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Effects of Cannabidiol on Adaptive Behavior and Quality of Life in Pediatric Patients With Treatment-Resistant Epilepsy

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Background and Purpose Data regarding the effects of cannabidiol (CBD) on the quality of life (QOL) are currently inadequate. We assessed the QOL of pediatric patients with epilepsy who were treated with CBD.

Methods This prospective, open-label study included pediatric and adolescent patients (aged 2–18 years) with Dravet syndrome or Lennox-Gastaut syndrome. Oral CBD was administered at 10 mg/kg/day. The Korean version of the Quality Of Life in Childhood Epilepsy (QOLCE) questionnaire was administered when CBD treatment began and again after 6 months. Adaptive behavior was measured using the Korean versions of the Child Behavior Checklist (K-CBCL) and the second edition of the Vineland Adaptive Behavior Scales (Vineland-II).

Results This study included 41 patients (11 with Dravet syndrome and 30 with Lennox-Gastaut syndrome), of which 25 were male. The median age was 4.1 years. After 6 months, 26.8% (11/41) of patients experienced a ≥50% reduction in the number of seizures. The total score for the QOLCE questionnaire did not change from baseline to after 6 months of CBD treatment (85.71±39.65 vs. 83.12±48.01, respectively; p=0.630). The score in the motor skills domain of Vineland-II reduced from 48.67±13.43 at baseline to 45.18±14.08 after 6 months of treatment (p=0.005). No other Vineland-II scores and no K-CBCL scores had changed after 6 months of CBD treatment.

Conclusions CBD is an efficacious antiseizure drug used to treat Dravet syndrome and Lennox-Gastaut syndrome. However, it did not improve the patient QOL in our study, possibly because all of our patients had profound intellectual disabilities.

Keywords adaptive; Lennox-Gastaut syndrome; *SCN1A*; drug-resistant epilepsy.

INTRODUCTION

Cannabidiol (CBD) is an efficacious and well-tolerated antiseizure drug. Its efficacy has been confirmed for patients with treatment-resistant epilepsy, including those with Lennox-Gastaut syndrome and Dravet syndrome.[1] Previous studies found that after 14 weeks of treatment, patients with Lennox-Gastaut syndrome experienced a mean reduction of 43.9% in the number of seizures,[2] and 43% of patients with Dravet syndrome experienced a reduction of at least 50% in the number of seizures.[3]

However, data on the effects of CBD on the quality of life (QOL) are currently inadequate. QOL is an important concept representing the physical and mental health of an individual. Because the QOL of patients with epilepsy is affected by both their seizures and treatment, QOL is often measured after treatment with new antiepileptic drugs. A significant improvement in QOL was reported after 1 year of CBD treatment in adults with epilepsy, but that study did not include any pediatric patients.[4] A recent study found that CBD treatment improved QOL in pediatric patients, but only over a short follow-up of 12 weeks.[5] Data regarding the

long-term effects of CBD on QOL in pediatric patients with treatment-resistant epilepsy are inadequate.

The studies mentioned above did not find any correlation between QOL and changes in seizure frequency. This suggests that changes in adaptive function could have improved QOL, but adaptive or cognitive function was not investigated in conjunction with QOL.[4,5] Improvements of QOL should be evaluated after a sufficient period of time in conjunction with adaptive function.

Here we investigated changes in QOL for pediatric patients with Dravet syndrome and Lennox-Gastaut syndrome after 6 months of treatment with CBD. We aimed to determine the long-term effects of CBD on adaptive behavior concurrently with QOL in patients with treatment-resistant epilepsy.

METHODS

This prospective, open-label study included patients who were treated with CBD from May 2019 to December 2020 at Severance Children's Hospital. The inclusion criteria were as follows: 1) aged 2–18 years, 2) clinical diagnosis of Dravet syndrome or Lennox-Gastaut syndrome, 3) treatment-resistant epilepsy with the failure of more than two appropriate drugs, and 4) at least one seizure per month. Appropriate drugs included valproic acid, topiramate, lamotrigine, and rufinamide for Lennox-Gastaut syndrome, and valproic acid, clobazam, and stiripentol for Dravet syndrome. Consent forms were obtained from both caregivers and patients. The need to obtain patient consent was waived for patients whose IQ was below 49, and parental consent was instead obtained on behalf of these patients. Patients whose alanine aminotransferase or aspartate aminotransferase level was elevated to at least twice the upper normal limit were excluded. This study was approved by the Institutional Review Board of Severance Hospital (4-2020-0120).

