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소아청소년 환자에서 미주신경 자극술의 경련 조절 예측인자에 대한 분석

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의학과 중개의학 전공

양제열

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지도교수 김승기

이 논문을 의학 석사 학위논문으로 제출함

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양제열

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위 원 장 _____ (인)

부 위 원 장 _____ (인)

위 원 _____ (인)

Abstract

Predictors of seizure outcome for vagus nerve stimulation in children

Jeyul Yang
Department of Translational Medicine
The Graduate School
Seoul National University

Vagus nerve stimulation (VNS) is a palliative treatment for intractable epilepsy. While the expected outcome of VNS is well known, seizure reduction rates depending on various factors are not clearly defined. Hence, we investigated the predictors and seizure reduction rates of VNS in pediatric patients. We retrospectively reviewed pediatric patients with VNS implantation at our institution. Outcomes of post-operative 6 months, 1 year and 2 years were analyzed. The overall mean age at seizure onset was 6.4 years (range, 0.2–15 years), and the mean age at the time

of VNS surgery was 14.7 years (range, 5–26 years). The mean interval from seizure onset to surgery was 8.3 years (range, 2–16 years). Responders (defined by ≥50% reduction in seizure frequency) included 22/47 patients (47%), 25/47 patients (53%) and 22/35 (63%) at post-operative 6 months, 1 year and 2 years, respectively. The overall mean seizure frequency was reduced from 8.0 per week to 5.1 and 4.3 per week at one and two years after operation. At post-operative 2 year, patients with focal onset epilepsy on electroencephalography (EEG) had reduction rate of 51% (p=0.009). Patients who did not undergo resection surgery prior to VNS insertion had a reduction rate of 43% (p=0.037). Patients with infectious etiology had seizure reduction rate of 69% at post-operative 2 year. (p=0.026) Hence, pediatric patients with intractable epilepsy who have focal lesions in eloquent areas or unmatched ictal zones on EEG with multifocal lesions or, patients who infectious etiology could be good candidates for VNS.

Key words: vagus nerve stimulation; epilepsy; intractable; pediatric

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AEDs: Anti-epileptic drugs

VNS: Vagus nerve stimulation

US: United States of America

FDA: Food and Drug Administration

EEG: Electroencephalography

LRE: Localization-related epilepsy

LGS: Lennox-Gastaut syndrome

Contents

Introduction

Epilepsy is a worldwide health concern that includes children and affects developmental delay and quality of life. Despite the development of new anti-epileptic drugs (AEDs) over the last few decades, 30% of patients with epilepsy remain intractable to AED. [1] Ketogenic diet and resection surgery represent other options for intractable epilepsy patients. Recently, the role of resection surgery has been emphasized, yielding favorable outcomes.[2] However, adverse effects, such as neurological deficits or insufficient outcomes, have also been reported. [3] Thus, alternative treatments for intractable epilepsy have been constantly studied.

Vagus nerve stimulation (VNS) is a palliative treatment for intractable epilepsy and was approved by the United States of America (US) Food and Drug Administration (FDA) in 1997.[4] To date, VNS devices have been implanted into more than 100,000 patients worldwide. [5] Numerous studies on the outcome of VNS were conducted by measuring the percentage of patients who achieved a 50% seizure frequency reduction.[6] Moreover, clinical predictors such as etiology, imaging and electroencephalography (EEG) findings for favorable outcome have been reported with univariate and multivariate analyses. However, there have

been few studies regarding the seizure reduction rate after VNS implantation depending on various factors, especially in pediatric patients. In the present study, the clinical predictors and seizure reduction rates of VNS in pediatric patients with intractable epilepsy were investigated.

Materials and Methods

Materials

We retrospectively reviewed medical records, radiological data, EEG, and clinical outcomes of pediatric patients who underwent VNS implantation in our institution from January 2006 to January 2018. Medical records were reviewed for demographic data, age at onset, age at surgery, duration of epilepsy, seizure types, frequency of seizures and the number of AEDs. The present study was approved by the institutional review board at our institution. Informed consent was waivered by the IRB since this study is a retrospective study.

Categorization

All patients underwent brain MRI and surface EEG prior to surgery. MRI findings were categorized into normal, focal lesions, multifocal lesions and diffuse lesions. A focal lesion was defined as a lesion that was

localized in only one brain lobe. A multifocal lesion was defined as a lesion that was localized in two lobes. A diffuse lesion was defined as a lesion found in more than two lobes.

The predominant type of seizure was separately analyzed according to seizure semiology and EEG. Seizure semiology was diagnosed according to patients' ictal behavior that was observed during the video EEG monitoring. Diagnosis was made based on classification of seizure semiology.[7] Frequency of seizures were measured for predominant seizure occurred per week.

EEG based epilepsy type was divided into three categories, and those were focal, generalized and combined generalized and focal. EEG findings and the type of epilepsy were diagnosed by pediatric neurologists. Localization-related epilepsy (LRE) and Lennox-gastaut syndrome (LGS) have been diagnosed by a pediatric neurologist on a clinical and imaging and EEG basis.

