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Original Article

Relationship between Serum Malondialdehyde (MDA) Levels with Seizure Frequency in Epilepsy Patients with Combination of Phenytoin and Valproic Acid

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Abstract

Background : Oxidative stress is believed to be one of the factors involved in the pathogenesis of epileptogenic where lipid peroxidation occurs which produces Malondialdehyde (MDA). Epilepsy and some Antiepileptic Drugs (AEDs) can improve or worsen seizure frequency thereby significantly changing blood MDA levels. The objectives of this study was to determine the relationship between serum MDA levels and seizure frequency in epileptic patients treated with AEDs, a combination of phenytoin and valproic acid.
Methods : A cross-sectional study with consecutive sampling of 46 subjects (with epilepsy receiving combination therapy with phenytoin and valproic acid. The research was conducted at the Neurology Policlinic at RSUP Dr. Kariadi in December 2022 – February 2023. MDA levels were measured using the Enzyme Linked Immunosorbent Assay (ELISA) method. The relationship between serum MDA levels and seizure frequency was analyzed using Spearman's test since both of the variables are ordinal scale, the results were significant if $p<0.05$.
Results : There was no relationship between MDA levels and seizure frequency in epileptic patients with the combination of phenytoin and valproic acid. ($p=0.516$) There is a significant relationship between the frequency of seizures and the length of treatment ($p=0.026$) with a weak negative correlation ($rho=0.328$). There is a significant relationship between the frequency of seizures and the age of onset of epilepsy ($p=0.037$) with a weak negative correlation ($rho=0.309$).
Conclusion : There is a significant relationship between the frequency of seizures with the length of treatment and the age of onset of epilepsy.

Keywords : MDA, frequency of seizures, length of treatment, age of onset of epilepsy

INTRODUCTION

Oxidative stress is believed to be one of the factors involved in the pathogenesis of epileptogenesis.[1,2] The brain and nervous system are very vulnerable to lipid peroxidation because lipid membranes are very rich in polyunsaturated fatty acid chains that can increase peroxidation and prevent neuron regeneration[3–5] and can exacerbate some forms of seizures.[6–8]

A review of studies conducted on epilepsy and oxidative stress showed that the parameters of oxidative stress increased.[9] Lipid peroxidation is an indicator of free radical metabolism and oxidative stress in humans and other organisms. Among the aldehydes produced from lipid peroxidation, Malondialdehyde (MDA) and 4-hydroxynonenal (HNE) have received the most attention, because MDA is produced in large quantities during lipid peroxidation, so it is generally used to measure the level of oxidative stress, being a simple and easy marker to determine Lipid peroxidation due to oxidative stress in human subjects.[10,11] The serum MDA level in healthy individuals is 0.8 ± 0.20 µmol/L.[12]

Epilepsy causes increased oxidative stress and increases MDA levels.[13] MDA levels are affected during administration of anti-epileptic drugs (OAE).[14] Many studies have shown a significant increase in peripheral blood MDA serum levels in epileptic patients compared to controls, but none has assessed the relationship between MDA serum levels and seizure frequency in epileptic patients.

Dr. Kariadi hospital is a referral hospital where epilepsy patients referred from regional hospitals who have previously taken anti-epileptic drugs are referred because their seizures have not been resolved. This is what underlies the fact that the majority of epilepsy patients at Dr. Kariadi hospital in the BPJS era received combination drug therapy, including phenytoin and valproic acid.

METHODS

This research is an observational study with a cross sectional approach. The inclusion criteria included all epilepsy patients with the main combination therapy of phenytoin and valproic acid with a length of treatment of more than 6 months because shorter treatment duration was significantly associated with higher seizure frequency, subjects who received anti-epileptic treatment for one to five years and those for more than five years had a lower prevalence of risk of increased frequency of seizures. The next inclusion criteria are aged 18–60 years and patients who were cooperative and willing to participate in the research program by signing an informed consent. Exclusion criteria included secondary epilepsy with a history of mass etiology in the brain, trauma, infection and patients with hypertension, DM and chronic kidney disease. The selection of research subjects was by consecutive sampling, sample selection by determining subjects who meet the inclusion criteria and are included in the research for a certain period of time. Based on the Lameshow formula, there were 46 research subjects. In this study, the independent variable was the serum MDA level, namely the median cubital vein blood MDA level in blood plasma which was examined using the ELISA spectrophotometric method and expressed in units of µmol/l. The normal serum MDA level is 0.8 ± 0.20 µmol/L which is an ordinal scale grouped into: normal MDA levels (600 – 1000 pg/mL), increased MDA levels (more than 1000 pg/mL), decreased MDA levels (less than 600 pg/mL). The dependent variable is the frequency of seizures, namely the number of seizures that occurred in the last 1 year, obtained from anamnesis and medical records, divided into less than 10 times and more than or equal to 10 times, which is an ordinal scale. Duration of treatment and age of onset were confounding variables, both being ordinal scales. The duration of treatment was obtained from the history and medical records, namely the duration of treatment for a combination of phenytoin and valproic acid, which was divided into more than or equal to 5 years and less than 5 years. Age of onset is the age at which the patient was diagnosed with epilepsy obtained from the history and medical records, divided into age more than 24 years and age 18–24 years.

