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Original Article

Role of antioxidants in reducing oxidative stress and seizure frequency in drug-resistant epileptic patients

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Abstract

Drug-resistant epilepsy presents significant challenges in treating epileptic patients, leading to recurrent seizures and necessitating the use of polypharmacy with anti-epileptic drugs. Both of these conditions contribute to increased oxidative stress, which is detrimental to the brain. The aim of this study was to determine the role of vitamins C and E in reducing oxidative stress and seizure frequency in drug-resistant epileptic patients. This was a double-blinded, randomized clinical trial with a placebo, parallel design, and block randomization. The subjects were drug-resistant epileptic patients aged 1–18 years who received routine treatment. Randomization was performed on 100 patients who were divided into the treatment or placebo groups. The patients received a combination of vitamin C (100 mg/day) and vitamin E (200 IU/day for those <5 years or 400 IU/day for those ≥5 years) or a placebo for eight weeks. Malondialdehyde (MDA) levels and seizure frequency were measured prior to and after the intervention. A total of 42 and 46 patients were followed till the end of the study in the intervention and placebo groups, respectively. Our data indicated that the MDA levels prior to treatment were not significantly different between the treatment and placebo groups (0.901 vs 0.890 mmol/mL, p=0.920) and were significantly reduced after the treatment in both the treatment group (p<0.001) and placebo group (p=0.028). The changes in MDA levels (between post- and pre-treatment) were also not significantly different between the two groups (p=0.181). Our per-protocol analysis indicated that the reduction in seizure frequency was significantly higher in the treatment group compared to the placebo group (95% vs 35%, p<0.001), with 92% and 60% relative and absolute risk reduction, respectively. The intention-to-treat analysis also indicated that the reduction in seizure frequency was significantly higher in the intervention group than in the control group (80% vs 32%, p<0.001), with relative and absolute risk reduction of 70% and 48%, respectively. There was no significant relationship between changes in MDA levels and seizure frequency in either group. In conclusion, vitamins C and E could reduce seizure frequency and, therefore, could be considered as adjuvant therapy in drug-resistant epileptic patients.

Keywords: Drug-resistant epilepsy, oxidative stress, ascorbic acid, α-tocopherol, MDA

Introduction

Drug-resistant epilepsy is one of the challenges in the treatment of epileptic diseases. It is defined as the failure to achieve a seizure-free state after adequate administration of two or more anti-epileptic drugs (AEDs), as monotherapy or in combination [1,2]. Approximately 60% to 70%

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of epileptic patients have a good response to treatment, while drug-resistant epilepsy ranges from 30% to 40% in adults and 20% to 25% in children [3].

One condition in epileptic patients is oxidative stress, an imbalance between prooxidant and antioxidant substances in the body triggered by a limited number of endogenous antioxidants and excessive production of free radicals. These changes could damage cellular function due to an alteration in the structure and function of various enzymes in the body, such as cell membranes, that result in disruption of neurotransmitter receptors and ion-exit activity [4-6]. Patients with drug-resistant epilepsy experienced more oxidative stress than patients who received only one or two types of anti-epileptic drugs. Previous studies have found a decreasing level of vitamin E serum in patients with epilepsy [7-9]. However, research on the role of antioxidants, especially vitamins C (ascorbic acid) and E (α-tocopherol), in reducing the incidence of oxidative stress and the seizure frequency in children is still limited [10-13]. Therefore, the antioxidant potential benefits to prevent deterioration caused by increasing oxidative stress due to seizures and anti-epileptic drugs need to be further studied.

Vitamin E is a fat-soluble and powerful antioxidant that protects the cell membrane integrity from free radicals, prevents lipid peroxidation in cell membranes, and reduces oxidative stress [6,14]. Vitamin C is a water-soluble antioxidant found in the cytosol and extra-cellular fluids that can interact directly with free radicals, thus inhibiting the process of oxidative stress and promoting the recycling process of vitamin E. The combination of vitamins C and E has demonstrated better antioxidant properties than the two vitamins alone [15]. The incorporation of antioxidant therapy as an additional treatment in pediatric epilepsy patients is still not routinely carried out, even though studies have indicated that antioxidants can reduce the occurrence of oxidative stress and lower seizure frequency [9-12]. The aim of this study was to determine the role of vitamins C and E as an additional treatment in reducing oxidative stress and seizure frequency in drug-resistant epileptic patients.

