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Outcomes of Therapeutic Modalities for Intractable Childhood Epilepsy

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= **국문요약** =

난치성 소아 간질에서 치료 방법에 따른 성적

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목 적: 난치성 소아 간질 치료를 위해, 최근 개발된 항간질 약물, 프레드니솔론, 케톤생성 식이요법, 간질수술, 미주신경자극술의 임상적 결과를 평가하였다.

방 법: 1995년 7월부터 2003년 4월까지 상계백병원 간질센터에서 치료한 난치성 간질 환아 297명의 임상 결과를 후향적으로 분석하였다.

결 과: 최근 개발된 항간질 약물이 투여된 290명 환아에서 20명(6.9%)에서만 추적 관찰 기간 중 간질 완해를 유지하였다. 프레드니솔론을 투여한 138명 환아에서 58명(42.0%)에서 약물 투여 중 간질 완해를 보였으나, 41명 환아에서 약물 중단 후 재발되었다. 케톤생성 식이요법은 162명에서 시도되어 74명(45.7%)에서 12개월 이상 식이요법을 유지하였으며, 간질 완해를 보인 37명(22.8%)을 포함하여 68명(42.0%)에서 50% 이상의 간질 횟수의 감소를 보였다. 간질 수술은 38명에서 시행되었으면 25명(65.8%)에서 Engel 구분 I을 보였다. 미주신경자극술은 5명 환아에서 시행되어 2명에서만 50% 이상의 간질 횟수 감소를 보였다.

결 론: 케톤생성 식이요법과 간질수술은 난치성 소아 간질 치료에 상당히 효과적인 치료였으나 프레드니솔론은 잦은 재발을 보였고 새로 개발된 항간질 약물은 난치성 간질의 완해를 유지함에 있어 한계가 있었다.

Key Words: Intractable childhood epilepsy, Anti-epileptic drugs, Prednisolone, Ketogenic diet, Epilepsy surgery, Vagus nerve stimulation

Introduction

The therapeutic goal in cases of childhood epilepsy is to control the seizures and resume developmental progression[1]. To this end, the intractability should be controlled as soon as possible through various evidence-based therapeutic modalities. Fortunately, many anti-epileptic drugs (AEDs) that act by various mechanisms have been developed[2]. Moreover, ketogenic diet (KD)[3], rapidly-advancing surgical

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techniques, and other tools including functional neuroimaging and magnetoencephalography for localization of the epileptic focus and eloquent area[4] as well as recently-approved vagus nerve stimulation (VNS)[5] can now be used to manage intractable childhood epilepsy.

Pediatric epilepsiologists now find themselves with more diverse therapeutic modalities than were possible in the past, and there is a growing body of literature on the outcomes of these various modalities. Yet there is no consensus on when each option should be exercised[6]. The present study is intended to provide such guidance by reviewing the authors' experiences in the management of intractable childhood epilepsy.

Materials and Methods

The present analysis consisted of a clinical retrospective study of the treatments performed during 7 years and 6 months from October 1995 to April 2003, at the epilepsy center of Sang-gye Paik Hospital. All the subjects had experienced more than four seizures per month that had not been relieved by combinations of two or more conventional AEDs such as sodium valproate, carbamazepine, phenobarbital, phenytoin, and ethosuximide. The included patients were those who had been followed up at least six months after the administration of the last therapeutic modality for any types of childhood epilepsy or epileptic syndrome. According to the evidence-based guidelines of our epilepsy center (Fig. 1A, 1B), therapeutic modalities such as newly-developed AEDs, prednisolone, KD, epilepsy surgery, and VNS were tried.

Newly-developed AEDs approved in our country include topiramate, lamotrigine, vigabatrin, zonisamide, oxcarbazepine, and gabapentine, and these were prescribed in addition to conventional AEDs as indicated except for seven patients with Sturge-Weber syndrome, brain tumors, and hippocampal sclerosis. Vigabatrin and oxcarbazepine were also prescribed as the first choice (vigabatrin for West syndrome and oxcarbazepine for localized epilepsies), with these patients being excluded from the data of newly-developed AEDs. Among intractable generalized epilepsies and epileptic syndromes, cryptogenic patients with no evidence of abnormal magnetic resonance imaging (MRI) findings or laboratory screenings for underlying metabolic diseases were primarily given prednisolone at doses of 1 to 2 mg/kg/day for six weeks followed by tapering over two weeks.