Patients were asked to visit the clinic four times. At the initial screening, caregivers were asked to keep a seizure diary. Baseline seizure type and frequency were assessed, and liver function tests were performed. The Korean version of the second edition of the Bayley Scales of Infant and Toddler Development (K-BSID-II), or the Korean version of the fifth edition of the Wechsler Intelligence Scale for Children (K-WISC-V) was administered to determine baseline cognition and development.

CBD was added to the baseline antiseizure drugs at 1 month after the first visit. An oral pharmaceutical formulation of highly purified CBD (100 mg/mL; Epidiolex, GW Research, Cambridge, United Kingdom) was used. The starting dosage of CBD was 5 mg/kg/day (administered as two 2.5 mg/kg doses per day), which was titrated to 10 mg/kg/day after 1 week and maintained for the duration of the study (Fig. 1). After 3 and 6 months of treatment, patients returned to the clinic for a regular checkup and evaluation. Details of the study are available elsewhere.[6]

Patients underwent multiple tests when the CBD treatment was initiated and after 3 and 6 months of treatment. At these three visits, caregivers completed the Korean version of the Quality Of Life in Childhood Epilepsy (QOLCE) questionnaire. In addition, the Korean version of the Child Behavior Checklist (K-CBCL) test and the Korean version of the sec-

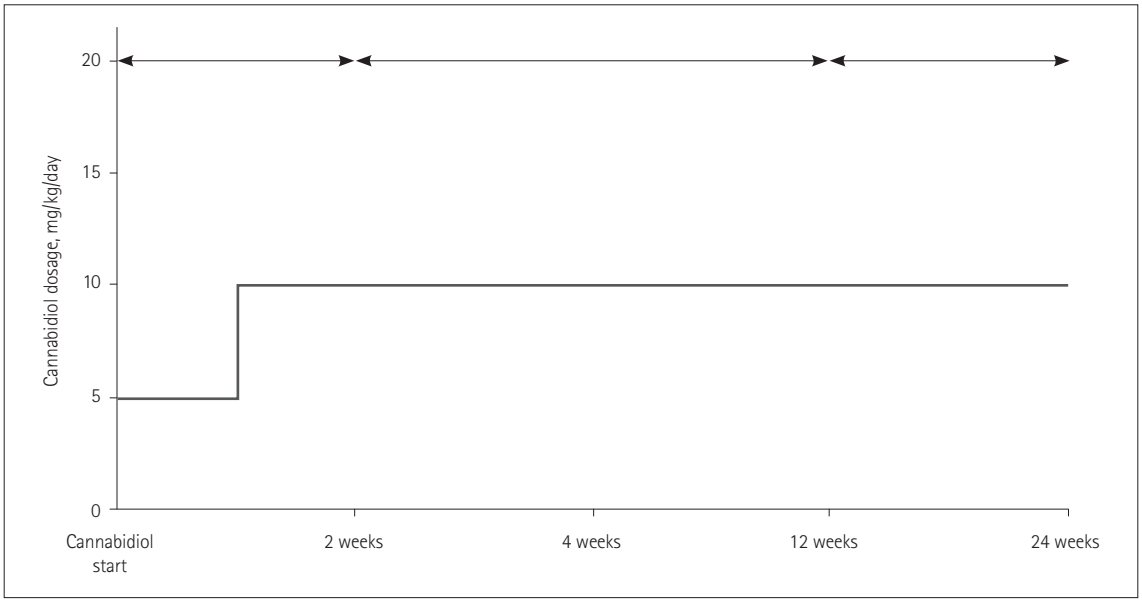

Fig. 1. Study design. A 2-week of titration was followed by 22 weeks of maintenance period. Patients underwent multiple tests when the cannabidol treatment was initiated and after 12 and 24 weeks of treatment.

ond edition of the Vineland Adaptive Behavior Scales (Vineland-II) were applied to measure the adaptive function of patients. Vineland-II is a tool used to operationalize intellectual disability. Vineland-II has four domains: communication, daily living skills, socialization, and motor skills. The communication domain comprises receptive, expressive, and written subscales; the daily-living-skills domain comprises personal, domestic, and community subscales; the socialization domain comprises interpersonal relationships, play and leisure, and coping skills subscales; and the motor skills domain comprises gross motor and fine motor subscales. The seizure frequency and adverse events were noted at each visit. The seizure frequencies after 3 and 6 months of treatment were compared with that during the baseline period. Patients were assigned to one of the following four groups: 1) seizure-free, 2) 50%–99% reduction, 3) 1%–49% reduction, and 4) no change or early withdrawal. Reasons for treatment discontinuation were also noted for patients who withdrew early from the study. Physicians were allowed to adjust other antiseizure drugs if they deemed this necessary.

