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Effectiveness of Selenium Supplement on Cognitive Function in Patients with Epilepsy

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ABSTRACT

Objective: There is much evidence about the development of cognitive problems from the early stages of the epilepsy. Selenium can be beneficial for cognitive function because of its lowering effect on oxidative stress. This study was aimed to evaluate the effect of selenium on the cognitive performance of patients with epilepsy.

Methods: Seventy patients between 20 and 65 years old with idiopathic generalized tonic-clonic epilepsy were enrolled with a simple randomized single-blind method and divided into case and control groups. The cognitive evaluation was performed by the Montreal Cognitive Assessment (MoCA) test at the beginning of study and 2 and 4 months after the treatment. The case group and control group received selenium and placebo, respectively.

Results: At 2 months, MoCA test average score was 24.49 in the placebo group and 24.91 in the case group. At the end of the fourth month, the MoCA test average score was 24.54 in the placebo group and 26.31 in the case group. These findings did not demonstrate any significant difference between groups.

Conclusion: The results of this study showed that selenium supplementation does not improve cognitive function in patients with epilepsy with mild cognitive impairment. Future studies with a longer course of trial and higher doses of selenium along with the measurement of serum selenium levels are recommended.

Keywords: Cognition, epilepsy, selenium

INTRODUCTION

Behavioral disorders or different types of epilepsy are a health problem in humans; epilepsy, as a common neurological disorder in humans, is the most prevalent one after all types of heart attacks and strokes. Various reports indicate that changes in the levels of some electrolytes and trace elements in the body play a vital role in epilepsy.[1]

Selenium is a rare and essential mineral for human health that exerts its effects mainly through its dependent enzymes. Selenium is a major component of several enzymes with antioxidant activity, and a deficiency of this element predisposes a person to a variety of damages caused by oxidative stress. Some research shows that increasing the production of free radicals and reducing the activity of the body's antioxidant defense system increases the risk of seizures. Nerve cells are especially vulnerable to these free radicals, and any defense deficiency or increase in these radicals can lead to cell death.[2]

Selenium as an essential micronutrient may be of particular relevance owing to its importance for the maintenance of brain homeostasis. The biological effects of selenium on brain health are mediated by selenium-containing proteins (selenoproteins). Because selenium was shown to be involved in diverse functions of the central nervous system, such as motor performance, coordination, memory

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and cognition, a possible role of selenium and selenoproteins in brain signaling pathways may be assumed.[3] These roles might include 1) antioxidant properties, 2) inflammation, 3) influencing protein phosphorylation and ion channels, 4) alteration of calcium homeostasis, 5) brain cholesterol metabolism, 6) a direct signaling function for selenoprotein P through interaction with postsynaptic apolipoprotein E receptors 2 (ApoER2), 7) enhancing hippocampal neuronal survival,[4] 8) suppression of amyloid-β accumulation, and 9) inhibition of neuronal apoptosis.[5]

Evidence from animal and human studies suggests the importance of selenium for cognitive performance, mood, and behavior through protection against oxidative damage to substrates including low-density lipoproteins (LDLs), hydroperoxide, hydrogen peroxide, peroxynitrite, and tert-butyl hydroperoxide (t-BHP).[6] Glutathione peroxidase, thioredoxin reductase, and methionine sulfoxide reductase are selenium-dependent enzymes involved in antioxidant defense and regulation of intracellular redox. Decreased selenium resources in living organisms reduce the activity of selenium-dependent enzymes, resulting in cell destruction. Some studies also show an improvement in the antioxidant status of patients with epilepsy after treatment with antiepileptic drugs. Supplements and antioxidants are additive therapies that because of the etiological mechanisms of seizures may help to improve the mental and physical condition of patients with epilepsy.[7,8] Of course, validating this efficacy requires further interventional research.

Different studies have yielded different results regarding the possible role of selenium in epilepsy, but the relation between selenium and epilepsy is still unknown, and there is no definite opinion about the effect of these elements on epilepsy. Accordingly, and considering the importance of the issue, in this study, we aimed to investigate the effectiveness of selenium supplement on the cognitive function of patients with epilepsy. By better understanding the etiology and pathogenesis of epilepsy and the mechanisms involved in various areas of cognitive function, the effective and new potential treatments for this disease will be found.

METHODS

In this randomized clinical trial, 70 patients with epilepsy aged 20 to 65 years who were referred to the Neurology Clinic of Zanjan Vali-e-Asr Hospital from March 2018 to October 2019 and were willing to participate in the study were enrolled. After signing the consent form, they were examined and divided into case and control groups, according to the list of patients, subject to the inclusion criteria, using a random number table. One group received the drug, and the second group received a placebo, but the patients were blind about the receiving treatment.

MAIN POINTS

- The relation between selenium and cognitive function in patients with epilepsy is still unknown.
- Because of the antioxidative potential of selenoproteins by keeping free radical numbers in check, selenium could play an important role in mental functions.
- The selenium supplementation does not improve cognitive function in patients with epilepsy with mild cognitive impairment.
- Cognitive impairment is frequent in any age in patients with epilepsy; however, the underlying mechanisms and treatment options are still known.