The etiology of epilepsy was categorized into structural, genetic, infectious, metabolic, immune and unknown.[8] If the patient's history or laboratory examination indicated central nervous system infection, genetic mutation or metabolic disease, the patient was categorized into

the corresponding class. If the patient had no significant history or laboratory finding but had abnormal finding in image such as brain MRI, the patient was categorized into "structural". Unknown etiology was classified when there was no identified cause of the seizure.

Candidates for VNS insertion surgery were selected among patients who failed to demonstrate seizure control after adequate treatment with AEDs regardless of the presence of a lesion, type of epilepsy, or etiology. AEDs were prescribed by pediatric neurologist and the number of AEDs were calculated on a daily basis. Surgical candidates were screened for whether they should receive resection surgery or VNS insertion surgery, and VNS insertion was performed if resection surgery was not indicated or if legal guardians preferred VNS insertion.

All VNS insertion surgeries were performed as a standard method and were performed on the left side with no exceptions.[9] Patients were discharged one day after surgery. The output current was initiated as 0.25 mA, at a frequency of 30 Hz and a width of 500 Hz 2 weeks after VNS insertion. Adjustment was performed in accordance with the guidelines of Cyberonics Inc. (Houston, TX) at the outpatient clinic.

Outcome analysis

Surgical outcomes were analyzed 6, 12 and 24 months after implant operation. A responder was defined as a patient who achieved more than a 50% reduction in seizure frequency.[10] Demographic comparison between responder and non-responders was analyzed at 12 months and 24 months after the operation. In addition, mean seizure frequency reduction of LRE and LGS was measured. AED reduction group was analyzed at first and second postoperative year regarding effects of AEDs and to find who could benefit by reducing AEDs. Mean output current was calculated for responders and non-responders.

Chi-squared tests and Fisher's exact tests were used for categorical variables, and Student's t test was applied for continuous variables. A paired T test was used for the comparison of pre- and post-insertion for each variable. P values of 0.05 or less were considered significant. IBM SPSS Statistics version 23 (Chicago, IL, USA) was used for statistical analyses.

Complications

After VNS implantation, four (9%) patients complained of hoarseness and/or cough. Symptoms were managed by output current adjustment, and all were transient. Infection occurred in three patients (6%) when

including the two patients initially excluded from the analyses because of early deep layer infection and VNS removal. The other patient could be managed by oral antibiotics without device removal.

Results

Demographic characteristics

A total of 56 patients received VNS implantation in our institution during the study period. Nine patients were excluded from the outcome analyses: two patients who had to have their devices removed immediately postoperatively due to deep layer infection, six patients who were lost to follow-up within six months, and one patient who had additional resection surgery within six months after VNS insertion. Therefore, a total of 47 consecutive patients were included until the first postoperative year. Of these, 35 patients could be included until the second year after surgery. (Figure 1)

The overall demographic characteristics are shown in table 1. The mean age at seizure onset was 6.4 years (range, 0.2–15 years), and the mean age at VNS surgery was 14.7 years (range, 5–26 years). The mean interval of epilepsy from onset to surgery was 8.3 years (range, 2–16

years). Twenty-five patients were male (53%), and 22 patients were female (47%). The mean number of preoperative AEDs was 4.2 per day (range, 1–7). The mean follow-up duration was 58.5 months (range 12–156). The mean number of AEDs was kept steady for the first year postoperatively from 4.1 per day to 4.2 per day and have increase to 4.5 per day at second postoperative year.

Response rates

At 6 months postoperatively, there were 22 patients who were responders (47%), whereas 25 patients (53%) were responders 1 year postoperatively (Figure 2). The responders increased to 63% at post-operative 2 years. When the postoperative 1 year responder was analyzed, the age at seizure onset was 6.9 years, the age at operation was 14.6 years, and the interval from epilepsy onset to surgery was 7.7 years. Mean age was similar when the postoperative 2 year responder was analyzed. There was no statistically significant difference in the demographic characteristics between the responder and non-responder. However, responders showed a tendency of later onset of seizure and a shorter interval from seizure onset to VNS implantation than non-responders.

MRI findings

Concerning pre-operative MRI findings, overall normal MRI findings accounted for 22 patients (51%), whereas focal, multifocal and diffuse lesions accounted for six (13%), seven (15%), and 12 patients (26%), respectively. Five out of six patients (83%) with a focal lesion became a responder at 1 year postoperatively, whereas three out of seven patients with multifocal (43%) and five out of 12 patients with diffuse lesions (42%) became responders at post-operative 1 year. (Table 1-1)

There was no significant difference when analyzing responders at postoperative 2 year. Twelve, five, six, nine patients with normal, focal, multifocal and diffuse lesions, were included in the post-operative 2 year analysis. As a result, 10 patients with normal MRI, four patient with focal lesion, three patients with multifocal lesion and five patients with diffuse lesion became responders. (Table 1-2)

Seizure semiology

Hypomotor, tonic-clonic and tonic seizures made up the most of seizure semiology. (Table 1-1, 1-2) One year postoperative analysis yielded statistically significant results, five of 16 hypomotor seizures, 10 of 14 tonic-clonic seizures and half (4/8, 50%) of tonic seizures became

responders. (p=0.028) In the post-operation 2 year analysis, hypomotor seizures tend to have more portion of responders compare to post-operation 1 year analysis (7/11, 64%), whereas tonic-clonic seizures showed decreased portion of responders (7/13, 54%).