The scores for the QOLCE questionnaire and adaptive function test results after CBD treatment were compared with those at baseline using paired *t*-tests. Only patients who completed 6 months of CBD treatment were included. Because some data were not normally distributed, the signed-rank test was also performed. SAS software (version 9.4, SAS Institute, Cary, NC, USA) and the R package (version 3.4.3, https://www.r-project.org) were used for data analysis. *P* values less than 0.05 were considered statistically significant. Data are expressed as mean±standard deviation or median (interquartile range [IQR]) values.

Table 1. Clinical characteristics of the 41 patients

Characteristic	Value
Sex	
Female	16
Male	25
Age (yr)	4.07 (3.00–8.02)
Patients on concomitant ketogenic diet	5
Concomitant antiseizure drugs	3 (2–3)
Lennox-Gastaut syndrome	30 (73.2)
Malformation	3 (7.3)
Encephalomalacia	3 (7.3)
Tuberous sclerosis	1 (2.4)
Intraventricular hemorrhage	1 (2.4)
Dravet syndrome	11 (26.8)
SCN1A mutation	8 (72.7)

Data are presented as *n*, *n* (%), or median (interquartile range).

RESULTS

This study enrolled 41 patients (25 males, 16 females) with treatment-resistant epilepsy: 11 patients had Dravet syndrome and 30 patients had Lennox-Gastaut syndrome. The median age was 4.1 years (IQR=3.0–8.0) (Table 1). Of the 41 enrolled patients, 33 (26 Lennox-Gastaut syndrome, 7 Dravet syndrome) completed 3 months of CBD treatment, and 26 (20 Lennox-Gastaut syndrome, 6 Dravet syndrome) completed 6 months of CBD treatment.

Among the 35 patients who completed K-BSID-II, 33 (94.3%) achieved the lowest score of 50 for the mental developmental index and the psychomotor developmental index. The median K-BSID-II score was 50 (IQR=50–50). The six patients who completed K-WISC-V achieved a median score of 50 (IQR=45–52.5).

All 41 patients had severe developmental delays, with all but five patients having Full-Scale Intelligence Quotients (FSIQs) of lower than 40 on K-WISC-V. These five patients had moderate-to-borderline intellectual disability, with FSIQs ranging from 52 to 79. Their median social age was 1.16 years (IQR=0.59–2.41).

The total score for the QOLCE questionnaire did not change from baseline to 6 months after CBD treatment (85.71±39.65 vs. 83.12±48.01, respectively; p=0.630). Comparing the after-treatment scores with those at baseline revealed no differences in the physical function, well-being, cognition, social function, or behavior domain (Table 2).

The only Vineland-II score that differed between baseline and 6 months after CBD treatment was that for motor skills, which decreased from 48.67±13.43 to 45.18±14.08 (p=0.005) (Table 3). The scores for daily living skills increased from 52.59±20.46 to 57.08±20.62 after 6 months of treatment, which was significant in the signed-rank test (p=0.010) but not in the paired *t*-test (p=0.240). No K-CBCL scores changed after 6 months of CBD treatment (Table 4).

After 3 months of CBD treatment, 36.6% (15/41) of patients experienced a reduction of at least 50% in the number of seizures, including 8 (19.5%) patients who became seizure-free. After 6 months, 26.8% (11/41) of patients continued to experience a reduction of at least 50% in the number of seizures. Two (4.9%) of the patients maintained their seizure-free status after 6 months. CBD was discontinued after between 0 and 6 months of treatment in 36.6% (15/41) of patients due to treatment ineffectiveness (n=11, 73.3%), adverse events (n=3, 20.0%), or high cost (n=1, 6.7%) (Table 5).

Sixteen (39.0%) patients experienced adverse events. Behavioral change was the most common adverse event (n=5, 12.2%), followed by seizure aggravation (n=4, 8.0%), vomiting (n=3, 6%), diarrhea (n=2, 4.0%), acute pancreatitis (n=1,

Table 2. Quality of life in childhood epilepsy questionnaire scores at baseline and after 6 months of cannabidiol treatment (*n*=26)