The duration of the project was 4 months, and the type of drug used in the case group was selenium capsules (200 micrograms) from the 21st Century Company (Tempe, Arizona, USA). In the control group, a placebo made by the manufacturer with the same shape and material of selenium capsules, containing a neutral substance, was utilized. Before starting the treatment, the cognitive function of all patients was assessed by the Montreal Cognitive Assessment (MoCA) test. Then, both groups were given medication. After 2 months of using the treatment and at the end of the fourth month (completion of the project), again the MoCA test was used for evaluation.

MoCA questionnaire is a cognitive screening test that has a maximum possible score of 30 and includes an examination of language, attention, memory, abstract thinking, and other cognitive aspects of the patient.[9] A score above 24 is normal, and a score below it is considered abnormal. If the patient has an undergraduate level of education, a score will be added to the patient's score to adjust the test. At the end of the study, the effect of drug and placebo on patients' cognitive function in the case and control groups was compared, respectively.

The Ethics Committee for Research approved this study on March 28, 2018, with the Code of Ethics (ZUMS.REC.1396.267). The protocol was registered on Iranian Registry of Clinical Trials (IRCT) under the ID: IRCT20101209005352N3.

Statistical Analysis

Simple randomization was used to allocate patients in two groups. The *t* test was applied to compare the group differences. For statistical analysis, we used Kolmogorov-Smirnov, repeated measure, and regression analysis (Enter Method) tests; Statistical Package for the Social Sciences (IBM SPSS Corp., Armonk, NY, USA) software version 25.0.0.1 was used, and *P* values less than .05 were considered statistically significant.

RESULTS

In this study, 70 patients with epilepsy aged 20 to 65 years were studied in two experimental groups of cases (n = 35) and placebo (n = 35). Demographic data results are presented in Table 1.

The frequency distribution of the number of seizures in the placebo group was as follows: 11 people had seizures once in 1 to 6 months, 10 people had seizures once in 6 to 12 months, and 14 people had seizures once every 12 months. In the treatment group, 9 people had seizures once in 1 to 6 months, 10 people had seizures once in 6 to 12 months, and 16 people had seizures once every 12 months, and according to the P value, there was no significant difference between the two groups in terms of the number of seizures.

There was no statistically significant difference in the frequency distribution of the type of drug used in the placebo and treatment groups, according to the P value, except for topiramate, which was used only by the treatment group and showed a statistically nonsignificant difference.

At the beginning of the study, the placebo group had a mean score of 24.31 (ranging from 20 to 28), and the treatment group had a mean of 22.80 (ranging from 15 to 28) on the MoCA test. The mean score of the MoCA test 2 months after treatment in the placebo group was 24.49 (ranging from 19 to 30), and in the treatment group, it was 24.91 (ranging from 16 to 30).

Four months after treatment, the mean score of the MoCA test in the placebo group was 24.54 (maximum 30 and minimum 19), and in the treatment group, it was 26.31 (maximum 30 and minimum 16). The compari-

Table 1. Frequency distribution of demographic characteristics in study groups

Variable	Subtype	Group	
		Case (treatment)	Placebo
Gender	Female	17	17
	Male	18	18
Age of the participants (years)	Minimum	20	20
	Maximum	57	53
	Mean	32.89	34.80
Educational level	Elementary	12	8
	Middle school	0	5
	High school diploma	14	12
	University	9	10

Table 2. Comparison of mean MoCA test scores between the two groups using t test

MoCA test	Groups	Number	Mean ± SD	Mean error
At the beginning	Placebo	35	24.31 ± 2.483	0.420
	Treatment	35	22.80 ± 3.677	0.621
After 2 months	Placebo	35	24.49 ± 2.863	0.484
	Treatment	35	24.91 ± 3.689	0.624
After 4 months	placebo	35	24.54 ± 3.023	0.511
	Treatment	35	26.31 ± 3.716	0.628

SD: standard deviation

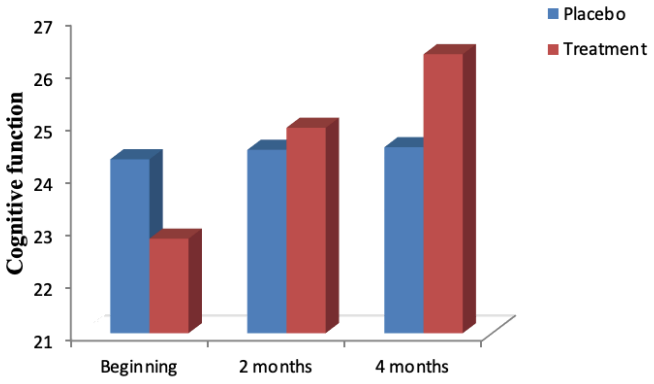

Figure 1. Difference in cognitive function between the two groups

son of mean MoCA test scores between the two groups is demonstrated in Table 2. Owing to the small difference between the two groups, cognitive function was not significantly different in both groups. This difference is shown in Figure 1. The only effective variable was age. Therefore, the regression model for the MoCA variable 4 months after treatment, because of the negative age parameter, showed that the score of MoCA 4 months later (drug effect) decreases with increasing age. For each year, the effect of the drug decreased by 0.11, and because of the small difference between the means of the two groups and the large standard deviation, this decrease was not clinically significant