EEG findings

Thirty-six patients showed focal onset epilepsy on pre-operative EEG whereas seven patients showed generalized onset epilepsy and two patients showed focal & generalized or normal EEG findings, respectively. Four out of 7 (57%) generalized seizure patients and 19 out of 36 (53%) focal seizure patients showed a response at postoperative 1 year, respectively. Twenty eight patients of focal EEG findings were included in the post-operative 2 year analysis, and 18 patients became responders. However, neither post-operation 1 nor 2 year analysis showed significant result.

Etiology

Regarding overall etiology, nine patients (19%) had structural lesions, five patients (11%) had genetic backgrounds such as SCN1A mutations or ATP1A3 mutations, nine patients had histories of central nervous system infections (19%), one patient (2%) had a lesion due to metabolic causes,

and one patient had a lesion due to immune causes. Six out of nine (67%) patients with a history of infection, and one out of four patients with a history of trauma had a response to VNS according to the etiology. Half of the patients with metabolic and genetic backgrounds were responders. Although both post-operative 1 and 2 year analysis did not yield significant result, which is probably due to small number of patients with known etiology, patients who had infection history constantly showed higher response rate compare to the others.

History of prior epilepsy surgery

Seven patients (15%) received resection or disconnection surgery prior to VNS implantation, and those were two temporal lobectomies, two total callosotomies, two focal cortical dysplasia removals, and one tumor (pleomorphic xanthoastrocytoma) removal. Three of five (60%) patients with a history of resection became responders at post-operative 1 year analysis. Post-operative 2 year analysis showed similar results. (Table 1-1, 1-2)

Mean seizure reduction rate

The overall mean seizure frequency was reduced from 8.0 per week to 5.1 per week at post-operative 1 year (36%, p=0.006, Figure 2) and

to 4.3 per week at post-operative 2 year (46%, p=0.025), showing increased efficacy over time. The mean seizure frequency reduction rate was analyzed for the same variables used for analyses of ≥50% responders (Table 2). Of all variables, focal onset epilepsy on EEG and no prior surgery was statistically significant for the reduction in the frequency of seizures in both the first and second years after the operation. In addition, patients with infectious etiology had significant reduction rate at 2 years after operation.

Patients with focal onset epilepsy on EEG had 7.5 seizures per week preoperatively, which was reduced to 5.1 seizures per week (32%, p=0.009) at post-operative 1 year and to 3.7 seizures per week (51%, p=0.001) at post-operative 2 year. Likewise, the seizure frequency reduction rate was 43% (p=0.006) and 46% (p=0.037) at post-operative 1 and 2 year in patients who had not undergone previous resection. Patients with infectious etiology had mean reduction rate of 69%. (p=0.026)

Mean seizure frequency reduction of LRE and LGS was separately analyzed. (Table 3) LRE showed reduction in seizure frequency but LGS did not. The reason why LGS did not achieve significant result is maybe

due to the small number of patients (n=5), considering that the LGS is one of the indications of VNS.

AED reduction

AED reduction rate also have increased over time. Nine percent (n=7) were able to reduce their AEDs by a mean of 1.4 AED per patient at the first year after operation. At post-operative 2 year, 11% of patients achieved to decreased their AEDs (n=4). The characteristics and comparisons of AED reduction and non-reduction groups are shown in table 3. The AED reduction group demonstrated a shorter mean interval from epilepsy onset to operation than the non-reduction group. However, no statistical significance was obtained for the factors.

Output current

Output current parameters of responders at post-operative 6 months, 1 year and 2 years are shown in the table 5. Output current increased over time. Output current of responders increased from 1.56 mA to 1.93 mA and 2.18 mA at post-operative 6 months, 1 year and 2 years whereas output current of non-responders was changed from 1.66 mA to 2.15 mA and 2.50 mA during the corresponding period.

Battery change

The VNS battery was discharged in ten patients. The patients were consulted as to whether to maintain the VNS. Seven patients chose to keep their VNS treatment and underwent a battery change. One of the three patients who decided to discontinue VNS treatment remained in a seizure-free state for four years. The other two patients had minimal responses.