The primary recommendation for symptomatic patients with destructive lesions or non-localized malformations of cortical development (MCDs) was KD. Eighty-seven patients were treated with the Hopkins protocol[7], while the remainder underwent a revised protocol without initial fasting and fluid restriction. All the patients received the classic KD with a lipid to non-lipid ratio of 4 : 1. In order to prevent various complications that have been reported in conjunction with KD, multivitamins, calcium of 30 mg/kg/day, and vitamin D2 of 40 IU/kg/day were given as supplements to the diet throughout its course. L-Carnitine of 66 mg/kg/day was also added to the diets of 159 patients since 1998. AEDs except acetazolamide were maintained at the same doses, although the formulas were changed to contain as little carbohydrate as possible.

For intractable localized epilepsies, surgical

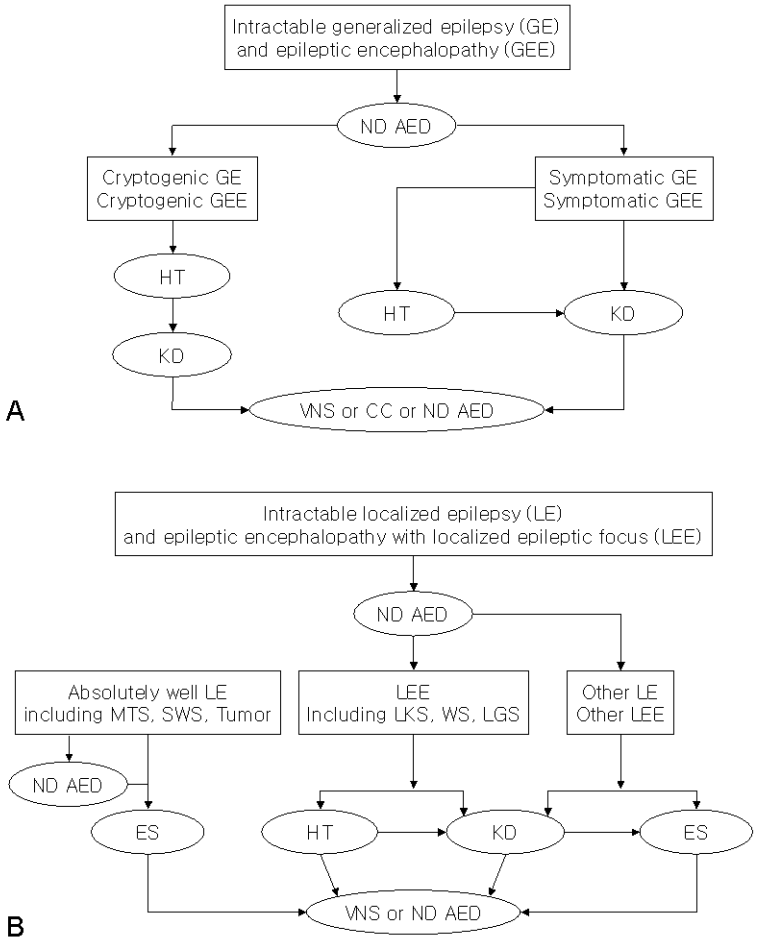

Fig. 1. Therapeutic algorithms for intractable childhood epilepsy at the epilepsy center of Sang-gye Paik Hospital(ND AED : newly developed antiepileptic drug, HT : prednisolone, KD : ketogenic diet, ES : epilepsy surgery, VNS : vagus nerve stimulation, CC : corpus callosotomy, MTS : mesial temporal sclerosis, SWS : Sturge-Weber syndrome, WS : West syndrome, LGS : Lennox-Gastaut syndrome).

treatment was the primary recommendation in patients with Sturge-Weber syndrome, brain tumors, and hippocampal sclerosis. Epilepsy surgery was also considered for West syndrome and Lennox-Gastaut syndrome (LGS) with localized epileptic foci, but prednisolone and/or KD were attempted initially in these cases. Most parents, especially in the oriental culture, resist neurosurgical therapy, and when the parents indeed refused epilepsy surgery, KD was tried first. VNS and palliative surgery, including multiple subpial transection and corpus callosotomy, were considered as last resorts.