This research was conducted in December 2022 – February 2023 at the Outpatient Installation of the Merpati Neurology Polyclinic, RSUP Dr. Kariadi Semarang. The research was carried out by requesting approval from the Medical Research Ethics Committee of FK UNDIP/RSUP Dr. Kariadi with number 1247/EC/KEPK-RSDK/2022. The research subjects underwent neurological examination and blood laboratory examination of serum MDA levels. Blood samples were examined in the GAKI laboratory. The MDA examination procedure, namely the venous blood sample is stored in a tube then centrifuged and serum is collected. Examination of MDA serum levels was carried out using the ELISA method, with an ELISA kit produced by Elabscience (Catalog No: E-EL-0060), then the results were recorded and the data analyzed.

The data that has been collected is checked for completeness and correctness, then the coding process is carried out, tabulated and processed to a computer using a statistical software program. Results are presented in tabular form. To determine the relationship between serum MDA levels and seizure frequency in epileptic patients with a combination of phenytoin and valproic acid, Spearman's correlation test was performed with a 95% confidence level. Confounding variables, namely duration of treatment and onset of epilepsy, were subjected to a bivariate test using the Spearman correlation test. Results are said to be significant if $p < 0.05$.

RESULTS

There were 46 subjects obtained in this study who met the inclusion criteria.

This study used 46 subjects, consisting of 29 male subjects (63%) and 17 female subjects (37%). Based on age, there were 40 subjects aged 19–44 years (87%) and 6 subjects aged more than or equal to 45 years (13%). A total of 8 subjects had elementary school education (17.4%), 5 junior high school subjects (10.9%), 21 high school subjects or equivalent (45.7%), 2 D3 subjects (4.3%) and 10 S1 subjects (21.7%). Based on the type of work, 6 subjects did not work (13%), 8 student subjects (17.4%), 9 housewife subjects (19.6%), 12 self-employed subjects (26.1%), 9 private employee subjects (19.6%) and 2 subjects Civil servants (2%). Based on therapy, 25 subjects received combination therapy with phenytoin and valproate (54.3%) and 21 subjects received combination therapy with phenytoin, valproic acid and other OAE (45.7%) (Table 1).

A total of 46 samples were taken to check serum MDA levels and the results obtained were 7 subjects with MDA levels of 600–1000 pg/mL (15.2%), 12 subjects with MDA levels >1000 pg/mL (26.1%) and 27 subjects with levels MDA <600 pg/mL (58.7%). Based on the anamnesis, it was found that 17 subjects had a frequency of seizures in 1 year of less than 10 times (37%) and 29 subjects with a frequency of seizures in 1 year of more than or equal to 10 times (63%). A total of 25 subjects received the main combination therapy with phenytoin and valproic acid for more than 5 years (56.5%) and 21 subjects received the main combination therapy with phenytoin and valproic acid for less than 5 years (43.5%). In anamnesis, there were 28 subjects with age of onset of epilepsy more than 24 years (60.9%) and 18 subjects with age of onset of 18–24 years (39.1%) (Table 2).

Based on Table 3, the Sperman correlation test found no relationship between serum MDA levels and seizure frequency in epileptic patients on combination therapy with phenytoin and valproic acid (p=0.516) with a very weak negative correlation rate (rho=-0.098). (Hypothesis 1 is not proven). There was a significant relationship between the frequency of seizures and the length of treatment in patients on combination therapy with phenytoin and valproic acid (p=0.026) with a weak negative correlation rate (rho=-0.328), the longer the

TABLE 1
Characteristics of research subjects

Variable		Epilepsy patient Total (n=46)	
		f	%
Gender	Man	29	63
	Woman	17	37
Age	19-44 years	40	87
	≥ 45 years	6	13
Education	SD	8	17.4
	SMP	5	10.9
	SMA/SMK/MA	21	45.7
	D3	2	4.3
	S1	10	21.7
Work	Doesn't work	6	13
	Student	8	17.4
	Housewife	9	19.6
	Self-employed	12	26.1
	Private sector employee	9	19.6
	Civil servant	2	4.3
Therapy	Phenytoin and valproic acid	25	54.3
	Phenytoin, valproic acid and other OAEs	21	45.7

