Effect of Phenytoin Usage Duration Against Hs-Crp Levels in Epilepsy Patients

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Abstract

Background: Patients with epilepsy have a higher risk of death than the normal population. Epilepsy patients have increased mortality due to cardiovascular disease with standardized mortality ratios ranged between 1.2 and 2.5. The incidence of non-fatal coronary heart disease also increased significantly between 34% and 63%. Atherosclerosis as an inflammatory state has an important biomarker namely hs-CRP. Long-term use of phenytoin will have an effect on hs-CRP. hs-CRP is an atherosclerotic biomarker with a better cardiovascular predictor than blood lipid and homocysteine levels

Methods: This study was conducted in epilepsy patients who fulfill ESR the criteria of inclusion and exclusion in Outpatient Unit of Dr. Soetomo General Hospital from October 2014 to April 2015. Patients were divided into a control group and case group. The control group was patients with hs-CRP levels <1.7 meanwhile, control group was >1.7. Tracking of phenytoin usage duration was performed in both groups.

Results: Thirty-four subjects were enrolESR in this study which consisted of 21 males (61.76%) and 13 females (38.23%). The mean age of subjects in the case group was 31.6 + 12.6 years and control group was 26.52 + 11.3. Data of phenytoin usage duration and hs-CRP levels were analyzed.

Conclusion: There was no significant difference between hs-CRP levels on phenytoin usage duration of >2 years and <2 years with p = 0.290

***Keywords**: Phenytoin Usage, Hs-Crp Levels, Epilepsy Patients*

Introduction

Patients with epilepsy have a higher risk of death than the normal population. It was found a positive correlation between epilepsy and vascular comorbidity with mortality of 5.3 and morbidity up to 7[1]. This was a reason why this group has a higher risk of death. Epilepsy patients have increased mortality due to cardiovascular disease with standardized mortality ratios (SMRs) between 1.2 and 2.5. The incidence of non-fatal coronary heart disease also increased significantly between 34% and 63%. An increased mortality caused by cardiovascular disease in epilepsy patients They found an increased mortality in patients with epilepsy who used the old type of anti-epilepsy drugs. Studies conducted on epilepsy group treated with phenytoin found intima media thickening of the carotid artery. This was a risk factor for the incidence of cerebrovascular and cardiovascular diseases. This supports the study that atherosclerotic factors were involved in vascular death and morbidity in epilepsy patients[2].

It was needed to measure the thickening of the media tunica and intima tunica in the carotid artery in order to determine the presence of atherosclerosis. This measurement in epilepsy patients treated with phenytoin showed a strong association with the risk of stroke and myocardial infarction at all ages. There was a significant increase in the thickness of the media tunica and intima tunica in epilepsy patients with phenytoin therapy[3]. Long-term use of phenytoin has altered metabolic

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function thus it increases atherosclerosis in epilepsy patients. He further mentioned that long-term use of phenytoin has been found to increase the thickness of the intima tunica and the media tunica of the carotid artery[4].

Atherosclerosis as an inflammatory state has an important biomarker namely hs-CRP. hs-CRP increased in patients with epilepsy phenytoin[5]. There was a conducted study about changes in the use of anti-epilepsy drugs (AEDs). They substituted carbamazepine or phenytoin with non-enzyme-inducing AEDs then they found that hs-CRP levels dropped to> 30%[6]. This results suggested a substantial role of phenytoin to the atherosclerosis process [7]. This process underlies the occurrence of cardiovascular and cerebrovascular disorders thus it is necessary to examine the biomarkers of atherosclerosis in epilepsy patients with phenytoin usage. Atherosclerotic biomarker was better as cardiovascular predictors than blood lipid levels and homocysteine. Professionals from the National Academy of Clinical Biochemistry mentioned that hs-CRP was the most acceptable biomarker and also served as a marker. There has been atherosclerosis that may progress to cardiovascular and cerebrovascular disease[8].

The correlation between phenytoin usage duration and the levels of hs-CRP in the blood remains unclear. Phenytoin has an influence on the immune system by stimulating macrophages to secrete IL-1 and IL-6. IL-1 and IL-6 will stimulate hepatocyte cells to secrete hs-CRP. Therefore, the presence of hs-CRP is a result of phenytoin and the process of atherosclerosis.