Methods

Study design, setting and sampling method

The double-blind randomized clinical trial with a placebo, parallel design, and block randomization was conducted at Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, between January and May 2023. Randomization of the intervention was conducted using a 4:2 block randomization. The patients were given an intervention according to the code given by the pharmacist. Researchers and patients were double-masked for the group placement (treatment or placebo). The patients were treated for eight weeks. The assessments were conducted before, during, and post-treatment. Evaluation of the side effects of vitamins C and E administration, medication compliance, and placebo were conducted by communicating with parents every week, conducting a monthly direct examination of the patient, and assessing the frequency of seizures every month.

Patients and criteria

The samples were drug-resistant epileptic patients of 1–18 years of age who had been prescribed two or more anti-epileptics medications for at least one month yet still experiencing seizures and had no renal dysfunction as evidenced by blood creatinine and urea levels falling within the normal benchmark before the intervention. The study excluded patients on a ketogenic diet and those with a diagnosis of epilepsy due to established metabolic abnormalities. It also excluded patients who did not follow the study protocol, withdrew, or died from the final analysis.

Study groups and intervention

The participants were divided into the treatment group (administered vitamin C and E) and the placebo group. Vitamin E doses were 200 IU/day for patients under five years old and 400 IU/day for those aged five years and above, while vitamin C dosage was 100 mg/day. Placebo and vitamins were filled in capsules with the same shape and color. The placebo contained glycerin from palm oil. The vitamins and placebo were given orally once a day for eight weeks. The

participants were randomly assigned using block randomization to ensure a balanced distribution across both groups. The sampling technique employed consecutive sampling.

Study procedure

Prior to the study, the assessments were conducted with anamnesis, physical examinations, and 24-hour dietary analysis (food recall). The evaluation of vitamins C and E intake was conducted prior to the study with the 24-hour food recall method by a dietician, where the parents were asked to remember and mention the type of food consumed in the last 24 hours, the name of the food or drinks, how they process it, the ingredients within, and the portions consumed relative to the size of the household. The percentage assessment (%) of nutrition adequacy was calculated based on how many mg of vitamins C and E (mcg) were consumed compared to the needs that correspond to age and gender. Vitamins C and E levels are considered sufficient if they reach 100% based on the recommended dietary allowance (RDA).

The patients underwent a first blood draw of 7.5 mL for routine blood tests, aspartate transaminase (AST), alanine aminotransferase (ALT), lipid profile, urea, creatinine, and malondialdehyde (MDA) levels. MDA was used as an oxidative stress indicator in the patients. The patients were then administered with the intervention (vitamin C and vitamin E) or placebo for eight weeks. Compliance with placebo or vitamin intake was assessed using a Morisky Medication Adherence (MMAS) questionnaire consisting of eight questions; a score >2 indicated high compliance, a score of 1–2 as moderate compliance and a score of 0 classified as low compliance [17].

A monthly screening, seizure frequency assessment, as well as vitamin and placebo intake consistency were conducted. After eight weeks, a second blood sample was collected to measure the MDA levels.

Study outcomes

The outcomes of this study were the MDA levels and frequency of seizures post-intervention. MDA level was measured using a spectrophotometer by the thiobarbituric acid-reactive substances (TBARS) principle. MDA values decreased or increased after administration of vitamins or placebo, compared to before administration. Seizure frequency is defined as the number of seizures that occur within one month. The frequency of seizures was categorized as reduced if there was a decrease in frequency of seizures at least 50% compared to the prior study. Seizures do not decrease; that is, the frequency of seizures remains the same or decreases but does not reach 50% of the initial frequency or more frequency than before.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Science (SPSS) version 2.2 (IBM, New York, US). The normality test of variables was carried out using the Shapiro-Wilk test. To determine the difference between the MDA levels before and after the intervention, the paired Student t-test or the Mann-Whitney test was carried out as appropriate. The Wilcoxon test was used to compare the levels of MDA between pre- and post-intervention within the group. Statistically significant was considered at p-values<0.05. Intention to treat analysis and per-protocol analysis were conducted to determine the effectiveness of vitamin C and E administration in drug-resistant epileptic patients.

Results

Study overview

Out of 50 patients in each group, 8 (16%) of the treatment group and 4 (8%) of the placebo group were dropped out. It was mainly due to the failure to perform the second MDA examination or did not take the placebo or vitamin due to did not attend to the follow up session (nine subjects), admitted to intensive care (two patients), and had surgery due to secondary illness (one patient). The Consort flow diagram for selecting research subjects is presented in **Figure 1**.