TABLE 2
Results of research variable data

Variable		Epilepsy patient Total (n=46)	
		f	%
MDA levels (pg/mL)	600–1000	7	15.2
	>1000	12	26.1
	<600	27	58.7
Awakening frequency	Less than 10 times	17	37
	≥ 10 times	29	63
Treatment duration	≥ 5 years	26	56.5
	< 5 years	20	43.5
Age of onset of epilepsy	Over 24 years	28	60.9
	18 – 24 years	18	39.1

TABLE 3
Relationship between seizure frequency and MDA serum levels, length of treatment and age of onset of epilepsy

Variable	rho	p.s	Significance
MDA Serum Levels	-0.098	0.516*	Meaningless
Treatment duration	-0.328	0.026*	Meaningful
Age of Onset of Epilepsy	-0.309	0.037*	Meaningful

*Spearman Correlation Test is significant if $p<0.05$

treatment, the frequency of seizures will decrease. (Hypothesis 2 is proven). There is a significant relationship between the frequency of seizures and the age of onset of epilepsy in patients on combination therapy with phenytoin and valproic acid (p=0.037) with a weak negative correlation rate (rho=-0.309).

DISCUSSION

Relationship between Serum MDA levels and seizure frequency

In this study, there was no association between serum MDA levels and seizure frequency in epileptic patients on the main combination therapy with phenytoin and valproic acid (p=0.516) with a very weak negative correlation rate (rho=-0.098). There are several factors that affect MDA levels including the anti-epileptic drugs used. The drugs that increase GABA-ergic transmission (eg, vigabatrin, tiagabine, gabapentin, topiramate) or other antiepileptics (eg, lamotrigine, levetiracetam) reduce neuronal oxidation markers.[15] Valproic acid shows a significant antioxidant effect by reducing MDA levels. This can lead to a decrease in seizure activity that occurs due to the efficacy of OAE and the simultaneous neuroprotective effect of ROS modulation.[16] Erythrocyte MDA levels increased significantly among people with epilepsy compared to the control group, indicating the formation of free radicals in epilepsy. The results of this study on post-treatment epilepsy subjects showed that antiepileptic drugs can provide antioxidant effects and the addition of antioxidants to conventional drug therapy can increase further reductions in epileptic activity; also helps restore the antioxidant balance to normal status among epileptic subjects.[17] MDA levels were higher in the control group and this difference was statistically significant. It is thought that the lower MDA levels in epileptic patients may be due to the antiepileptic drugs used. In this case, MDA levels should be lower in patients undergoing polytherapy, while MDA levels should be higher in patients undergoing monotherapy compared to those undergoing polytherapy. This suggests that the type of antiepileptic drug used is also important at the MDA level. In a different experimental study, it was reported that MDA levels decreased with ethosuximide,

phenytoin and primidone.[13]

Other factors that affect serum MDA levels include a study in 97 DM patients with a control of 50 healthy people showing a significant increase in MDA levels in DM patients compared to controls.[12] Meanwhile, study of 82 DM patients found that consumption of vegetables, fruits, legumes and nuts was associated with lower MDA levels.[12] It was found that the average MDA level was highest in the hypertensive group, followed by prehypertension and the group of healthy subjects.[18] Study on 50 hypercholesterolemic subjects and 50 healthy control subjects showed that subjects with hypercholesterolemia had significantly higher MDA levels compared to healthy control subjects.[19] A study of 21 obese subjects with a control of 21 non-obese subjects, the results of which showed that the MDA levels of obese subjects were significantly higher than those of non-obese.[20] Another supporting study was conducted on 300 DM subjects with a control of 100 healthy subjects, showing that there was a significant positive relationship between the increase in BMI and MDA serum levels.[21] In several studies, higher serum MDA levels were found in CKD patients compared to healthy control subjects.[22] MDA levels increase with the development of kidney damage.[23] MDA was negatively correlated with glomerular filtration rate and differed significantly among patients with CKD stages 2, 3, 4, and 5. Higher serum MDA levels were also found in hemodialysis patients.[24] Serum MDA levels in kidney transplant patients were significantly lower than in dialysis patients.[25]