Discussion

The concept of stimulating the vagus nerve electronically to control seizures dates back to the late 19th century. It took nearly a century thereafter for the medical society to accept clinical application of the concept. The prototype of the currently used VNS device appeared in 1987, and the first human insertion of the device was performed in 1988.[11] Numerous papers thereafter have reported that the outcome of VNS shares a common result with a ≥50% reduction rate in approximately 50% of patients.[12] The results seem to be similar in children.[13] In addition, the proportion of responders correspondingly increased as the follow-up duration increased.[14, 15] This is in line with our result, which

also showed an increase from 47% to 53% and 63% of responders at postoperative 6 months, 1 and 2 years, respectively.

Previous surveys have attempted to document predictors of outcome regarding various variables such as age and seizure type. However, the results differ across papers. VNS has been shown to be effective in intractable focal onset epilepsy, generalized onset epilepsy, and epileptic syndromes such as LGS and Rett syndrome.[13, 16, 17] Studies in children with a mean age of 11.1 years old showed a reduction rate of 59% with a mean duration of VNS therapy of 5.2 years.[14] Because of the broad indications for and unknown mechanism of VNS, a predictor of better outcome has been an issue.

Age at implantation, duration from onset to implantation and seizure types have been repeatedly presented as predictors of favorable outcomes in VNS. Ghaemi et al. reported that younger age at implantation was associated with better outcomes. [18] A shorter duration of epilepsy was also reported as a factor for a favorable outcome.[19] Conflicting results coexist, however, such that older age at implantation and a longer duration of epilepsy are beneficial. [20] In our study, there was no statistically significant predictor of outcome in the ≥ 50% responder

analysis except for seizure semiology of post-operative 1 year analysis. However, seizure semiology was no longer a significant factor until the post-operative 2 year analysis despite the result was similar to previous papers. [21] Several studies also could not determine the predictors of outcome based on demographic characteristics, or seizure semiology. [22-24] This is probably due to the ambiguous mechanism of VNS and widespread projection fibers of the nucleus solitarius tract, which is a transfer center of the vagus nerve.[25] Variable mechanisms have been proposed for VNS, such as cerebral blood flow changes, increases in neurotransmitters, and effects of inflammation.[26-29] In other words, no one particular factor seems to explain the mechanism.

In contrast to the responder analysis, analysis of the mean seizure reduction frequency yielded some statistically significant factors. Our overall seizure frequency reduction rate was in line with a meta-analysis of 1,798 patients that showed a seizure reduction rate of 36.2% (range, 3–12 months) after surgery.[13] In addition, our results showed a statistically significant mean reduction rate for focal onset epilepsy on EEG. This corresponds to the US FDA opinion that VNS is approved for focal seizures.[4, 30]

One interesting finding in our study is that patients with no history of resection or disconnection surgery had a significant reduction rate of, whereas patients with the history showed minimal effects. VNS implantation with such a history was done because of seizure recurrences. Amar et al. reported the outcome of VNS after failed cranial surgery for epilepsy, and patients with a history of failed cranial surgery had a lower response rate compared to patients without prior epilepsy surgery.[31] The factors of failure were physiological and anatomic limitations, such as the presence of an eloquent cortex or the improper identification of true lesions.[31]

One other interesting result is that patients with infectious etiology had significant seizure reduction rate of 69% at post-operative 2 year. All of our infectious etiology patients were post-viral encephalitis, which are known to cause chronic epilepsy.[32] One of the causes of chronic drug-resistance epilepsy after encephalitis is pro-inflammatory mediators produced by activated microglia.[33] In addition, cytokines such as TNF-α is known to promote astrocytic glutamate release contributing to seizures.[33] Regarding that VNS mediates neuro-inflammation, the patients might benefited from the effect. Further study is mandatory.[34]

Previous papers have reported VNS in relation to AED reduction. One study reported that AED reduction occurred in 43% of VNS patients, with an average of 0.43 AEDs per patient.[35] AED reduction is especially important in pediatrics, considering the adverse effects of long-term use. Prolonged use of AEDs is well known to result in cognitive and psychological dysfunction.[36, 37] The characteristics of the reduction group in our study correspond to other analyses in terms of a shorter interval and focal onset epilepsy in EEG.

Interestingly, output current was lower in the responder group. This is may be because responders initially achieved seizure frequency reduction at the lower output current whereas non-responders had to increase the output current until either seizure frequency reduction or adverse effects such as neck pain or sore throat occurred. In other words, predisposing factors of patients are may be more important than output current.

It is intriguing that 70% of patients chose to maintain their therapy by changing batteries. The reasons for the decision were improved alertness, decreased seizure intensity, and overall improvements in quality of life. One patient had improvements in subjective cognitive function

rather than seizure control and chose to maintain the treatment. This implies that indications of VNS are not limited to epilepsy but can be applied to other conditions. To date, VNS has been suggested to show improvements in alertness and depression.[15, 38]

There are some limitations to our study. First, this was a retrospective study with a relatively small number of patients enrolled. Second, seizure outcome could be affected by various other factors, especially changes in AED doses. However, the study focused purely on children with intractable epilepsy. To overcome the low statistical power, we added an analysis of mean seizure frequency reduction to compensate for the ≥50% response criteria.