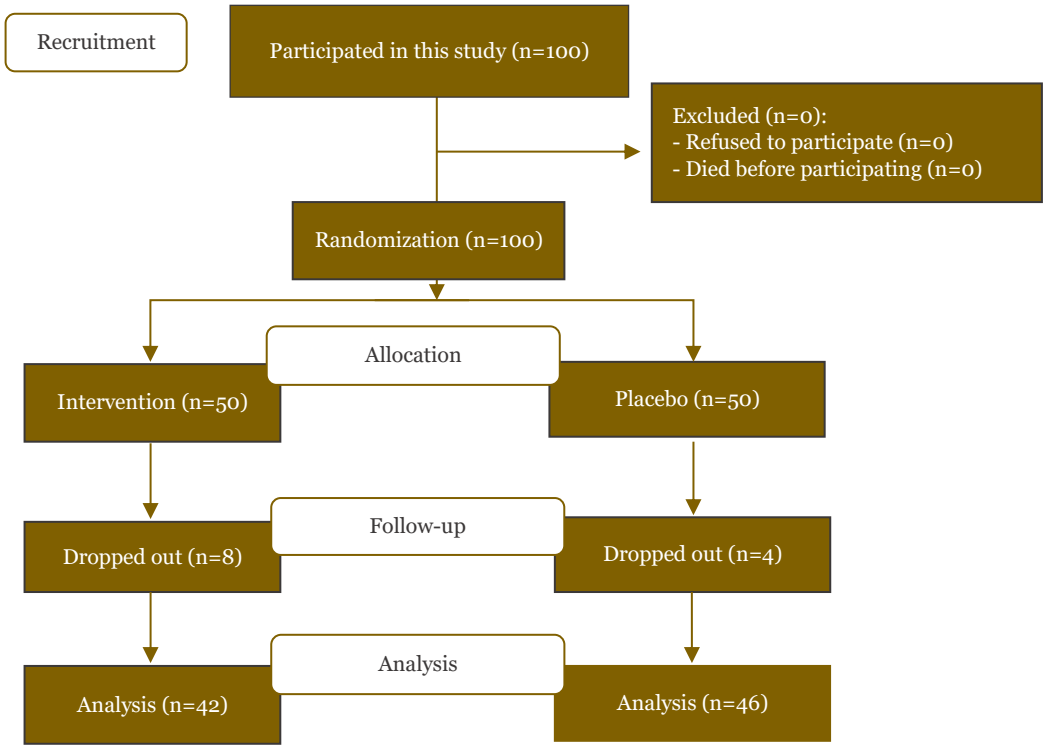

Figure 1. Consort flow diagram on the selection of the patients included in the study.

Characteristics of patients

One hundred children with drug-resistant epilepsy were involved in the study and their characteristics are presented in **Table 1**. The median age was eight years old (5–15) in the treatment group and nine years old (5–13) in the placebo group. The median age of first seizure was 12 months for the treatment group (4–36) and 24 months for the placebo group (4–63). The median duration of treatment was five years for the treatment group (2–8) and six years for the placebo group (3–8). The pre-intervention data on vitamin C revealed that the deficient category was more prevalent in the placebo group, while the sufficient category was notably larger in the treatment group. Conversely, for vitamin E, the deficient category was more prominent in the treatment group, whereas the sufficient category was considerably prominent in the placebo group. In the treatment and placebo groups, the placebo/vitamin intake compliance rate was mostly moderate, 24% and 29%, respectively (**Table 1**). The characteristics of the patients were generally homogenous between treatment and placebo groups (**Table 1**).

Table 1. Pre-treatment characteristics and treatment compliance of drug-resistant epilepsy patients included in the study

