

inside the operating room.

Discussion

Anitepileptic medications are, in general, effective in treating epilepsies in children, but 32% of patients are pharmacoresistant - namely, their symptoms are resistant to more than three kinds of antiepileptic agents used in combination[6]. Various kinds of treatment were devised for treatment of such children, and three kinds of treatment modalities are currently favored, namely ketogenic diet, epilepsy surgery, and vagal nerve stimulation. VNS is a relative newcomer to this group, but the possibility of such treatment was first sown in 1938, when Bailey and Bremer published their article concerning EEG changes in cats induced by vagal stimulation[1]. In 1985, Jacob Zabara discovered that vagal stimulation was effective in prevention of seizures[2], and first human application was performed in 1988 by Kiffin Penry of Bowman Gray School of Medicine[3]. Approval for human application was granted in Europe in 1994, and FDA approval was granted in 1997 for "use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial seizures which are refractory to antiepileptic medications".

The anatomy of the vagal nerve is important in understanding the effects and adverse reactions of VNS. The superior portions of the vagus nerves are attached by multiple rootlets to the medulla, and exit the skull by way of jugular foramina. Covered by carotid sheath, the vagus nerve runs through the neck between the carotid artery and the jugular vein, and in the upper chest, distributes to the left and right side of the trachea. Afterwards, the vagi distributes to various viscera in the abdominopelvic cavities. Vagus nerve is composed of three types of fibers - A, B and C-fibers. Narrow-caliber, unmyelinated C-fibers comprise the majority of vagal nerve components, while myelinated, faster conducting A and B-fibers accounts for the rest[7]. The vagal nerve carries the somatic and visceral afferents and efferents. The efferent fibers mainly originate from neurons located in the medulla oblongata, and the afferent fibers mainly originate from two parasympathetic ganglia near the base of

the skull. Vagal efferents innervate the muscles of pharynx and larynx as well as most of the thoracoabdominal viscera. They are mostly parasympathetic projections to the heart, stomach, liver, pancreas and intestines. The left vagus nerve carries most of the parasympathetic fibers that less densely innervate the ventricles, and the right vagus nerve carries most of the parasympathetic fibers that more densely innervates the cardiac atria[8] (Hence, vagal anatomy favors left side over right to minimize the cardiac complications). Afferent component comprise about 80% of the fibers in the cervical portion of the vagus nerve. Majority of the special and general visceral afferents carry gustatory information, visceral sensory information, and other peripheral information, while smaller group of vagal somatosensory afferents carry sensory information from on and near the ear.

The exact mechanism by which vagal stimulation ablates or prevents seizures are not clearly understood. Traditionally, desynchronization of hypersynchronous epileptic brain activities were thought to be the reason behind the therapeutic effects of VNS[2]. Current findings suggest multitude of physiologic changes that might contribute to the anti-convulsive effect of the therapy. Decreased synchrony of synaptic activities and increased arousal due to better synaptic activities in thalamus and thalamocortical projections after timed stimulation of vagus nerve was considered as one of such changes. Other findings showed that synaptic activities were increased in components of central anatomical systems, such as insula and hypothalamus. Transiently decreased synaptic activities in components of limbic systems, such as amygdala and hippocampus, were noted. VNS, in the long run, resulted in increased concentration of serotonin and norepinephrine in Raphe nuclei[9], and increased cerebral blood flow[10, 11] that might contribute to the decrease in seizure frequency.

VNS was approved by FDA after five pilot studies (E01-E05) as treatment modality for medically intractable partial seizure disorders under the age of twelve. No age limitations are set in Europe, and its application is wider than in US. We did not set any age limitations in selecting candidates for this treatment, and all seizure types that are not responsive to medical treatment and ketogenic diet have been considered for implantation. As of year 2002, over 16,000 patients world-wide have received VNS implantation, with a quarter of them being under the age of 18 years, and half of the youngsters being less than 12 years of age[4]. After the first Korean patient has been implanted with VNS in 1999, 35 patients have received this treatment by year 2003 in Korea, and 15 of them are less than 18 years of age[5].