Conclusion

VNS is a palliative treatment, and various predictors of outcome are still under debate. Considering that VNS is not a curative treatment, selecting patients who will benefit from the treatment is important.

Based on a low morbidity rate and relatively easy procedure for neurosurgeons to perform, VNS could be a promising option for pediatric intractable epilepsy, especially for focal epilepsy patients who carry risks

of undergoing resection or disconnection epilepsy surgery for various reasons, such as an ictal zone in eloquent areas and for patients with infectious etiology. Moreover, patients may also benefit from reducing AEDs in addition to seizure reduction regarding the consensus that the efficacy of VNS increases over time. For pediatric candidates, it is advisable to perform VNS insertion sooner to maximize the efficacy of VNS and to prevent side effects of long-term AED use.

In conclusion, patients with intractable epilepsy who have focal lesions on EEG in eloquent areas, who have lesions that are not removable could be a good candidates for VNS. Furthermore, VNS may also be a good option for patients who have history of infection.

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Figure legends

Figure 1.

Flow chart of patients included in the study. Among 56 patients who underwent VNS insertion, a total of 47 patients and 35 patients were enrolled in the study at post-operative 1 year and at post-operative 2 years analysis.

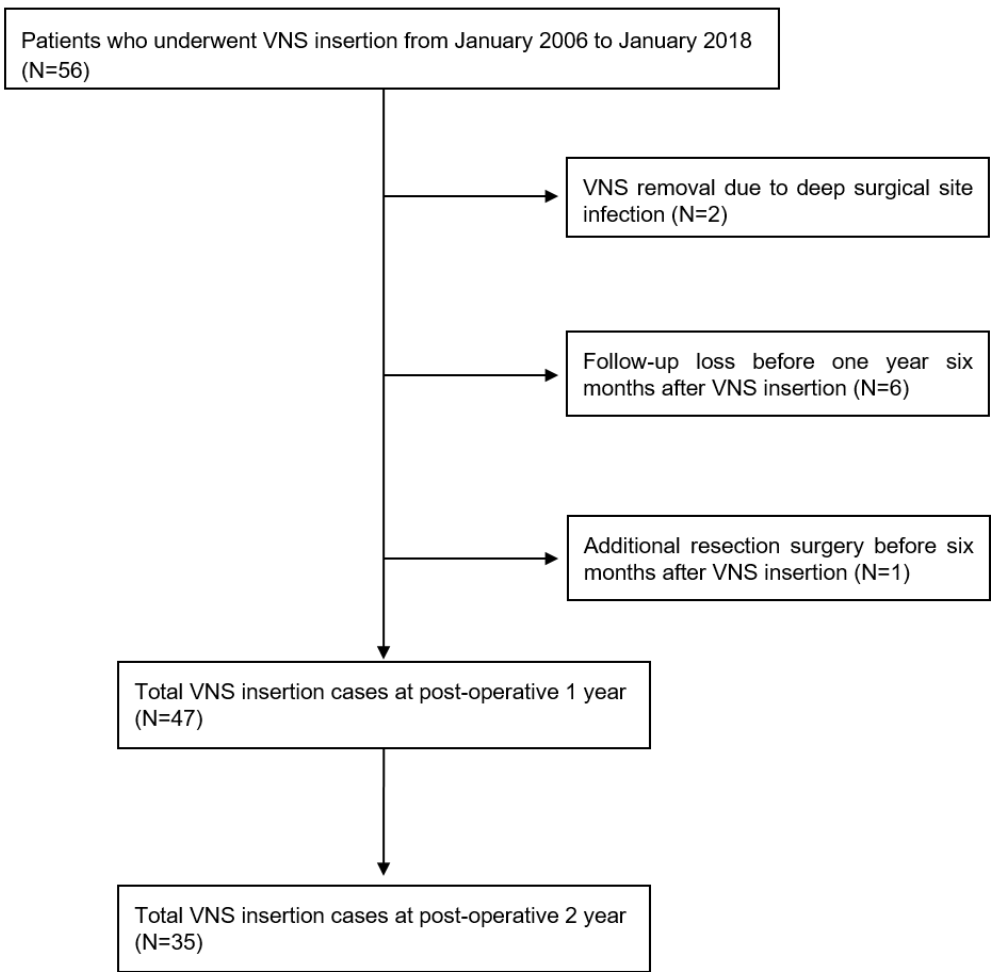

Figure 2.
Graph showing reductions and seizure frequency changes during the follow-up period. The left Y-axis is the mean seizure frequency, and the right Y-axis is the percentage of the responder.