DISCUSSION

Cognitive problems are common in patients with epilepsy for a variety of reasons, including brain lesions, frequency of seizures, type of treatment, chronic and severe epilepsy, and polytherapy.[10] There is evidence that cognitive impairment exists from the onset of the disease.[11] Therefore, early neuropsychiatric assessment is important in the course of the disease. Animal models have shown that a selenium supplementation can delay epilepsy progression.[12] Considering the role of antioxidants in the incidence of seizures and epilepsy, in this study, we evaluated the effectiveness of selenium supplementation on the cognitive function of patients with epilepsy.

Our data showed that selenium supplement was not associated with cognitive function in patients with epilepsy. Similar studies showed that there is a positive trend between plasma selenium and cognitive function, and cross-sectional study of the elderly in China showed that a decrease in selenium concentration was associated with lower cognitive scores.[13]

The effects of different concentrations of selenium in evaluating the results of clinical trials also lead to conflicting data. For example, the findings of the PREADVISE study showed that selenium supplements did not affect Alzheimer disease in elderly males.[14] In contrast, an increase in selenium (consumption of 288.8 micrograms of selenium per day) to improve the cognitive function in the elderly had shown a significant improvement in constructional praxis and the animal naming subset in a pilot study, supporting the relationship between selenium and cognitive function.[15] Overall, several studies have shown evidence that low plasma selenium concentrations are associated with decreased cognitive function in the elderly.[16–18]

Various studies have shown that aging results in structural and functional changes in the brain that lead to age-related cognitive decline, including decreased brain volume, synaptic density, and plasticity and increased oxidative stress and inflammation; selenium is effective in protecting neurons from this complication.[19] Likewise, neurotrophic factors are associated with the maintenance of plasticity and neuronal survival and, therefore, are considered essential factors for brain flexibility.[20]

Ashrafi showed that serum activity and selenium levels were significantly lower in patients with epilepsy.[21] Although selenium levels were not measured in our study, our data showed that selenium supplementation in patients with epilepsy did not affect patients' cognitive function. Lack of effect may be due to sufficient selenium concentration in these patients.

The study of Bhardwaj and Sattarinezhad showed that CoQ10 supplementation improved cognitive function and reduced dementia due to streptozotocin injection,[22] whereas in our study, there was no association between selenium supplementation and cognitive function, and it was not consistent with the results of this study.

The study by Pillai showed that selenium deficiency is associated with decreased cognitive function and increases the risk of seizures in patients with epilepsy. Selenium supplement increases lipid peroxidation by increasing glutathione peroxidase and helps to reduce seizures.[23] In our study, slightly improved cognitive function was seen in patients with epilepsy by taking selenium supplement, and it was associated with age variables but did not show a significant difference between the two groups and was not consistent with the results of this study.

The study of Gao et al.[13] showed that low selenium level is associated with lower cognitive function. In our study, a significant relationship was observed between ages and decreased cognitive function of patients, but their cognitive function was not related to selenium level and did not agree with the results of this study.

In 2018, Cardoso et al.[24] showed that plasma selenium was not associated with cognitive function, inflammatory markers, or neurotherapy factors, regardless of age, sex, body mass index, regular physical activity, APO status, education, and history of cardiovascular disease. In our study, the lack of this relationship was observed and was consistent with the results of this study.

The results of our study are affected by certain limitations, including the absence of cases with drug-resistant epilepsy, undetermined number of patients with monotherapy or polytherapy in each study group, inability to measure the serum level of selenium and antiepileptic drugs (AEDs), and inability to determine the effects of selenium on AEDs serum level and vice versa.

It is suggested that other studies be conducted based on the following design to explore the potential association of selenium with reduced cognitive function: 1) increase the duration of the project, 2) assess the blood selenium level by taking blood samples from patients before and after the project, 3) a higher dose of selenium (higher than the dose used in the current study [200 mcg] should be prescribed to patients), and 4) separated domains of cognitive function (by examining each area of cognitive function separately in each patient and comparing the changes in that area before and after the project).

In conclusion, the results of our study showed that selenium supplement was not associated with cognitive function in patients with epilepsy, and this lack of correlation may be due to optimized selenoproteins because of proper selenium consumption among this group of patients or a result of insufficient duration of the project and lack of measurement of serum selenium levels in patients. Although in our study, there was no significant relation between selenium levels and cognitive function in patients with epilepsy, as selenium is a very strong antioxidant in cellular reactions, reduced selenium intake can lead to enzymatic changes and increase of free radicals, eventually resulting in neurological disorders.

Ethics Committee Approval: The Ethics Committee for Research approved this study on March 28, 2018, with the Code of Ethics (ZUMS.REC.1396.267). The protocol was registered on IRCT.IR under the ID: IRCT20101209005352N3.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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