The outcomes of individual therapeutic modalities were analyzed according to the seizure diaries of the parents and medical records, with omitted data recollected by telephone inquiry. The SPSS (version 7.0) program for statistical analyses was used for the two-tailed

Student's t-test and binary logistic regression for the evaluation of the significance of differences of multiple variables about the responses to and prognosis after the completion of the KD. A P value <0.05 was regarded as statistically significant.

Results

1. Patient characteristics

The 297 patients included 122 males and 175 females. Seizure onset ranged from one month to 14 years and 8 months (mean±SD, 23.9±33.6 months) and the duration of seizures from eight months to 18 years and 11 months (mean±SD, 66.2±42.5 months). Follow-ups in all the cases were conducted for at least six months after the administration of the final therapeutic modalities (Table 1). Classifications of the epilepsies and epileptic syndromes are presented in Table 1, with the most common diagnoses being LGS (84 patients, 28.3%) and West syndrome (24 patients, 8.1%).

Underlying etiologies were identified through extensive studies that included advanced neuroimaging, laboratory screening tests for metabolic diseases, and, if indicated, muscle biopsy and enzyme analysis. One hundred patients (33.7%) with no evidence of underlying causes were classified as the cryptogenic group. The remaining patients had one or more possible underlying causes of epilepsies, as presented in Table 2.

The most common treatment modality, applied to 290 patients (97.6%) characterized by intractable epilepsies, was newly-developed AEDs, including topiramate, lamotrigine, vigabatrin, zonisamide, oxcarbazepine, gabapentine. In a decreasing order of application, other treatments included KD (162 patients, 54.5%), prednisolone (138 patients, 46.1%), epilepsy surgery (38 patients, 12.8%), and VNS (5 patients, 1.7%) (Fig. 1A, 1B).

Table 1. Patient Characteristics

Male : Female	122 : 175
Age at initial seizure	1 mo-14 yr-8 mo (mean±SD, 23.9±33.6 mo)
Duration of seizures	8 mo-18 yr-11 mo (mean±SD, 66.2±42.5 mo)
Follow-up duration*	6 mo-7 yr-4 mo (mean±SD, 45.7±22.6 mo)
	No. of patients (%)
Classification of epilepsies	
West syndrome	77 (25.9)
Lennox-Gastaut syndrome	84 (28.3)
Severe myoclonic epilepsy in infancy	21 (7.1)
Landau-Kleffner syndrome	9 (3.0)
Otahara syndrome	4 (1.3)
Doose syndrome	4 (1.3)
Periodic spasm	1 (0.3)
Other non-specified epilepsies	
Generalized seizures	19 (6.3)
Partial seizures	78 (26.2)

*Since the last therapeutic modality was applied

Table 2. Classification according to Underlying Etiologies

Etiology	No. of patients (%)
Cryptogenic	100 (33.7)
Symptomatic	197 (66.3)
Destructive lesion	79 (26.6)
Suspicious inherited metabolic disease	50 (16.8)
Mitochondrial cytopathy	11 (3.7)
Malformations of cortical development	48 (16.2)
Genetic disorder	7 (2.4)
Tumor	2 (0.7)
Total	297 (100.0)

2. Anti-epileptic drugs and prednisolone

37 out of 290 patients (12.8%) achieved complete seizure control by the addition of newly-developed AEDs to their primary conventional medications for more than six months. However, only 20 patients (6.9%) maintained the seizure-free state until the last follow-up date (mean±SD, 28.2±19.0 months). Seizure outcomes for the treatment with newly-developed AEDs are presented in Table 3.