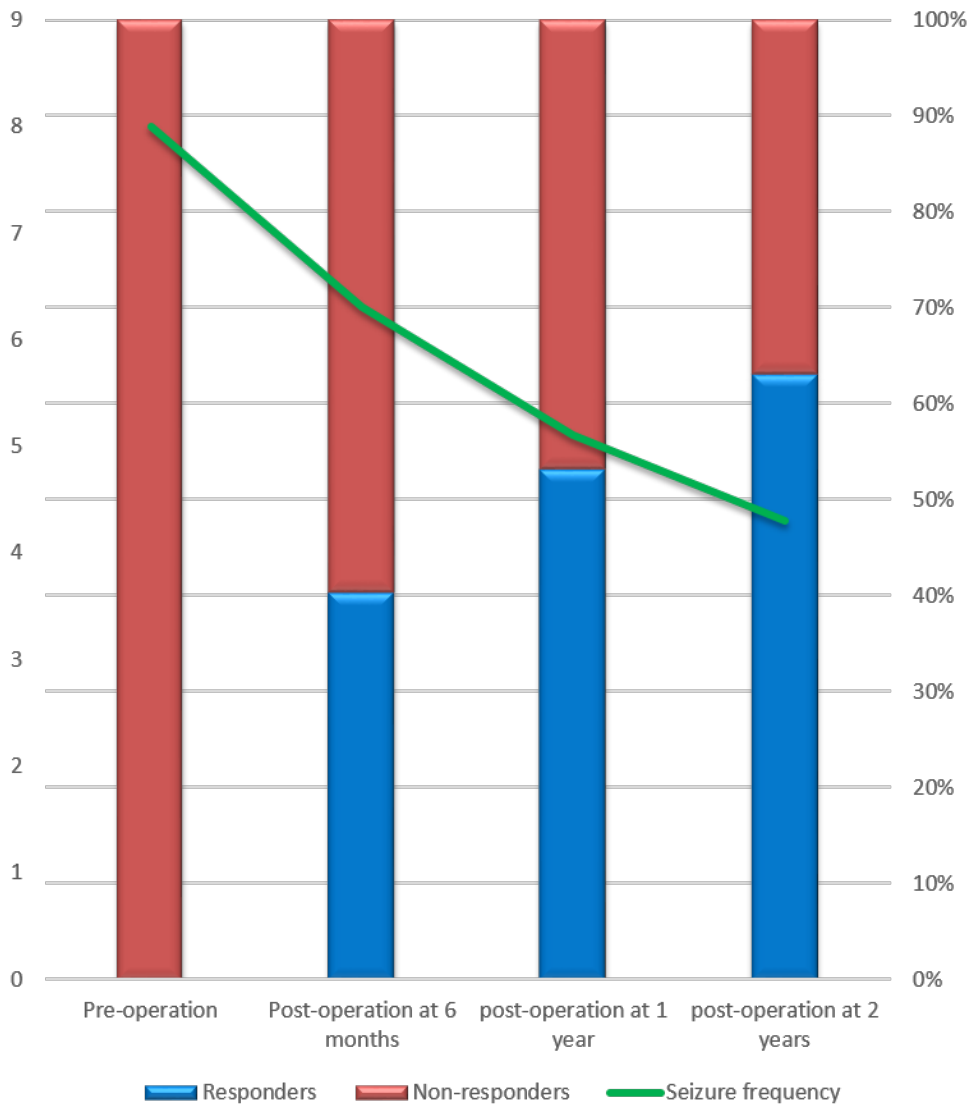

Table 1-1. Demographic characteristics of responders at postoperative 1 year and non-responders.

Variable	Total (N=47)	Responder (N=25)	Non-responder (N=22)	P-value
Mean age, years ± SD				
At epilepsy onset	6.4±4.2	6.9±4.2	5.8±4.1	.330
At implantation	14.7±5.7	14.6±5.1	14.7±6.4	.959
Interval from epilepsy onset to implantation	8.3±5.4	7.7±4.3	9.1±6.4	.391
Sex				.861
Male	25	13	12	
Female	22	12	10	
Mean number of preop. seizure medication ± SD	4.2±1.3	4.2±1.5	4.1±1.0	.949
Mean seizure frequency	8.0±9.0	8.6±9.6	7.4±8.3	.631
MRI finding (%)				.387
Normal	22	12	10	
Focal lesion	6	5	1	
Multifocal lesion	7	3	4	
Diffuse lesion	12	5	7	
Seizure semiology				.028
Hypomotor	16	5	11	
Hypermotor	2	2	0	
Tonic	8	4	4	
Clonic	2	0	2	
Automotor	2	2	0	
Atonic	1	0	1	
Dialeptic	1	1	0	
Tonic-clonic	14	10	4	
Spasm	1	1	0	
Type of epilepsy by EEG finding				.157
Focal onset	36	19	17	
Generalized onset	7	4	3	
Focal & generalized onset	2	0	2	
Normal	2	2	0	
Known etiology				.649
Structural	7	2	5	
Genetic	5	3	2	
Infectious	9	6	3	
Metabolic	1	0	1	
Immune	1	1	0	
Previous operation				.291
None	40	22	18	
Resection surgery	5	3	2	
Callosotomy	2	0	2	

Table 1-2. Demographic characteristics of responders at postoperative 2 years and non-responders.

