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. 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, and 43% of patients with Dravet syndrome experienced a reduction of at least 50% in the number of seizures.

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. A recent study found that CBD treatment improved QOL in pediatric patients, but only over a short follow-up of 12 weeks. 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-

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**Fig. 1.** Study design. A 2-week of titration was followed by 22 weeks of maintenance period. Patients underwent multiple tests when the cannabidiol treatment was initiated and after 12 and 24 weeks of treatment.
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=50–52.5). 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).

Sixteen (39.0%) patients experienced adverse events. 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. From 52 to 79. Their median social age was 1.16 years (IQR=0.59–2.41).

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, 2.4%).

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 (24.7) |

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

Despite early data suggesting that CBD can improve the QOL in pediatric patients, 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, patients and parents who participated in early studies may have had higher expectations about its efficacy. 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 from noticing.

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

### 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 |
|-----------------------|---------------|--------------|---------------|------------------|
| 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±3.37     | 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 |
|---------------------------|-----|--------------|--------------|---------------|------------------|
| 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.
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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 |
|-----------------------------------|----------------|----------------|---------------|------------------|
| 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±3.56     | 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     | 57.23±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. 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. In another study, scores increased in multiple QOLCE questionnaire domains, including energy, memory, cognitive function, social interactions, and behavior. CBD is considered to exert neuroprotective, anti-inflammatory, anti-oxidant, and neurogenesis effects that are beneficial to cognition. 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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REFERENCES
1. Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol 2016;15:270-278.
2. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Bendadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391:1085-1096.
3. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376:2011-2020.
4. Gaston TE, Szafarski M, Hansen B, Bebin EM, Szafarski JP; UAB CBD Program. Quality of life in adults enrolled in an open-label study of cannabidiol (CBD) for treatment-resistant epilepsy. Epilepsy Behav 2019;95:10-17.
5. Rosenberg EC, Louik J, Conway E, Devinsky O, Friedman D. Quality of life in childhood epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. Epilepsia 2017;58:e96-e100.
6. Koo CM, Kim SH, Lee JS, Park BJ, Lee HK, Kim HD, et al. Cannabidiol for treating Lennox-Gastaut syndrome and Dravet syndrome in Korea. J Korean Med Sci 2020;35:e427.
7. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav 2013;29:574-577.
8. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy Behav 2015;45:49-52.
9. Gaston TE, Martin RC, Szafarski JP. Cannabidiol (CBD) and cognition in epilepsy. Epilepsy Behav 2021;124:108316.