Among 138 patients who were prescribed prednisolone, 58 patients (42.0%) were seizure free while on the medication, but 41 of these patients showed relapse during tapering or after the discontinuation of the drug. Only 17 patients (12.3%) maintained a seizure-free state until the last follow-up date (mean±SD, 19.7±11.3 months). Seizure outcomes for the prednisolone treatment are presented in Table 4.

3. Ketogenic diet

KD was applied to 162 patients (54.5%), regardless of the types of epilepsies or their etiologies, and was monitored over 12 months.

Table 3. Outcomes of Newly-Developed Anti-Epileptic Drugs

No. of patients (%)	290/297 (97.6)
Seizure free for at least 6 months	37 (12.5)
Seizure free until last follow up	20 (6.7)
Follow up duration after seizure free state	6-74 mo (mean±SD, 28.2±19.0 mo)
Epilepsy classification*	
West syndrome	3/77 (3.9)
Lennox-Gastaut syndrome	7/84 (8.3)
Doose syndrome	2/4 (50)
Non-specified generalized seizures	4/19 (21.1)
Non-specified partial seizures	4/78 (5.1)

*Of patients who showed seizure free until to last follow up

The effects of KD on seizure frequency are summarized in Table 5. At 12 months, 74 patients (45.7%) remained on the diet, and 68 patients (42.0%) showed a seizure reduction of 50% or more, including 37 patients (22.8%) who were seizure free. Looking at the specific epilepsy classifications, two of the four patients with Landau-Kleffner syndrome showed not only a seizure-free state, but also improvement of expressive and receptive aphasia.

One particularly successful application of KD occurred to a patient with Landau-Kleffner syndrome combined with mitochondrial complex I defect (below one standard deviation of the mean), who had never previously enjoyed any seizure relief from newly-developed AEDs, prednisolone, or intravenous immunoglobulin. In this case, KD was cautiously tried with a mitochondrial cocktail therapy that included CoQ-10 of 5 mg/kg/day, L-Carnitine of 66 mg/kg/day, rivoflavin of 5 mg/kg/day, and supplementary multivitamins. The patient exhibited a seizure-free state and normal EEG findings

Table 4. Outcomes of Prednisolone Therapy

No. of patients (%)	138/297 (46.1)
Age that prednisolone was prescribed	3 mo-16 yr-7 mo (mean±SD, 46.4±43.4 mo)
Duration of follow up after discontinuation	6-38 mo (mean±SD, 19.7±11.3 mo)
No. of patients seizure free (%)	17*/58†/138‡ (12.3*/42.0†)
West syndrome	11/31/60 (18.3/51.7)
Lennox-Gastaut syndrome	5/24/47 (10.6/51.1)
Landau-Kleffner syndrome	0/0/4
Severe myoclonic epilepsy in infancy	0/0/3
Doose syndrome	1/2/2 (50.0/100.0)
Early infantile epileptic encephalopathy	0/0/1
Periodic spasms	0/0/1
Non-specified generalize seizure	0/1/6 (0/16.7)
Non-specified partial seizure	0/1/14 (0/7.1)

*No. of patients who maintained a seizure-free state after the discontinuation of prednisolone, †No. of seizure-free patients, ‡No. of patients to whom prednisolone was prescribed

Table 5. Outcomes of Ketogenic Diet

Total (n=162)	Maintenance (%)	Seizure-free (%)	>50% (%)	<50% (%)
3 months	142 (87.7)	54 (33.3)	45 (27.8)	43 (26.5)
6 months	111 (68.5)	48 (29.6)	44 (27.2)	19 (11.7)
12 months	74 (45.7)	37 (22.8)	31 (19.2)	6 (3.7)

Table 6. Outcomes of Ketogenic Diet according to Classification of Epilepsies at 12 Months