Item	Baseline	6 months	Paired *t*-test	Signed-rank test
			p	*p*
Physical function	14.20±7.59	14.42±8.71	0.960	0.862
Physical restrictions	9.15±6.14	9.58±6.63	0.832	0.932
Energy/fatigue	5.07±2.37	4.85±2.92	0.518	0.425
Well-being	23.46±13.09	23.39±14.92	0.785	0.907
Depression	6.24±2.76	6.35±3.29	0.436	0.547
Anxiety	7.15±4.80	7.50±5.24	0.909	0.973
Control/helplessness	3.70±3.57	4.04±3.87	0.368	0.401
Self-esteem	6.37±4.39	5.69±5.17	0.736	0.807
Cognition	12.57±10.22	12.04±11.12	0.477	0.320
Concentration	3.30±2.51	2.89±2.88	0.265	0.306
Memory	2.17±2.53	1.96±2.71	0.595	0.366
Language	4.57±3.89	4.69±4.51	0.851	0.880
Other cognition	2.52±2.24	2.50±2.44	>0.99	>0.999
Social function	8.65±5.84	9.15±6.27	0.803	0.661
Social activity	5.83±3.63	6.31±3.95	0.649	0.425
Social interaction	2.83±2.64	2.85±3.09	0.957	>0.999
Behavior	20.70±10.45	18.39±11.28	0.101	0.060
General health	2.65±1.64	3.23±1.58	0.197	0.334
General quality of life	2.44±1.59	2.92±1.44	0.211	0.294
Total	85.71±39.65	83.12±48.01	0.634	0.342

Data are presented as mean±standard deviation.

Table 3. Korean version of the second edition of the Vineland Adaptive Behavior Scales scores at baseline and after 6 months of cannabidiol treatment (*n*=25)

Vineland-II domain	*n*	Baseline	6 months	Paired *t*-test	Signed-rank test
				p	*p*
Communication	25	48.65±18.18	51.20±18.72	0.951	0.958
Daily living skills	25	52.59±20.46	57.08±20.62	0.239	0.014*
Socialization	25	49.20±16.73	52.60±15.47	0.981	0.961
Motor skills	17	48.67±13.43	45.18±14.08	0.005*	0.010*
Total score	25	43.96±16.35	46.44±17.07	0.509	0.334

Data are presented as mean±standard deviation.
*$p<0.05$.

2.0%), and rash (*n*=1, 2.0%).

DISCUSSION

Despite early data suggesting that CBD can improve the QOL in pediatric patients,[5] we found that the QOL did not improve in patients with treatment-resistant epilepsy after 6 months of CBD treatment. Several hypotheses could explain the difference in these findings. The QOLCE questionnaire depends on reports by parents, which might result in both detection and selection biases. Further, the expectations of parents may have affected the results. Because previous studies were performed before CBD became widely available,[4,5] patients and parents who participated in early studies may have had higher expectations about its efficacy.[7] Now that CBD is accessible and more data are available, expectations about the efficacy of CBD may be lower and more realistic. Responses to questions such as "was he/she obedient?" and "did he/she demand a lot of attention?" can be highly subjective, and can vary depending on the patients' expectations.

In addition, we may have failed to detect differences because all of our patients had profound intellectual disabilities. Previous studies of QOL have suggested that mood changes are strong predictors of QOL but not freedom from seizures. Many of our patients had poor cognitive function that could not be measured using conventional scales of intelligence. Subtle changes in mood may have gone unnoticed by caregivers due to the intellectual disabilities of the patients preventing them

Table 4. Korean version of the Child Behavior Checklist scores at baseline and after 6 months of cannabidiol treatment

Item	Baseline	6 months	Paired *t*-test	Signed-rank test
			p	*p*
Total competence	26.15±6.44	31.67±7.92	0.115	0.250
Social competence	33.08±5.68	37.67±8.69	0.249	0.500
School competence	28.08±7.29	28.50±5.51	0.944	>0.999
Total behavior problem	57.30±15.15	54.13±9.70	0.204	0.237
Internalizing problem	54.72±13.73	53.75±11.23	0.245	0.379
Externalizing problem	52.48±13.29	51.25±11.11	0.667	0.678
Anxiety/depression	55.11±8.09	53.79±6.88	0.624	0.984
Withdrawn	61.85±10.90	61.00±9.56	0.124	0.155
Emotionally reactive	55.52±8.60	55.19±5.56	0.465	0.537
Sleep problems	56.10±10.04	55.44±8.30	0.837	0.766
Somatic complaints	55.76±7.24	54.29±6.03	0.105	0.158
Social problems	66.71±8.29	63.50±8.09	0.564	0.750
Thought problems	64.47±8.87	59.83±7.91	0.593	0.750
Attention problems	64.80±12.28	60.59±9.84	0.320	0.510
Rule breaking	58.41±8.02	57.33±7.21	>0.999	>0.999
Aggressive behavior	55.26±7.39	53.00±5.82	0.303	0.260
Other issues	60.02±9.72	57.67±8.32	0.255	0.344
Affective	61.76±9.80	59.04±9.28	0.166	0.224
Anxiety/depression	57.26±9.40	55.92±9.11	0.726	0.636
Somatic complaints	52.12±4.03	51.00±2.83	NA	NA
Pervasive developmental problems	61.27±10.91	58.81±8.07	0.140	0.135*
ADHD	58.94±9.64	55.25±6.03	0.266	0.302
Oppositional defiant problems	54.63±6.58	53.83±7.26	0.868	>0.999
Conduct problems	57.67±7.63	57.63±7.21	0.621	0.750