Variable	Total (N=35)	Responder (N=22)	Non-responder (N=13)	P-value
Mean age, years ± SD				
At epilepsy onset	6.5±4.0	7.0±4.0	5.7±4.3	.382
At implantation	14.8±5.6	14.8±4.5	14.9±7.2	.947
Interval from epilepsy onset to implantation	8.3±4.5	7.8±4.7	9.2±4.4	.375
Sex				.358
Male	15	10	5	
Female	20	12	8	
Mean number of preop. seizure medication ± SD	4.1±1.3	4.3±1.4	3.9±1.1	.356
Mean seizure frequency	6.6±7.2	6.2±6.4	7.4±8.6	.631
MRI finding (%)				.464
Normal	15	10	5	
Focal lesion	5	4	1	
Multifocal lesion	6	3	3	
Diffuse lesion	9	5	4	
Seizure semiology				.298
Hypomotor	11	7	4	
Hypermotor	2	2	0	
Tonic	4	3	1	
Clonic	2	2	0	
Automotor	1	0	1	
Atonic	1	1	0	
Dialeptic	1	0	1	
Tonic-clonic	13	7	6	
Spasm	1	0	1	
Type of epilepsy by EEG finding				.934
Focal onset	28	18	10	
Generalized onset	3	2	1	
Focal & generalized onset	2	1	1	
Normal	2	1	1	
Known etiology				.720
Structural	5	4	1	
Genetic	3	1	2	
Infectious	6	5	1	
Metabolic	1	0	1	
Immune	1	1	0	
Previous operation				.343
None	30	18	12	
Resection surgery	4	3	1	
Callosotomy	1	1	0	

Table 2-1. Mean seizure frequency reduction per week at post-operative 1 year.

Variable	Pre-implantation	1 year post-implantation	Mean reduction rate (%)	P-value
Mean seizure frequency ± SD	8.0 ± 8.9	5.1±6.6	36	.006
MRI finding				.
Normal	6.6±8.3	5.3±6.9	20	.274
Focal lesion	7.9±8.0	4.4±4.4	44	.305
Multifocal lesion	11.6±7.5	7.0±7.7	40	.085
Diffuse lesion	8.6±11.5	4.0±6.8	53	.119
Type of epilepsy by EEG finding				
Focal onset	7.5±7.9	5.1±7.2	32	.009
Generalized onset	14.5±12.8	7.8±9.3	46	.086
Focal & generalized onset	2.5±0.7	8.8±2.5	-352	.220
Normal	0.3±0.0	0.1±0.1	67	.156
Known etiology				
Structural	9.9±10.7	7.6±11.7	23	.158
Genetic	7.8±9.3	4.6±5.9	41	.306
Infectious	2.9±4.3	2.8±4.7	3	.723
Metabolic	3	1		-
Immune	21	21		-
Previous operation				
None	8.0±8.7	4.6±5.4	43	.006
Lesionectomy	11.5±12.4	11.3±12.6	2	.284
Callosotomy	0.6±0.2	1.0±0.0	-40	.205

Table 2-2. Mean seizure frequency reduction per week at post-operative 2years.

Variable	Pre-implantation	2 years post-implantation	Mean reduction rate (%)	P-value
Mean seizure frequency ± SD	8.0 ± 8.9	4.3±5.9	46	.025
MRI finding				.
Normal	6.6±8.3	4.2±6.3	36	.807
Focal lesion	7.9±8.0	4.1±3.0	48	.141
Multifocal lesion	11.6±7.5	6.8±8.6	41	.080
Diffuse lesion	8.6±11.5	3.0±4.7	65	.116
Type of epilepsy by EEG finding				
Focal onset	7.5±7.9	3.7±5.3	51	.001
Generalized onset	14.5±12.8	9.8±10.0	32	.285
Focal & generalized onset	2.5±0.7	8.8±7.4	-420	.180
Normal	0.3±0.0	0.3±0.0	0	1.000
Known etiology				
Structural	9.9±10.7	4.5±6.1	55	.138
Genetic	7.8±9.3	5.8±7.3	26	.317
Infectious	2.9±4.3	0.9±1.1	69	.026
Metabolic	3	1.5		-
Immune	21	21		-
Previous operation				
None	8.0±8.7	4.3±6.0	46	.037
Lesionectomy	11.5±12.4	3.6±6.9	69	.109
Callosotomy	0.6±0.2	7	-107	-

Table 3. Mean seizure frequency reduction of LRE and LGS.