	Total no. (%)	Maintenance (%)	Seizure-free (%)	>50% (%)	<50% (%)
Total	162	74/162 (45.7)	37/162 (22.8)	31/162 (19.2)	6/162 (3.7)
WS	28/162 (17.3)	7/28 (25.0)	6/28 (31.4)	1/28	–
LGS	57/162 (35.2)	27/57 (47.4)	18/57 (31.6)	7/57 (12.3)	2/57 (3.5)
SMEI	14/162 (8.6)	10/14 (71.4)	1/14 (7.1)	9/14 (64.3)	–
LKS	4/162 (2.5)	2/4 (50.0)	2/4 (50.0)	–	–
EIEE	2/162 (1.2)	0	–	–	–
Gen. seizure*	8/162 (4.9)	6/8 (75.0)	3/8 (37.5)	3/8 (37.5)	–
Part. seizure*	49/162 (30.2)	22/49 (44.9)	7/49 (14.3)	11/49 (22.4)	4/49 (8.2)

*Non-specified seizures, WS : West syndrome, LGS : Lennox-Gastaut syndrome, SMEI : severe myoclonic epilepsy in infancy, LKS : Landau-Kleffner syndrome, EIEE : early infantile epileptic encephalopathy

within one week and continued as such after the completion of the diet only with the mitochondrial cocktail therapy alone. In West syndrome and LGS, about 30% of the patients maintained the KD and a seizure-free state. Outcomes according to the classification of epilepsies are summarized in Table 6.

Of 88 patients who discontinued the KD within 12 months, 37 patients could not maintain the diet in spite of a 50% or more reduction in seizure frequency. These 37 patients were divided into three groups : 13 patients

who were intolerant to the diet, 19 patients who suffered from the complications, including four patients who died during the KD, and five patients who were dropped out. The complications which affected the above 19 patients were as follows : seven patients experienced gastrointestinal disturbances such as vomiting, diarrhea, and constipation; seven patients were struck by serious infectious diseases; one patient had persistent hypomagnesemia and tetany; and four patients died while on the KD. These deaths were due to cardiomyopathy with underlying pyruvate dehydrogenase deficiency in one patient, lipoid aspiration pneumonia with a prior history of perinatal hypoxic brain insult, possibly combined with gastroesophageal reflux, in the second patients, and serious infectious illnesses including hypoxic brain insults due to meconium aspiration syndrome in the third patient and previous encephalitis in the last patient. Lipoid pneumonia and serious infectious illnesses occurred within two months after initiating the KD in three patients.

During the follow-up period (mean±SD, 36.4 ±22.7 months), 47 patients (29.0%) maintained or completed the diet. Of 25 patients (15.4%) who maintained the diet, 22 patients showed a reduction of 50% or more in seizure frequency, including 14 patients who were completely seizure free. Twenty of the 32 patients who completed the diet were in a seizure-free state at the time of the completion. During the follow-up period, however, (mean±SD, 23.6±22.8 months) seven patients showed relapse within 12 months and one patient relapsed 20 months after the completion of the diet. The KD group was subdivided into favorable and unfavorable, with the former being defined by a reduction in seizure frequency of more than 50% while maintaining the KD for over 12 months (n=65), and the latter characterized by less than 50% reduction in seizure frequency and less than 12 months on the diet (n=38). No statistically significant differences on the variables such as the classification of focal000000 or generalized seizures, age, or underlying etiologies could be identified between the favorable and unfavorable groups, although the prognosis after the completion of the diet was weakly related to the classification (P=0.05) and underlying etiologies (P=0.051) (Table 7).

Table 7. Comparison between Favorable and Unfavorable, or Non-relapsed and Relapsed Groups

	Favorable group (Non-relapsed group)	Unfavorable group (relapsed group)	p-value (p-value)
Number of patients	65 (23)	59 (8)	–
Duration of KD (mo) (Follow up duration, mo)	22.9, SD±7.9 (19.1, SD±17.5)	4.5, SD±2.7 (17.5, SD±16.0)	0.00 (0.58)
Cryptogenic : Symptomatic	25 : 40 (10 : 13)	26 : 33 (1 : 7)	0.49 (0.051)
Age at initiation of KD			
<2 years	11 (5)	16 (2)	0.49 (0.83)
2-6 years	38 (14)	31 (6)	0.29 (0.95)
7-11 years	11 (3)	8	0.75 (0.96)
≥12 years	5 (1)	4	0.89 (0.97)
Generalized : Partial seizure	35 : 30 (18 : 5)	29 : 30 (4 : 4)	0.45 (0.05)