Data are presented as mean±standard deviation.
*$p<0.05$.
ADHD, attention-deficit hyperactivity disorder; NA, not available.

Table 5. Seizure outcomes after 3 and 6 months of cannabidiol treatment (n=41)

Outcome	Treatment duration	
	3 months	6 months
Seizure-free	8 (19.5)	2 (4.9)
Seizure reduction 50%–99%	7 (17.1)	9 (22.0)
Seizure reduction 1%–49%	18 (43.9)	15 (36.6)
No change or early withdrawal	8 (19.5)	15 (36.6)

Data are presented as *n* (%).

from self-reporting accurately. The cognitive function of patients was not reported for the previous study, and those patients could have had higher IQs.[5] In contrast to our study, only about 40% of the patients in the previous study had Lennox-Gastaut syndrome or Dravet syndrome, with other patients having conditions that were associated with milder degrees of cognitive dysfunction, such as Jeavons syndrome .

Along with its antiseizure effects, CBD exerts several beneficial effects. In previous studies, several parents and patients reported increased alertness, better mood and sleep, and improved language and motor skills when they receive CBD-enriched cannabis.[7,8] In another study, scores increased in multiple QOLCE questionnaire domains, including energy, memory, cognitive function, social interactions, and behavior.[5] CBD is considered to exert neuroprotective, anti-inflammatory, anti-oxidant, and neurogenesis effects that are beneficial to cognition.[9] However, we did not see any changes in QOL after CBD treatment in the present study. Our study results suggest that CBD does not improve the QOL in patients with Dravet syndrome or Lennox-Gastaut syndrome, which is probably because these patients have severe intellectual disabilities. Changes in mood and improved QOL are less likely to be reported in patients with worse cognitive function.

Changes in adaptive function were analyzed after CBD treatment. No changes were found in K-CBCL scores, but the score in the motor skills domain of Vineland-II was reduced after CBD treatment. This finding suggests that the gross and fine motor skills of patients deteriorate after 6 months of CBD treatment. These findings might have been related to psycho-

motor regression, which often occurs in Lennox-Gastaut syndrome. Because our patients were severely impaired, changes in other domains may have been less definite. Further investigations are needed to clarify these findings.

Our results suggest that CBD does not improve adaptive function in patients with Dravet syndrome or Lennox-Gastaut syndrome, especially when they already have severe intellectual disabilities and treatment-resistant epilepsy. The impact of early trials of CBD on QOL remains to be investigated in patients with Dravet syndrome or Lennox-Gastaut syndrome.

As a new antiseizure drug and a natural component of cannabis, many questions arise regarding the effects of CBD. The effects of CBD on cognition, QOL, and neuropsychiatric adverse events remain unclear. We found that CBD did not affect QOL in pediatric patients with treatment-resistant epilepsy. These findings should be investigated further once CBD is approved for patients with forms of epilepsy that are less severe than Dravet syndrome and Lennox-Gastaut syndrome.

This study had some limitations. The included patients had severe intellectual disability and developmental delay along with treatment-resistant epilepsy. There was selection bias since the parents of highly impaired patients are more likely to want to try a new drug. The small sample was another limitation. However, it should also be emphasized that the patients included in this study are likely to represent patients who receive CBD in typical clinical situations. CBD has only recently been approved for patients with Lennox-Gastaut syndrome and Dravet syndrome in Korea.

In conclusion, CBD has been found to be an efficacious antiseizure drug for patients with Lennox-Gastaut syndrome and Dravet syndrome, but it did not improve QOL in pediatric patients with treatment-resistant epilepsy in our study. These findings suggest that the relationship between CBD and QOL needs to be investigated in larger patient populations.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

Hoon-Chul Kang, a contributing editor of the *Journal of Clinical Neurology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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