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Research Article

Comparison between Effect of Fenitoin and Valproic Acid on Total Cholesterol in Epilepsy

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ABSTRACT
The use Anti Epilepsy Drugs (OAE) drugs for a long time can cause side effects, one of the examples is an increase in total cholesterol levels. Phenytoin and Valproic Acid are examples of OAE drugs which can cause an increase in total cholesterol levels. The purpose of this study was to determine the difference in average total cholesterol in epilepsy patients with single phenytoin therapy and epilepsy patients with single treatment of valproic acid. This research design uses a cross-sectional study. Type of research is observational analytic. Retrieval of data obtained from medical records at the Bhayangkara Grade I Raden Said Sukanto Hospital and measurement of total fasting cholesterol levels. Data analysis was performed univariate and bivariate using the unpaired t-test. The prevalence of an increase in total cholesterol levels in epilepsy patients is 47.5%. There was a significant difference in total cholesterol in the phenytoin monotherapy group and valproic acid monotherapy group. Total cholesterol mean in patients with phenytoin monotherapy is higher by 27.8 mg/dl than the mean valproic acid monotherapy. There were no significant differences in the total cholesterol in female and male epilepsy patients. There was no significant difference in total cholesterol in epilepsy patients with duration of therapy ≤6 months and > 6 months. The mean total cholesterol in epilepsy patients with phenytoin monotherapy is higher than epilepsy patients with valproate acid monotherapy.

Keywords: Epilepsy, Phenitoin, Valproic Acid, Total Cholesterol

INTRODUCTION

Epilepsy is a chronic disease that occurs repeatedly for a long time. This disease is said to affect the quality of life because there are still many social stigmas about epilepsy [1]. The quality of life of an epileptic patient may be ascertained about 70-80% can live like a normal person if they take therapy and get appropriate treatment [2]. Need to be reminded the medication for this disease need long term approach cause the purpose of epilepsy treatment is not to cure the epilepsy itself, but to avoid seizures or recurrence instead [3]. Epilepsy's treatment can last for years or even a lifetime which may change the normalities in patient body [4]. In [5] stated that one of the side effects of long-term use of OAE is the change in lipid profile. Changes in lipid profile may result increase in total cholesterol, LDL cholesterol, triglycerides, and a decrease in HDL cholesterol. According to [6]-[7], one of the effect an imbalance of lipid profile can increase the risk of atherosclerosis incidents. Atherosclerosis may deliver to increase the risk of ischemic heart disease, stroke, or death.

The American College of Cardiology/American Heart Association (ACC/AHA) recommends measuring lipid serums as a screening method for atherosclerotic events that should be carried out as early as possible, for instance from the time of late adolescence where the age range is 17-21 years. It is expected that at this age there are still no abnormalities in the lipid fraction because the body's function at metabolizing lipids is still works fine. If abnormalities are found at those range of ages, it is necessary to be aware of genetic lipid metabolic disorders or change of life style for example a treatment for chronic disease that need long term medication. As for the increase in cholesterol levels found in most men aged >45 years and women >55 years, due to decreased physiological function of the body due to degenerative factors [8].

In Indonesia, in [9] stated that there was a significant relationship between the duration of anti-epileptic drug therapy with total cholesterol and triglyceride levels where the shortest duration to the appearance of lipid profile abnormalities was 5 months. In a systematic review study conducted by [10], they stated that the drugs that

have affect to cholesterol levels are phenytoin and valproic acid.

According to [11], the mean total cholesterol in the group with phenytoin therapy was significantly higher than the mean total cholesterol in the group with valproic acid therapy and the control group. But there were no significant differences in the mean total cholesterol, HDL-C, LDL-C, and triglycerides in the groups with valproic acid therapy and the control group.

Based on research conducted by [12], they concluded that there were no significant changes to the lipid fraction in epilepsy patients who undergo single therapy of phenytoin or valproic acid. But the mean total cholesterol in the single therapy group valproic acid was significantly higher than the single therapy group phenytoin.

Based on the result differences from several previous studies, researcher feel the importance to do a research on the differences in mean total cholesterol in epilepsy patients with single phenytoin therapy and single treatment of valproic acid.

METHODOLOGY

This research design used a cross sectional study. The type of research used was analytic observational. Univariate analysis in this study was done to determine the distribution value, frequency, average subject data, and bivariate analysis was done to assess differences in the mean total cholesterol between the 2 groups using t-test. Analysis of the data in this study was done using SPSS.

RESULTS AND DISCUSSION

The total calculation of the number of samples was 40 epilepsy patients with 20 epilepsy patients undergo single phenytoin therapy drugs and 20 epilepsy patients undergo single valproic acid therapy drugs. Data was collected at Bhayangkara Grade I Raden Said Sukanto Hospital from November 2019 to January 2020.