KD : ketogenic diet

4. Epilepsy surgery and Vagus nerve stimulation

Epilepsy surgery was executed in eight patients who were diagnosed as temporal lobe epilepsies, including four patients with dual pathology of mesial origin, as well as 30 patients with extratemporal lobe epilepsies that included various types of epilepsies and etiologies as summarized in Table 8. The mean follow-up period after surgical intervention was 2 years and 9 months for extratemporal lobe epilepsies and 4 years and 1 month for temporal lobe epilepsies. Surgery revealed the following : Engel class I in 19 of 30 patients (63.3%) with extratemporal lobe epilepsies, six of eight patients (75%) with temporal lobe epilepsies, Engel class I or II in 21 patients (70%) with extratemporal lobe epilepsies and all the patients with temporal lobe epilepsies (Table 8).

In eight patients with MCDs (six of cortical dysplasia, one of tuberous sclerosis, one of hemimegalencephaly), the KD had been tried previously. Overall, the KD was attempted in 20 patients with MCDs (15 of cortical dysplasia, two of hemimegalencephaly, one of lissencephaly, one of schizencephaly, and one of tuber), which resulted in 13 refractory patients and seven patients with favorable outcomes (including six patients who were seizure free). However, two of the three patients who completed the diet and one of the four patients who maintained the diet for longer than 12 months showed relapse. For these patients, resective surgery was the next course of action. The surgical outcomes of the eight MCD patients previously treated with the KD ranged from Engel class I in three patients and to class III in two patients to class IV in three patients.

VNS was set up in five patients, including two patients with LGS, one patient with gelastic seizures due to hypothalamic hamartoma, and two patients with non-specified partial seizures. All the patients were monitored for 12 months following the treatment. Only two patients, including one with LGS and one with cryptogenic partial seizures, obtained a seizure reduction of more than 50% with over three

Table 8. Outcomes of Epilepsy Surgery

Classifications	No. of patients (No., pathology)	Outcomes* (No.)
Temporal lobe epilepsy	8	
	4 (3, HS+CD; 1, HS+CD+DNET)	I (4)
	4 (2, CD; 1, CD+ODG; 1, old infarction)	I (2), II (2)
Extra-temporal lobe epilepsy	30	
West syndrome	5 (3, TS; 2, CD)	I (5)
Lennox-Gastaut syndrome	8 (6, CD; 1, CD+HIE)	I (2), III (1), IV (5)
Landau-Kleffner syndrome	2	II (1), IV (1)
Sturge-Weber syndrome	2	I (2)
Rassmussen encephalitis	1	Vegetative state
Nonspecified partial seizures	12 (11, CD; 1, HIE)	I (10), II (1), III (1)

*Engel classification, HS : hippocampal sclerosis, CD : cortical dysplasia, DNET : dysembryoplastic neuroepithelial tumor, ODG : oligodendroglioma, TS : tuberous sclerosis, HIE : hypoxic ischemic encephalopathy

months of VNS therapy.

Discussion

Despite recent advances in AEDs, up to 30 % of childhood epilepsy patients show intractability to appropriate AED therapies[8, 9]. In a study of newly-diagnosed patients, 47% were seizure-free with the first AED, 13% after the second drug, and 1% after the third drug[10]. In our epilepsy center, we found only 37 patients (12.8%) who showed a seizure-free state for more than 6 months with AED treatment. Moreover, only 20 patients (6.9%) maintained a seizure-free state until the last follow up (mean±SD, 28.2±19.0), but even then nobody was sure of the long-term results. Furthermore, most pediatric patients with intractable epilepsies also have co-morbidities such as mental retardation or developmental delay[11]. Overuses of newly-developed AEDs can further hinder developmental progress, so that prolonged additional retrial of newly-developed AEDs is not recommended.

Although the mechanisms of action remain to be identified, steroids have been shown clinically effective in treating various intractable epilepsies and epileptic syndromes such as West syndrome, LGS unrelated to seizure types, and Landau-Kleffner syndrome, especially in cryptogenic patients[12]. In our country, ACTH is not manufactured, and prednisolone has typically been prescribed in cases of West syndrome, LGS, Landau-Kleffner syndrome, and other unspecified seizures, especially for cryptogenic patients.