Characteristics	Treatment group n=50	Placebo group n=50	*p*-value
Age (years), median (IQR)	8.0 (5.0–15.0)	9.0 (5.0–13.0)	0.631
Gender, n (%)			0.548
Male	28.0 (56.0)	25.0 (50.0)	
Female	25 (50.0)	22.0 (44.0)	
Vitamin C RDA (%), median (IQR)	98.5 (44.7–171.7)	90.5 (27.0–180.0)	0.679
Vitamin C RDA category, n (%)			0.548
Sufficient	25.0 (50.0)	22.0 (44.0)	
Deficient	25.0(50.0)	28.0 (56.0)	
Vitamin E RDA (%), median (IQR)	54.5 (32.0–94.0)	53,0 (30.5–93.2)	0.893
Vitamin E RDA category, n (%)			0.812
Sufficient	11.0 (22.0)	12.0 (24.0)	
Deficient	39.0 (78.0)	38.0(76.0)	
Hb (g/dL), median (IQR)	12.9 (11.9–14.1)	12.6 (12.07–13.7)	0.374
Thrombocytes (10^3/µL), median (IQR)	278.0 (190.7–325.2)	292.5 (249.7–382.2)	0.087
AST (U/L), median (IQR)	22.0 (17.0–28.0)	26.5 (20.5–31.2)	0.099
ALT (U/L), median (IQR)	16.0 (9.7–23.7)	19.5 (14.7–31.0)	0.064
Leukocytes, median (IQR)	8.8 (7.5–10.9)	9.1 (7.2–10.9)	0.757

Characteristics	Treatment group n=50	Placebo group n=50	*p*-value
Urea (mg/dL), median (IQR)	19.6 (12.3–21.4)	21.4 (12.8–23.5)	0.477
Creatinine (mg/dL), median (IQR)	0.4 (0.3–0.6)	0.4 (0.3–0.5)	0.453
Age of first seizure (month), median (IQR)	12.0 (4.0–36.0)	24.0 (4.0–63.0)	0.156
Duration of treatment OAE (year), median (IQR)	5.0 (2.0–8.0)	6.0 (3.0–8.0)	0.849
Patient compliance, n (%)			0.400
Low	8.0 (16.0)	4.0 (8.0)	
Moderate	24.0.0 (48.0)	29.0 (58.0)	
High	18.0 (36.0)	17.0 (34.0)	

IQR: inter-quartile range; RDA: recommended dietary allowance

Comparison of MDA levels between intervention and placebo groups

The levels of MDA were significantly reduced after the treatment compared to pre-treatment both in the treatment group ($p<0.001$) and placebo group ($p=0.028$). However, our data indicated that the levels of MDA were not significantly different between intervention and placebo groups both for pre- or post-treatment, with $p=0.920$ and $p=0.880$, respectively (**Table 2**). The changes in MDA levels (between post- and pre-treatment) were also not different between the two groups ($p=0.181$).

Table 2. Differences in MDA levels before and after intervention by groups

MDA (nmol/mL)	Group		*p*-value *
	Treatment (n=42)	Placebo (n=46)	
Before, median (IQR)	0.901 (0.739–1.083)	0.890 (0.175–1.15)	0.920 [a]
After, median (IQR)	0.727 (0.474–0.893)	0.698 (0.320–0.965)	0.880 [a]
Difference, median (IQR)	-0.172 (-0.458)–(-0.034)	-0.131 (-0.537)–(-0.034)	0.181 [a]
p-value **	<0.001 [b]	0.028 [b]	

[a] Analyzed with Mann-Whitney test
[b] Analyzed with Wilcoxon test
* Comparative analysis of pre- and post-intervention MDA levels between groups
** Analysis of MDA level changes within the group

The post-hoc power was calculated using the G Power instrument [16] and found the post-hoc power was 12.35%. The present study power value for the statistical test of MDA levels as an oxidative stress indicator was less than 80%; this lack of power value could be caused by the smaller number of samples used.

Comparison of seizure frequency between intervention and placebo groups

A significant reduction in seizure frequency was observed in the treatment group, experienced by 40 out of 42 participants (95%), compared to 16 out of 46 participants (35%) in the placebo group, with a $p<0.001$ (**Table 3**). Our per-protocol analysis indicated that the control event rate (CER) was 65%, experimental event rate (EER) of 5%, relative risk reduction (RRR=(CER-EER)/CER) of 0.92 or 92% absolute risk reduction (ARR=CER-EER) of 0.6 or 60%, and number needed to treat (NNT=1/ARR) of 1.6 (**Table 3**). A 92% RRR suggests that administering vitamins C and E could reduce the seizure frequency by 92% compared to a placebo. The NNT indicated that the administration of vitamin C and vitamin E to approximately two drug-resistant epilepsy patients would result in one patient with a reduced seizure frequency.