Effectiveness of VNS was established after multicenter, double-blind, randomized, parallel, active-controlled studies, of which E03 and E05 trials were pivotal. In these studies, patients were randomly assigned to either high (30 Hz, 30 seconds ON, 5 minutes OFF, 500 μsecond pulse width) or low (1 Hz, 30 seconds ON, 90 to 180 minutes OFF, 130 μsecond pulse width) stimulation. Percentage change of seizure frequency compared to that of baseline after treatment was evaluated for both study groups. In both pivotal trials, the mean percentage of seizure reduction was significantly greater in the high stimulation group, 24.5% versus 6.1% (P= 0.01) in the E03 study[12] and 28% versus 15% (P=0.039) in E05[13]. Overall, median seizure re-

duction was 34% after 3 months and 45% after 12 months (P=0.0001). Furthermore, after 12 months, 20% of the patients had seizure frequency reductions of 75% or more. According to data supplied by Cyberonics company accumulated until January 2002, 57% of patients showed mean seizure reduction of more than 50%, and 36% of patients showed a mean reduction of more than 75%[14]. These reports, along with report published by Degiorgio et al[15], also states statistically significant long-term, gradual reduction of seizure after chronic implantation. In a multicenter report published by Korean Epilepsy Society, 29% of patients implanted with VNS showed more than 50% reduction in seizure frequency after 3 months, but the proportion increased to 43% after 12 months, implicating cumulative therapeutic effect[16]. Study on long-term responders of VNS published by Morris also reports increased seizure reduction rate as time passes, with 23% of patients showing more than 50% reduction of seizure at 3 months, 37% at 1 year, and up to 43% at 2 and 3 years[17]. Although VNS was permitted in United States for use in patients over 12 years of age, the treatment appears equally as effective in reducing seizures in children younger than 12 years as in other age groups. According to data supplied by Cyberonics, by January 2002, 50% of VNS implant patients between the age of 0 to 6 showed more than 50% reduction in seizure frequency after 3 months, while 59% showed more than 50% decline in seizures by 12 months post-operatively. This figure is not so different from results obtainable in other groups - between the age of 7 to 11, responders with more than 50% seizure reduction accounted for 50% of all patients at 3 months and 61% at 12 months, while in age group between 12 to 18, the results were 53% at 3 months and 61% at 12 months. Older patients between the ages of 19 to 35 showed 53% of total patients with more than 50% reduction of seizure by 3 months, with the proportion increasing to 56% of all by 12 months. In patients between the ages of 36 to 55, 47% of all patients showed more than 50% reduction in seizure frequency at 3 months, with the proportion increasing to 56% of total after 12 months[4]. Murphy et al[18] reported similar result in their study of 100 children treated with VNS - effectiveness of VNS is similar in children both under 12 years and older. In patients with Lennox-Gastaut syndrome, one third of 43 patients treated with VNS showed more than 75% reduction of baseline seizure frequency[19]. In refractory childhood epilepsy associated with tuberous sclerosis, VNS was effectively reduced seizure frequency by more than 50% in 9 out of 10 patients, with 5 patients showing seizure reduction of more than 90%[20]. Finally, Renfroe et al reported their findings that 90% of pediatric patients treated with VNS showed statistically significant improvement in seizure frequency by 5 years post-operatively, suggesting earlier implementation of the device in children who satisfy the indications[21]. VNS also possesses the merit of being a mechanical antiepileptic modality that does not utilize antiepileptic medications, which are known to have negative effects on cognitive functions. More than 70% of refractory epilepsy patients who are candidates of VNS have some form of mental retardation or delayed development, VNS can prevent excessive seizure activities and lower usage of higher dosages of anticonvulsants, helping cognitively delayed patients

overcome their neurologic problems and facilitate neural development[4].

Our results showed similar efficacy of the treatment in young patient groups. Although the number of samples are too small to draw any statistical conclusions, our results agree to the reports derived from other VNS patient groups. Eight out of twelve patients showed more than 50% reduction in seizure frequency. Four patients showed a 50% reduction in seizure frequency at the time of last follow-up, while one patient showed a 75% drop and one showed a 90% drop in seizure frequency. Two patients showed total control of seizures after 3 months of treatment. VNS therapy, as opposed to other antiepileptic treatment such as antiepileptic medications, ketogenic diet and epilepsy surgery, does not show immediate and radical improvement in seizure reduction in most cases, rather its effect is gradual and cumulative, with ongoing clinical improvement observable after 2 years in some cases[17]. Our cases also shows this cumulative effect of treatment in two out of five patients who were followed up for more than 24 months. In all five cases where long term follow-up was possible, none showed clinical deterioration of symptoms after VNS therapy, even in those cases where VNS was not effective.

Bipolar lead of the device was implanted in left vagus nerve in all patients due to fewer cardiac effects associated with its anatomical location. All patients received their first impulse inside the operating room to monitor the presence of acute complications such as arrhythmia or asystole. No such problems occurred in all cases. No acute surgical complications were observed post-operatively, and initiation of treatment was begun, in most cases, two weeks after the surgery. Application of device parameters were mostly concordant with the manual and published reports[22, 23]. However, in cases where patient tolerance is obvious and satisfactory, settings were increased as situations warranted. Seizure control was obtained at high output currents in most cases. In cases where therapeutic effectiveness was less than satisfactory, alteration of duty cycle was applied, with ratio as high as 36% applied in non-responsive cases. Changes in duty cycles, however, was not effective in reducing seizure in those patients, and ultimately, resulted in a return back to baseline cycles with increased output current.