Prednisolone is usually accompanied by several dangerous adverse effects[12], so that it was prescribed for at most eight weeks and then tapered over four weeks. Fifty-eight out of 138 patients (42.0%) who tried prednisolone became seizure free while on the medication. This can be compared to the initial outcomes of newly-developed AEDs : 12.5% of the patients the seizure free. Only 17 patients (12.3 %), including 11 with West syndrome, five with LGS, and one with Doose syndrome, retained the benefits after ceasing the prednisolone regimen.

Snead et al.[13] reported that prednisolone was not effective in any types of seizures, but Sinclair[14] recently reported that among 28 children aged 18 months to 10 years, 13 patients (46%) became seizure free on prednisolone. Sinclair further concluded that prednisolone was the most effective treatment for children, especially in the absence of seizures and LGS. The follow-up period in that study ranged from one to five years. In our patients, the initial responses during prednisolone administration were similar to the outcomes of the previous reports, yet a majority of our patients relapsed during follow ups (mean±SD, 19.7± 11.3 months).

The ketogenic diet (KD) was first reported by Geyelin[15] in the 1920s as producing similar biochemical changes as does starvation. The KD recently gained spotlights as a treatment for intractable epilepsy, especially in children[7], and the anti-epileptic efficacy of the KD has been reported in many studies[16-18]. In the present study, 74 of 162 patients (45.7%) who had been followed for over 12 months after the initiation of the diet remained on the diet at 12 months, 42.0% (68/162) with a reduction of seizure frequency greater than half, and 22.8% (37/162, included in the above 42.0%) with complete cessation of seizures. This result is

concordant with previous reports[16-19].

No statistically significant variables that would have influenced the outcomes of the KD could be identified, with the statistical analysis performed for age, etiology, and the classification of epilepsies as focal or generalized. Nevertheless, only one of the 14 patients with severe myoclonic epilepsies in infancy could be completely controlled by the KD, while the remaining patients showed convulsive seizures, particularly when in a state of febrile illness. Three patients with early infantile epileptic encephalopathy were not controlled by the KD.

Fifteen patients were forced to stop the KD because of various serious complications. Unfortunately, additional four patients died while on the KD, the details of which are explained previously[20]. Most of the complications of the KD are transient and can be managed easily with various conservative treatments. Life-threatening complications do arise, however, and should obviously be monitored closely during follow-up. Finally, of 32 patients (19.8 %) who successfully completed the KD, relapse during the follow-up period was observed in eight. In general, relapsed patients had more symptomatic etiologies, while the group of non-relapsed patients had a higher ratio of generalized seizures (P=0.051 and 0.050). There was no statistical significance here, though, and further studies will be required to draw meaningful conclusions.

The finding that KD can be successfully employed in an Asian population, whose customary diets contain substantially less fat than traditional Western ones, is the evidence of the broad applicability of the KD. In an effort to improve the tolerability of and thus compliance of the KD, we have revised the initial non-fasting ketogenic diet (NFKD) such that fluid restriction is not demanded. Half of the patients who tried the KD treatment began with the revised protocol. Indeed, the authors have already observed and reported significant benefits from NFKD insofar as improving tolerability and reducing the incidence of acute dehydration without significant differences in duration taken to the onset of strong ketosis or efficacy for seizure remission[21].

It is worth noting that the KD has been successfully employed in patients with Landau-Kleffner syndrome combined with an oxidative phosphorylation disorder, such as mitochondrial complex I deficiency, despite the metabolic burden presented by the KD[22]. One recent report suggests that the KD could also be tried preferentially in selected candidates who are otherwise being considered for callosotomy, non-lesional resections, or extratemporal resections[23]. As of yet, no consensus has been reached as to whether the KD could be applied to patients with MCDs. In our study, 20 patients with MCDs attempted to follow the KD; two patients successfully continued the diet, and only one patient maintained a seizure-free state after the completion of the diet. Additionally, the surgical outcomes of eight patients who had previously tried the KD were less than favorable. These unfavorable results might be attributable to somewhat ill-defined diffuse MCD lesions of these patients, but this cannot be stated with confidence. We can conclusively state, however, that the KD represents a viable option that should be considered for patients who are either very young infants facing a high risk of surgical intervention or have ill-defined, or non-localized lesions. Further studies are urgently needed on this topic.