Table 1: Distribution of Age, Gender, Duration of Therapy, and Total Cholesterol

Variable	Frequency	Percent (%)
Age		
Late adolescent (17-25 years old)	12	30.0
Early adulthood (26-45 years old)	28	70.0
Gender		
Male	16	40.0
Female	24	60.0
Duration of therapy		
≤6 months	6	12,5
>6 months	34	87.5
Total cholesterol		
Normal (<200 mg/dL)	21	52.5
Elevated (≥200 mg/dL)	19	47.5

Table 1 explains how the data distribution was obtained. Most respondents were patients who reached the age of early adulthood which range from 26-45 years old with a percentage of 70%. There was more female respondent (24 respondents, 60%) compared to male. The duration of therapy in patients who have undergo the therapy for more than 6 months was more often found, with 34 respondents and 89%. While for the results of cholesterol levels, normal respondents or <200 mg/dL was found more than the other category (21 respondents, 52.5%).

Table 2: Mean Differences of Total Cholesterol Levels between Anti-Epilepsy Drug Users Groups

Anti-Epilepsy Drug	Mean Total Cholesterol (SD)	p Value	Confidence Interval (CI 95%)
Valproate acid (n=20)	182.0 (34.15291)	0.013	27.8 (6.3-49.3)
Phenytoin (n=20)	209.8 (33.10843)		

Note: SD: Standard Deviation, CI: Confidence Interval

Table 3: Mean Difference in Total Cholesterol Levels between the Gender Groups

Gender	Mean Total Cholesterol (SD)	p Value	Confidence Interval (CI 95%)
Female (n=24)	200.791 (38.037)	0.299	12.229 (-11.300-35.758)
Male (n=16)	188.562 (32.663)		

Note: SD: Standard Deviation, CI: Confidence Interval

Table 3 illustrates the difference in average total cholesterol levels between the gender group, with p value = 0.299 (p> 0.05) in conclusion there is no statistically significant difference in the average total cholesterol levels between the female and male groups.

Table 4: Mean Difference in Total Cholesterol Levels in Duration of Therapy Groups

Duration of Use	Mean Cholesterol Total (SD)	p Value	Confidence Interval (CI 95%)
≤6 months (n=6)	176.5(32.623)	0.155	22.823 (-9.056-54.703)
>6 months (n=34)	199.323(35.987)		

Note: SD: Standard Deviation, CI: Confidence Interval

Table 4 illustrates the difference in mean total cholesterol levels in the duration of therapy groups, with p value = 0.155 (p> 0.05) in conclusion there is no statistically significant difference in the mean total cholesterol levels in groups with duration of therapy between ≤6 months and > 6 months groups.

Total respondent for this study was 40 epileptic patients, divided into 2 groups, Group with Phenytoin drug user and group with valproic acid drug user. It was found that 70% respondent in early adulthood. In [13] stated that epilepsy incidence in adults may occurred cause of complication from other disease, such as stroke, head trauma, and infection. In group of age 26-45 years old, stroke might happen on someone hinge the way of someone's life, for example smoking, often drinking alcohol, and consume high fat food [14]. Infection is very common health problem in developmental country, it may cause of low sanitary, unauthorized antibiotic usage, and nutrient deviancy [15].

It is said from previous study that epilepsy may occur to any race, age, and any gender. According to [16], the incidence of epilepsy in women is more common as generalized seizure other than any other type of seizure. It is also said that seizure in women may be related to sexual hormone, proven from the incidence of seizure often occurs in the age range of 15-50 and will decrease as the age increase until menopause occurs.

Epilepsy is a complex disease involving the brain, thus addressing symptomatic treatment only is insufficient. The main principle of epilepsy treatment is to prevent recurrence by inhibiting charge release in the brain, not curing epilepsy. There is a misperception where patients had no recurrence after consuming medicine, thus felt that there is no need to continue medication, therefore they stopped the medication. On the contrary, sudden stop on medication could stimulate recurrence. Therefore, epilepsy treatment requires long-term period. However, it is not impossible to be free from medication. One of the indications of complete epilepsy treatment is if there is no recurrence within 3 years. It should be noted that stopping medication should only be accompanied by the approval of the physician in charge. The release of anti-epileptic drug should not be sudden and should be done slowly with gradual dose decrease, which may require 3-6 months [17].