Based on the research there are factors that influence the emergence of the frequency of arousals including respondents who reported lack of sleep in the last 2 months had a 41% rate (AIRR = 1.41, 95% CI [1.02, 1.94]) the rate of occurrence of seizures higher than their counterparts. Studies from Denmark and Norway also support this finding. Seizure frequency in patients with generalized epilepsy was found to be very sensitive in sleep-deprived patients.[26] This study also found that responders who adhered to their OAE treatment had a lower risk of seizures which increased the probability of a score of zero for seizure frequency compared to non-adherents. This is in line with a retrospective study and a cross-sectional study that found a statistically significant association between a higher risk of seizures and non-adherence to OAE. A pilot survey of the association between poor medication adherence and seizures also found a statistically significant association between drug dosage lost and a higher risk of revival attacks.[27] In the study it was found that emotional stress was the most frequently reported trigger in this study. Based on clinical experience and the results of these studies have shown a strong relationship between the occurrence of emotional stress and/or tension and the occurrence of seizures. Temkin and Davis claim that difficulties in everyday life increase the risk of increased seizures, while pleasurable experiences have the opposite effect.[28] The opinion that emotional stress lowers the arousal threshold is also consistent with the results of psychopharmacological and behavioral intervention studies, in which reduced levels of stress and anxiety are associated with decreased arousal frequency.[29] Among those who reported seizure triggers, 4.4% indicated they were sensitive to flickering light. This figure is consistent with previous findings that 5% of people with epilepsy are photosensitive.[28] Alcohol consumption was the fourth most frequent trigger (5.7%) of study participants. Given a person's reluctance to admit alcohol use, these results may represent an underestimation. Similar concerns related to reports of OAE drinking non-adherence (3.7%). It is therefore very possible that the reported frequency of alcohol use and medication nonadherence as seizure triggers may not reflect the actual results. Some women (3.3%) reported that their seizures were triggered by menstruation, as many women reported an increased frequency of menstrual cramps from a seizure diary, which often indicated that seizures did occur throughout the menstrual cycle.[28]

The relationship between the frequency of seizures and the duration of treatment

There was a significant relationship between the frequency of seizures and the length of treatment in patients receiving combination therapy with phenytoin and valproic acid (p=0.026) with a weak negative correlation (rho=-0.328). This is in accordance with the study of Kaddumukasa *et al* (2013), where subjects who had received antiepileptic drugs for more than one year had reduced seizure frequency with a p value of 0.0001. Shorter treatment duration was significantly associated with higher seizure frequency. Subjects who received anti-epileptic medication for one to five years and who for more than five years had a lower prevalence of increased risk of seizures.[30] Based on the research, it was also found that the frequency of seizures increased when the duration of treatment was less than five years.[26] However, in a study found a statistically significant positive relationship between treatment modalities and seizure attacks. Respondents who had undergone two or more treatments at the same time had a higher incidence of seizure attacks than those who had only used one treatment. The possible reason is that polytherapy increases the potential for drug-drug interactions, can affect adherence and is associated with higher costs of treatment. treatment for therapeutic drug monitoring.[31]

Relationship between seizure frequency and age of onset of epilepsy

There was a significant relationship between the frequency of seizures and the age of onset of epilepsy in patients on combination therapy with phenytoin and

valproic acid (p=0.037) with a weak negative correlation rate (rho=-0.309). This is in accordance with the study which found that the highest age of onset of epilepsy was 15–24 years (42.89%). In the study it was found that the highest frequency of epilepsy was found at the age of onset 15–24 years (56.35%). This study found an association between age and seizure frequency, indicating that patients in the 25–34 age group had a lower incidence of seizures than those in the 15–24 age group. This is different from a study conducted in the United States, which showed no significant correlation between change in seizure frequency from baseline to late follow-up and age. This could be because patients aged 25–34 years may have good adherence compared to those aged 15–24 years.[31] In the study 47% of patients had an age of onset <40 years, 38% of patients were between 41–60 years, and 15% were over 60 years.[32] Similar findings were reported where 46.9% were in the 21–40 year age group similar to other studies from India and other developing countries. In contrast, in studies in developed countries the number of patients with the age of first seizure onset was more in the age group >60 years with EPIMART (48.1%); Lars Forsgren (41.8%); Perre Jallon (40.1%). This variation may be because, in developing countries and rural areas, first seizures occurring in the elderly are often overlooked. India's main population belongs to the age group of 21–40 years, so the number of first seizure patients in this group is higher when compared to the elderly (>60 years).[33]

RESEARCH LIMITATIONS

This study has limitations including not assessing the factors that influence MDA levels including blood sugar levels, cholesterol levels, urea-creatinine levels, food recall and BMI status. This study did not assess the precipitating factors that influence the high frequency of seizures including the level of emotional stress, the level of adequate sleep, the level of fatigue, the level of alcohol consumption, the amount of light exposure and the level of adherence to taking OAE. This study did not record the frequency of awakenings using an awakening diary. In addition, this study did not assess the dose of phenytoin and valproic acid used in relation to the frequency of seizures.

CONCLUSION

There was no relationship between serum MDA levels and seizure frequency in epileptic patients with the combination of phenytoin and valproic acid. There is a relationship between the frequency of seizures and the duration of treatment in epilepsy patients with a combination of phenytoin and valproic acid. There is a relationship between the frequency of seizures and the age of onset in epilepsy patients with the combination of phenytoin and valproic acid.

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