The association of intractable childhood epilepsy with cortical pathology is important because focal surgical resection can at times lead to a complete remission and developmental recovery in medically-intractable cases[24]. And advances in diagnostic tools and techniques, including MRI and functional neuroimaging, make it feasible to diagnose the underling cortical pathology[25, 26]. Herein, epilepsy surgery was undergone in cases of absolutely well-localized seizures as well as in patients for whom the efficacy of epilepsy surgery has already been demonstrated (Sturge-Weber syndrome, mesial temporal lobe epilepsy, and tumors) without any attempts of other therapeutic modalities. Surgery was also used for a portion of the localized epilepsies that were not relieved by prednisolone or the KD. The most common etiology of refractory epilepsy was MCDs on extratemporal regions[27]. Through surgical intervention, 19 patients (63.3%) with extratemporal lobe epilepsies and six patients (75%) with temporal lobe epilepsies were classified as Engel class I. While the number of the patients comprising our data set was relatively small, our results were similar to those in other reports[27-29].

VNS therapy appears to be successful regardless of seizure type or cause, with an improvement in seizure control increasing over time in both the pediatric and adult populations [5]. The non-pharmacologic aspects of the therapy make it particularly attractive for use in this population, especially in pediatric cases concomitant with mental retardation and delayed development, who otherwise experience unique side effects and cognitive impairments associated with anti-epileptic drugs[5]. Recent data from Helmers et al.[30] on the efficacy of VNS therapy in children indicate that 30% of patients obtained more than a 75% decrease in seizure frequency at six months after VNS implantation. Murphy et al.[31] reported that 45% of patients achieved greater than 50% seizure reduction. Medical insurance in South Korea typically did not cover VNS therapy, rendering it too expensive to use pervasively and allowing us to apply it only to five patients. Only two patients showed more than 50% decrease in seizure frequency at three months and more than 75% decrease at 12 months.

We conclude that considerable controls over intractable childhood epilepsies can be attained through various therapeutic modalities, especially the KD and epilepsy surgery when the epileptic focus is well-localized. Meanwhile, our results indicate that prednisolone, a more traditional therapy, leads to somewhat more frequent relapses and that newly-developed AEDs present only limited controls of intractable childhood epilepsy.

Abstract

Purpose : This study sought to evaluate the clinical outcomes of various therapeutic modalities, including newly-developed anti-epileptic drugs (AEDs), prednisolone, ketogenic diet (KD) epilepsy surgery, and vagus nerve stimulation (VNS), in treating intractable childhood epilepsy.

Methods : Data of refractory epilepsy patients (n=297) treated from July 1995 through April 2003 at the epilepsy center of Sanggye Paik Hospital were retrospectively analyzed.

Results : Newly-developed AEDs were primarily prescribed to 290 patients, although only 20 patients (6.9%) maintained a seizure-

free state. Of 138 patients for whom prednisolone was prescribed, 58 patients (42.0%) showed complete seizure controls while 41 patients experienced relapse. KD was attempted and evaluated at 12 months in 162 patients, at which time 74 (45.7%) remained on the diet and 68 (42.0%) showed seizure reduction of greater than 50%, including 37 (22.8%) who were completely seizure free. Epilepsy surgery was undergone in 38 patients, and Engel class I was identified in 25 (65.8%) patients. VNS was administered to five patients, only two of whom obtained a seizure reduction of more than 50%.

Results : Taken together, these findings suggest that considerable controls over intractable childhood epilepsy can be gained through KD and epilepsy surgery, whereas prednisolone treatment leads to somewhat more frequent relapses, and newly-developed AEDs are comparatively limited in their controls of refractory epilepsy.

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