In this study it was found that epilepsy patients with normal total cholesterol levels (<200 mg/dl) and epilepsy patients with elevated total cholesterol levels (≥200 mg/dl) were 52.5% and 47.5% respectively. The American Heart Association (AHA) mentions several factors could affect the total cholesterol levels in the human body, simple example but crucial, lifestyle. Lifestyle factors talk surrounding food; what kind of food you usually consume in a day, how much portion that you consume in a day and so on, not to mention daily activities; is the person physically active or spend all day in one place, is the person give some time to exercise and how many time in a week this person go to gym [18]. In [19] stated that habits such as consume low fat food and vegetables can affect total cholesterol levels in the body, this is related to lipid metabolism exogenous pathways that are influenced by lipids contained in food. In addition, activities such as exercise are said to affect cholesterol levels because they are involved in lipid metabolism. AHA also stated that body weight may not reflects lipid fractions, meaning overweighs and obsesses may or may not have high cholesterol levels, but it may increase the risk of a lipid fraction [18].

There was a significant mean difference between the two groups, it was found that the group of phenytoin drug users (mean 209.8 mg/dl, SD 33.10843) had a mean cholesterol level higher than the group of valproic acid drug users (mean 182.0 mg/dl, SD 34.15291) with a difference of 27.8 mg/dl. This is consistent with the results of research conducted by other researchers [11], [20], [21]. According to [11], high levels of total cholesterol in patients with single-drug phenytoin therapy are related to drug properties and biotransformation of the drugs. Phenytoin tends to induce the CYP450 enzyme [11], [20]. In addition to metabolizing the drugs, CYP450 also has a role to change the nature of water-soluble serum

lipids to be water-soluble so that they can be excreted through urine and feces [22]. Long term effect of phenytoin drugs to the body may cause competition between the metabolism of phenytoin drugs and catalysis of serum lipids, if CYP450 is less catalyzing the serum lipids then the lipids in the blood cannot be removed from the body so it will accumulate and increase cholesterol levels [20].

Specifically, the phenytoin induces CYPA151 which also has function in lipid formation. CYP450 induction will trigger the activation of nuclear receptors: Constitutive Androstane Receptor (CAR), Liver X Receptor (LXR), Pregnant X Receptor (PXR), Farnesoid X Receptor (FXR). Activating these receptors will increase the occurrence of lipogenesis [22], [23].

Valproic acid drugs are not inducing liver enzymes. This explain why in the group with a single treatment valproic acid drug has a lower total cholesterol than the group with a single therapy drug phenytoin. In addition, patients with a single therapy of valproic acid tend to have normal total cholesterol levels. As for the group with a single therapy of valproic acid drug, it was found several patients with total cholesterol levels above the normal limit, this occurs because in the long-term treatment of valproic acid may cause excessive insulin expenditure resulting in insulin resistance [24]. An increase in total cholesterol levels in patients with insulin resistance not merely playing a direct role, but there are mechanisms such as a decrease in serum HDL cholesterol, an increase in serum VLDL cholesterol, and rarely, an increase in LDL cholesterol. These three events accumulate resulting in an increase in total cholesterol levels [25].

In this research, there was no significant difference in the average total cholesterol level in epilepsy patients of female and male groups. In a study conducted by Habib SS et al said there were significant differences in serum lipids in men and women. This is due to research conducted by [26] conducted on the average age of men was 46.62 years with a standard deviation of 1.78 and the average age of women is 47.36 years with a standard deviation of 1.14. While in this study, data collection was carried out with a range of 17-45 years of age with an average age of men was 33.3 years with a standard deviation of 9.47 and women is 32.33 with a standard deviation of 12,107. The age range was considered too broad compared to research conducted by Habib SS et al. This is one cause there is no significant difference in total cholesterol. The broad age range of the subjects with more data distribution in early adulthood than late adolescents may cause the results in this study was not significant.

In this study, there were no differences in the mean total cholesterol levels in the 6 months therapy group and > 6 months therapy group. The increasing serum lipids in anti-epileptic drug users occurred in the range of drug use more than or equal to 1 year [27]. In this study, we compared the average duration of drug use ≤ 6 months with a range of treatment duration of 5-6 months (prevalence: 12.5%) and duration of drug use> 6 months with a duration of treatment of 7 months-4 years (prevalence: 87.5%). In this study it was agreed that the mean between the groups was considered not comparable because the difference length of treatment in ≤ 6 months group was 1 month, and the difference length of treatment > 6 months may broadly vary. It can be seen from the prevalence of patient data with a duration of treatment ≤ 6 months was very little to compare with the group duration of treatment > 6 months. This is one of the reasons why the results obtained were not significantly different.

CONCLUSION

Based on the results of the research on the mean difference between anti-epilepsy drugs phenytoin and valproic acid on total cholesterol in epilepsy patients it can be concluded that there are significant mean differences in total cholesterol levels between patients with single-therapy phenytoin and single therapy of valproic acid. The mean difference in total cholesterol levels in the group treated with phenytoin was 27.8 mg/dl and it is higher than in the group treated with valproic acid. Further research is recommended, and it is advisable to find a location with higher population of epilepsy patients and to examine other lipid fractions so that the data obtained is more extensive.

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CONFLICT OF INTEREST

None

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