Method

This study was an observational analytic using a case-control study design that was performed from June 2014 to April 2015 in the Neurology Outpatient Unit of Dr. Soetomo General Hospital Surabaya. The subjects were all epilepsy patients who received Phenytoin therapy and fulfill ESR the inclusion and exclusion criteria. The sampling technique used was consecutive sampling.

Preliminary data were obtained by performing anamnesis, physical and neurological examination, and confirmation of medical records. All recorded data were collected for data tabulation and statistical analysis. Collected categorical data were analyzed using chi-square test with $\alpha = 0.05$. Meanwhile, the normality test was performed for numerical with Saphiro Wilk test. Numerical data with normal data distribution (age, BMI, leukocytes, GD2) was analyzed using an unpaired t-test, whereas, numerical data with abnormal data distribution was analyzed using Mann Whitney U test in order to determine differences in both groups.

Results

Subjects Characteristics by Sex

There are two characteristics of subjects, such as male and female. Thirty-four subjects were enroll ESR in this study that consisted of 21 males (61.76%) and 13 females (38.23%). The case group has male subjects by 10 people (58.8%), it was less than in the control group by 11 people (64,7%), meanwhile female subjects in case group was 7 people (47,6%), more than control group that has 6 people (35.3%) ($p = 0.724$). Different percentage of sex in each group was not statistically significant ($p = 0.724$)

Subjects Characteristics based on Leucosyt Amount

Table 1. Subjects Characteristics based on Leucosyt Amount

	Group				P
	Case		Control		
	Mean	SD	Mean	SD	
Leucosyt	6.78	1.97	7.222	1.53	0.460

The number of leukocytes in the case group was 6.781 + 1.970 years, it was higher than the control group by 7.229 + 1.53 years. It was found that the data distribution of leukocytes was normal ($p = 0.428$) in both case and control groups. 2-independent sample T-test was conducted to identify the difference of leukocyte in case and control group and it was found that there was no significant difference with $p = 0.460$.

Subjects Characteristics Based on Postprandial Blood Sugar (GD 2)

Blood sugar levels 2 hours post-prandial in case group was 96.529 + 16.144, it was slightly higher than control group by 84.564 + 12.631. It was found that the data distribution for blood sugar 2 hours post-prandial was normal with p = 0.149 for case group and p = 0.253 for the control group. Therefore, 2-independent sample T-test was conducted to identify the difference of blood glucose in case and control group, thus it was found that there was no significant difference between two groups with p = 0.279 (Table 2).

Table 2. Subjetcs Characteristics based on Postprandial Blood Sugar (GD 2)

	Group				P
	Case		Control		
	Mean	SD	Mean	SD	
Blood Sugar	96.529	16.144	84.564	12.631	0.279

The distribution of data for fasting blood sugar was abnormal (p = 0.011 for case group and p = 0.627 for the control group). The mean difference test to identify using Mann Whitney U test found that there was no significant difference of fasting blood glucose in case and control groups with p = 0.634 (Table 3).

Table 3. Subjects Characteristics based on Fasting Blood Sugar (GD 1)

	Group				P
	Case		Control		
	Mean	SD	Mean	SD	
Fasting Blood Sugar	81.82	4.91	80.06	6.02	0.634

Subjects Characteristics Based on Erythrocyte Sedimentation Rate (ESR)

The ESR in the case group was 8.41 + 4.89; it was higher than the control group by 3.76 + 2.704. It was found that the data distribution for ESR was not normal (p = 0.150 for case group and p = 0.02 for the control group). Mann Whitney U test was performed to identify the difference between LED in case and control groups. There was a significant difference with p = 0.003 (Table 4).

Table 4. Subjects Characteristics Based on Erythrocyte Sedimentation Rate (ESR)

	Group				P
	Case		Control		
	Mean	SD	Mean	SD	
ESR	8.41	4.89	3.76	3.129	0.003

Subjects Characteristics Based on Phenytoin Usage Duration

Based on the duration of phenytoin usage, 12 (70.6%) subjects with phenytoin therapy >2 years were found in the case group; it was more than the control group by 9 subjects (52.9%). Subjects with phenytoin therapy <2 years from the case group was 5 subjects (29.4%); it was less than the control group by 8 subjects (47.1%). The differences in case and control groups were not statistically significant with p = 0.364 (Table 5).