Table 3. Seizure frequency based on per-protocol analysis and intention-to-treat analysis

Analysis type	Seizure frequency		*p*-value
	Decreased	Unchanged	
Per-protocol analysis			
Treatment group (n=42)	40 (95%)	2 (5%)	<0.001
Placebo group (n=46)	16 (35%)	30 (65%)	
Intention-to-treat analysis			
Treatment group (n=50)	40 (80%)	10 (20%)	<0.001
Placebo group (n=50)	16 (32%)	34 (68%)	

The analyses based on intention-to-treat analysis found the CER of 68%, EER of 20%, RRR of 70%, ARR of 48%, and NNT of 2. These suggested that treatment with vitamins C and E would reduce the seizure frequency by 70% compared to the placebo.

Relationship between changes in MDA levels and seizure frequency in drug-resistant epileptic patients

Relationships between changes in MDA levels and reduction of seizure frequency in drug-resistant epileptic patients are presented in **Table 4**. Our data indicated that there was no relationship between changes in MDA levels and the seizure frequency in both treatment (p=0.967) and placebo groups (p=0.065) (**Table 4**). The results of this study suggested that reduction of the seizure frequency in the patients was not due to reduction of the MDA levels post-treatment.

Table 4. Relationship between changes in MDA levels and seizure frequency

Study group	Variable	Seizure frequency		p-value
		Decreased (n=56)	Constant (n=32)	
Treatment	Delta MDA (nmol/mL) median (IQR)	-0.172 (-0.42)–(-0.039)	-0.310 (-0.620)–(-0.001)	0.967
Placebo	Delta MDA (nmol/mL) median (IQR)	-0.207 (-0.649)–(-0.129)	0.011 (-0.501)–(0.065)	0.065

IQR: inter-quartile range

Discussion

The study involved 100 drug-resistant epilepsy patients aged 1–18 years to determine the role of vitamins C and E in reducing MDA level and seizure frequency. Our food recall analysis revealed that children with drug-resistant epilepsy were in the category of vitamin C and E deficiency. Nevertheless, a blood test is recommended to determine the level of vitamins C and E in the blood. A decrease in serum levels of vitamin E, catalase, and total antioxidant capacity usually occurs in epileptic patients receiving anti-epileptics. Studies found that vitamin E levels are lower in pediatric epileptic patients who received more than one AED therapy compared to those who received a single AED [7,8,9].

The results of routine blood tests, AST, ALT, urea, and creatinine in both intervention groups were within normal limits (**Table 1**). The administration of anti-epileptic drugs showed no side effects, such as thrombocytopenia, increased levels of transaminase enzymes, and increased urea creatinine from the use of valproic acid as one of the risk factors for increased oxidative stress that can, in turn, increase the MDA levels [18,19]. Increased oxidative stress caused by liver and kidney problems could lead to bias in the results of MDA examinations. The overall characteristics of the subjects of the study are equivalent in the treatment group and the placebo group (**Table 1**).

Our data suggested that the pre-intervention MDA levels in both treatment and placebo groups were high, with a median of 0.901 and 0.890 nmol/mL, and there was no significant difference between the two groups (p=0.920). This increase in pre-treatment MDA level is consistent with a previous study that demonstrated significant increases in lipid peroxidation products (MDA) as an oxidative stress marker in epileptic patients in both pediatric and adult patients [20]. Previous studies found elevated MDA levels in patients with epilepsy aged 1–12 years compared to the control group (healthy children), before vitamins C and E intervention, and in drug-resistant patients aged 20–50 years [10,11,17].

This study's results also showed a significant decrease in post-intervention MDA levels compared to pre-treatment in both treatment and control groups, with the median delta value was -0.172 nmol/mL and -0.131 nmol/mL, respectively. This study is consistent with previous studies that found a significant decrease in MDA levels after the intervention [10,12]. The results of the study can be explained since several factors or mechanisms could affect the MDA levels. The level of MDA as a product of lipid peroxidase from increased reactive oxygen species (ROS) is influenced by levels of endogenous antioxidants such as superoxide dismutase, catalase,

glutathione, and levels of exogenic antioxidants such as vitamin C, vitamin E, vitamin A, coenzyme Q, zinc, and other essential metals in the body [12,21,22]. Endogenous antioxidants could reduce the formation of free radicals by disrupting chain reactions and turning them into more stable products. The reduction of MDA levels in placebo patients may occur because the placebo group had better levels of endogenous antioxidants than the intervention group. MDA dropped even though they were not given the exogenous antioxidants vitamins C and E. Since infections could increase oxidative stress in patients [18], further examinations in addition to leukocyte tests are needed, such as the neutrophil-lymphocyte ratio (NLR), blood absorption rate, C-reactive protein, and procalcitonin level. The albumin test can be used as one of the indicators to evaluate the effectiveness of AED [23].