All patients continued their antiepileptic medication treatment post-operatively. At the time of their last follow-up, all patients were still on medications, mostly without changes in types or numbers, except the two patients who achieved 100% seizure reduction after 3 months, in whom number of medications taken were reduced from four to two in one case and from two to one in the other.

Electroencephalographic follow-up of patients after the implant showed no interval changes in most cases, but in two cases with complete seizure ablation, improvement of background rhythms with much less frequent generalized seizure activities were observed in one patient, while in the other, complete cessation of epileptic discharges were seen. Such improvement in electroencephalography was also reported by Koo after long-term treatment with vagal stimulation[24].

Various complications have been reported after VNS. Among them, hoarseness, respiratory difficulty, throat tightness and difficulty during swallowing are the most common com-

plications reported[14]. Report of VNS therapy in pediatric patients by Helmer et al[19] noted voice alteration in 57.9%, coughing in 37.8%, and motor incoordination and mild right-sided weakness in some others. Such complications were rarely life-threatening, and were corrected with lowering of output currents, reduction of frequency, or correction of pulse width from 500 μseconds to 250 μseconds. Three patients out of twelve showed some kind of side-effects in our patient population. Hoarseness and mild respiratory difficulty during sleep were present in one patient, which were corrected by lowering output current by 0.25 mA. He later developed infection of the surgical wound which was healed after wound revision. Increased salivation was observed in one other patient, which improved after clinical observation, and failure of pulse generator was observed in one, which required surgical removal of the device.

VNS is a safe and effective method, and possesses the advantage of having no adverse effect on cognitive functions, which is a major setback in utilization of antiepileptic drugs among pediatric patients undergoing critical stages of neural development. However, unlike surgery or ketogenic diet, complete ablation of seizures cannot be achieved in most cases, and the procedure itself is exponentially expensive, making wide-spread application of this procedure difficult. No official guidelines exist in Korea regarding the implementation of VNS, and if past experiences hold true, ultimate approval criterions will very likely be similar to FDA regulations. But VNS is equally effective in children under the age of twelve as in other age groups, and its merits in controlling seizures and helping cognitive development in children who are in the middle of their neurologic growth mandates more active and widespread application of this treatment in refractory pediatric epilepsy.

Abstract

Purpose : VNS has been used as a adjunctive treatment modality in medically intractable epilepsy patients since 1988, and is presently considered a safe and effective mode of treatment. However, its safety and efficacy in pediatric epilepsy patients have not been as well-studied. We the authors have experienced 12 pediatric patients who received VNS implantation, and evaluated the safety and efficacy of the procedure in the pediatric age group.

Methods : 12 patients who received VNS implantation in Yonsei University Medical Center and Sang-gye Paik Hospital Epilepsy Center from June 1999 to April 2004 have been evaluated for clinical symptoms, presence of reduction in seizure frequency, EEG changes and side-effects after VNS implantation. Datas were analyzed retrospectively through review of clinical records, with emphasis on evaluation of effectiveness and safety of the treatment.

Results : Mean age of the patients at the time of VNS implantation were 9 years 9 months (±60.5 months)(2 year 9 months-17 years 10 months). Mean duration of follow-up was 21.6 months (±23.3 months). Five patients out of twelve could be followed-up for more than 12 months. Nine out of twelve patients possessed Lennox-Gastaut syndrome, two were diagnosed as partial seizure with secondary generalization, and one patient had gelastic seizure caused by hypothalamic harmatoma. Eight patients showed more than 50%

reduction in seizure frequency compared with baseline 3 months after the implantation, with two patients exhibiting complete seizure ablation. One patient showed a 25% decrease in seizure frequency, and VNS was ineffective in three patients. Among the patients with more than 50% reduction of seizures, two patients respectively showed a 75% and 90% decrease in seizure frequency at 12 months and 24 months post-operatively. One case of hoarseness, one case of dyspnea during sleep, one case of post-operative wound infection and one case of generator malfunction were noted after VNS, but most of these adverse effects improved through manipulation of output current. Wound infection necessitated surgical revision and generator failure required surgical removal of the device. EEG patterns of the two patients with complete seizure ablation exhibited marked improvement of background rhythms and reduction of epileptogenic discharges, but others did not show any significant improvement in their EEG.

Conclusion : This study showed significant improvement in seizure frequencies among medically intractable pediatric epilepsy patients after VNS, and most of its adverse effects could be controlled without discontinuation of treatment. Therefore, we believe that VNS is a safe and effective treatment modality in pediatric patients with intractable epilepsy, and merits wider implementation for medically intractable epileptic children in the future.

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