Variable	Pre-operation	6 months post-operation	1 year post-operation	2 years post-operation	P-value
LRE (n=30)	5.3±5.8	3.8±4.5	3.5±4.5	3.1±4.2	.076
LGS (n=5)	8.3±8.8	6.8±6.6	8.8±8.6	9.1±6.1	.715

Table 4-1. Comparison between anti-epilepsy drug reduction group and non-reduction group at 1year post-operation

Variable	Reduction (N=7)	Non-reduction (N=40)	P-value
Mean age, years ± SD			
At epilepsy onset	8.3±5.0	6.1±4.0	.194
At Op.	14.4±5.0	14.8±5.9	.901
Interval from epilepsy onset to operation	6.1±4.4	8.7±5.5	.247
Sex			.690
Male	3	18	
Female	4	22	
MRI finding			.454
Normal	4	18	
Focal lesion	1	5	
Multifocal lesion	1	6	
Diffuse lesion	1	11	
Type of epilepsy by EEG finding			.639
Focal onset	5	31	
Generalized onset	2	5	
Focal & generalized onset	0	2	
Normal	0	2	
Etiology			.750
Structural	1	6	
Genetic	1	4	
Infectious	3	6	
Metabolic	0	1	
Immune	0	1	
Unknown	2	22	

Table 4-2. Comparison between anti-epilepsy drug reduction group and non-reduction group at 2 years post-operation

Variable	Reduction (N=4)	Non-reduction (N=31)	P-value
Mean age, years ± SD			
At epilepsy onset	6.0±3.6	6.6±4.2	.794
At Op.	14.0±3.7	14.9±5.8	.758
Interval from epilepsy onset to operation	8.0±5.4	8.4±4.5	.905
Sex			.603
Male	3	15	
Female	1	16	
MRI finding			.990
Normal	2	13	
Focal lesion	0	5	
Multifocal lesion	1	5	
Diffuse lesion	1	8	
Type of epilepsy by EEG finding			.639
Focal onset	3	25	
Generalized onset	1	2	
Focal & generalized onset	0	2	
Normal	0	2	
Etiology			.725
Structural	1	4	
Genetic	1	5	
Infectious	0	3	
Metabolic	0	1	
Immune	0	1	
Unknown	2	17	

Table 5. Output current parameters of responders at post-operative 6 months, 1 year and 2 years.

Post-operation	Mean output current (mA)	P-value
6months		.640
Responders	1.56	
Non-responders	1.66	
1 year		.338
Responders	1.93	
Non-responders	2.15	
2 year		.283
Responders	2.18	
Non-responders	2.50	

국문초록

미주신경자극술은 난치성 뇌전증의 고식적 치료법이다. 그간의 많은 연구로 미주신경자극술의 치료 성적은 어느 정도 알려져 있지만, 다양한 요인에 따른 개별적인 경련의 감소율은 명확하게 보고되지 않았다. 따라서 본 연구는 소아청소년환자에서 미주신경자극술의 경련 감소 예측인자와 여러 인자에 따른 경련 감소율을 보고자 하였다. 우리는 우리 기관에서 미주신경자극술을 시행 받은 소아청소년환자들을 후향적으로 검토했으며 수술 후 6 개월, 1 년, 2 년 결과를 분석했다. 나이, 성별, 뇌전증의 이환 기간, 뇌전증의 종류, MRI 소견, 뇌파 소견, 병인, 자극 강도 등에 따른 경련 감소 효과를 분석하였다. 그 결과 경련이 처음 시작했을 때의 평균 연령은 6.4 세(범위 0.2-15 세) 였고 미주신경자극술을 시행 받을 당시의 평균 연령은 14.7 세(범위 5-26 세)이었다. 뇌전증 시작부터 수술까지 걸린 평균 기간은 8.3 년(범위 2-16 년)이었다. 수술 전과 비교하여 경련의 발생 빈도가 50% 이상 감소한 환자들이 수술 후 6 개월, 1 년, 2 년 시 각각 22/47 명(47%), 25/47 명(53%), 22/35 명(63%) 였다. 평균 경련의 빈도는 수술 전에 비해 수술 후 1 년, 2 년 후 각각 주당 8.0 회에서 5.1 회, 4.3 회로 줄었다. 요인에 따른 감소율을 분석하였을

때, 수술 2 년 후 뇌파검사(EEG)상 국소 경련을 보인 환자 군에서 51%(p=0.009)의 경련 감소율을 보였다. 그리고 미주신경자극술 전에 뇌전증에 대해서 절제 수술을 받지 않은 환자들에서는 43%(p=0.037)의 경련 감소율을 보였다. 또한 감염성 병인을 가진 환자들에서는 수술 2 년 후 69%의 경련 감소율을 보였다. (p=0.026) 따라서, 뇌전증 발생 병소가 기능성 뇌피질에 위치하여 절제술 후 신경학적 장애가 예상되는 경우 혹은 뇌전증 발생병소가 다발성인 경우 그리고 감염의 병인이 있는 소아청소년 뇌전증 환자들에게 미주신경자극술은 좋은 치료 대안이 될 수 있을 것으로 보인다.

Key words: 미주신경자극술; 뇌전증; 난치성; 소아청소년

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