Our study also found a decrease in the seizure frequency among drug-resistant epileptic patients evaluated using per-protocol and intention-to-treat analysis. This study supports previous research findings, which indicated a decrease in MDA levels and seizure frequency in patients with drug-resistant epilepsy receiving vitamin E, and there was a significant difference in comparison with the placebo group [10,16,24]. For instance, a study in a treatment group of 1–12-year-old patients with drug-resistant epilepsy administered vitamin E at the upper RDA doses (aged 1–3: 200 IU/day, aged 4–8: 400 IU/day, and aged 9–13: 600 IU/day) for six months, obtained a significant difference in the reduction in seizures rate compared to the placebo group (p=0.037) [24]. Furthermore, another study among general epileptic patients aged 14–52 years with vitamin E administration at 400 IU/day for two months showed a significant decrease in MDA levels and a significant decline in seizure frequencies compared to the control group (p<0.001) [10]. Electroencephalography examination can help to evaluate whether reduced clinical manifestations of seizures correspond with a reduced seizure depiction on the electroencephalography. However, no EEG examination was performed in this study.

The study, however, found no significant association between changes in MDA levels and seizure frequency in both the treatment and placebo groups, suggesting seizure frequencies were unrelated to the MDA level. A decrease in seizure frequency may occur due to other factors such as levels of vitamins C and E in the blood, endogenous antioxidant levels, and other oxidative stress biomarkers such as ROS. Additional examinations are needed to assess oxygenated stress markers, including oxidation markers (ROS, reactive nitrogen species (RNS), and ROS derivatives) and antioxidant markers (superoxide dismutase, catalase, antioxidant total capacity) [21,22].

Strengths and limitations of the study

This study is the first in Indonesia to incorporate a prospective, randomized, double-blind, placebo-controlled clinical trial, the gold standard of clinical testing. It is one of the few studies worldwide assessing the effect of antioxidant administration of vitamins C and E in reducing oxidative stress among pediatric patients with drug-resistant epilepsy. The study covered the age range of 1–18 years, with more participants than the available studies. Administration of vitamins C and E in age-appropriate doses for eight weeks reduced seizure frequency by RRR 0.92 or 92%, compared to placebo, alongside low NNT values. This study could provide insights into the role of antioxidants in mitigating oxidative stress and reducing seizure frequency among drug-resistant epileptic patients to help improve their quality of life.

The study is subject to several limitations. There were no laboratory tests to measure the levels of vitamin E and vitamin C before and after the intervention, nor did they assess endogenous antioxidants in the blood, such as superoxide dismutase, catalase and glutathione peroxidase. These tests are needed to evaluate whether the MDA levels match the levels of endogenous and exogenous antioxidants in the body. The study also did not carry out an electroencephalographic examination to evaluate whether reduced clinical manifestations of seizures corresponded with a reduced seizure depiction on the EEG. Additionally, the administration of vitamins C and E and intake monitoring was limited to eight weeks. Lastly, this study only recorded sources of vitamins C and E from the patients' daily diet 24 hours before commencement (food recall), but not during the intervention period.

Conclusion

Our data indicated that the levels of MDA (baseline, post-intervention, and changes between post- and pre-intervention) were not significantly different between epileptic children receiving vitamin C and E as adjuvant therapy compared to children receiving anti-epileptics alone. However, the reduction in seizure frequency among those receiving adjuvant therapy was significantly higher compared to those receiving anti-epileptics alone. There was no significant relationship between the change in MDA levels and seizure frequencies in both groups. This study also found that those with drug-resistant epilepsy had low vitamin C and E intake prior to intervention and there were elevated MDA levels in both groups compared to healthy individuals. Therefore, it is recommended that drug-resistant epileptic patients improve their intake of foods rich in vitamins C and E, both in the form of daily diet and supplementation. Administration of antioxidants as adjuvant therapy with vitamin C (100 mg/day) and vitamin E (200 IU/day for <5 years or 400 IU/day ≥5 years) could be considered in drug-resistant epileptic patients. No side effects were found during the study at this dosage.

Ethics approval

This study was approved by the Research Ethics Committee of Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia (KET.1135/UN2.F1/ETIK/PPM.00.02/2022).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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