Tabel 5. Subjects Characteristics based on Phenytoin Usage Duration

Duration	Group		Total	P
	Case	Control		
>2 years	12 (70.6%)	9 (52.9%)	21	0.364
<2 years	5 (29.4%)	8 (47.1%)	13	
Total	17 (100%)	17 (100%)	34	

Effect of Phenytoin Duration >2 years and <2 years against hs-CRP Levels

There were 12 people (70.6%) who used phenytoin for >2 years in the case group, it was higher than in the control group by 9 people (52.9%). Meanwhile, there were 5 people (29.4%) in the case group who used phenytoin for <2 years, it was less than the control group by 8 people (47.1%). This difference was not statistically significant with p = 0.290 (Table 6).

Table 6. Effect of Phenytoin Duration >2 years and <2 years against hs-CRP Levels

Duration	**Group**			**P**	**OR (CI 95%)**
	Case	**Control**			
>2 years	12 (70.6%)	9 (52.9%)		0.290	2.133 (0.519 – 8.71)
<2 years	5 (29.4%)	8 (47.1%)			
Total	17 (100%)	17 (100%)		34	

This suggested that the use of phenytoin for >2 years has no significant relationship to elevated levels of hs-CRP (95% CI, OR = 0.516-8.761). It indicated that the use of phenytoin for >2 years was 2.133 times more frequent to increase hs-CRP compared to the use of phenytoin for <2 years (Table 9).

Discussion

We found no significant differences in basic characteristics of subjects. Clinical exclusion data of subjects in the form of ESR, leukocyte, GDI/GD2 were analyzed to eliminate bias against hs-CRP. The subjects were 34 patients that consisted of 21 males (61.76%) and 13 females (38.23%). This result was in accordance with epidemiological data in Indonesia which stated epilepsy occurred more frequently in male than female[10]. The mean age in the case group was 31.06 + 11.3 years and the control group was 26.53 + 11.3 years, there was no significant difference in both groups with p = 0.278. This demographic data were compared to a study by Teng-Yeow Tan, Cheng-Hsien Lu et al, which stated the mean age was 36.0 ± 11.3 in the case group and the control group was 36.2 ± 11.2 with p = 0.838. Age range was almost similar because older subjects often had accompanied metabolic disease which became one of the exclusion criteria[5].

Chi-square test on BMI, the number of leucocytes, GD1, GD2 did not obtain any significant difference between case and control groups. This indicated that

there was no effect of BMI, the number of leukocytes, GD1 and GD2 on hs-CRP levels in this study. In contrast, Teng-Yeow Tan et al. study did not control the BMI variable although Simionescu stated that fasting blood glucose, BMI, systolic blood pressure affected hs-CRP[12]. Subjects with increased ESR levels above the normal level have been excluded, hoewever, higher ESR levels was obtained in case group that by 8.41 + 4.89 than the control group by 3.76 + 3.129. There was a significant difference (p = 0.003) of ESR levels in case and control group. It was mentioned that increased production of hs-CRP will increase the blood viscosity, thus it was associated with increased levels of ESR.

There were 12 subjects (70.6%) who used phenytoin >2 years in the case group, it was more than in the control group by 9 people (52.9%). Meanwhile, there was 5 subjects (29.4%) in the case group who used phenytoin <2 years, it was less than the control group by 8 subjects (47.1%). The difference was not statistically significant p = 0.290 thus it indicated that the use of phenytoin for >2 years had no significant correlation to the increase in hs-CRP levels.

The function of drugs in the body is influenced by the activity of CYP 450 in the liver. The different levels of CYP 450 affect the activity of drugs in the body. Phenytoin is an inactive metabolite. CYP 1A2A will hydrolyze phenytoin to active hydroxyphenitoin[14]. CYP 450 has various variants. The emergence of some types of the allele is due to the occurrence of several mutations that occur in the reproductive cells of each individual. The difference of alleles in the individual is caused by the changes in the structure of DNA bases such as the change of one of the DNA bases, the deletion or the rearrangement of DNA in one of its locus of chromosome[15].

One variant of the CYP 450 is CYP 1A2A. CYP 1A2A is manufactured in the heart and is induced by some drugs such as oral contraceptives, coffee and cigarettes. That activity requires higher doses of phenytoin in smokers and female who use oral contraceptives. It was found that there were different types of phenotypes in each race. There was low CYP 1A2A activity <5% in Asian and African compared to CYP 1A2A activity in Caucasian. A Higher dose is required for phenytoin in Caucasian than in Asian1[6].

Cholesterol synthesis is influenced by CYP 51 A1 gene. A Higher dose of phenytoin leads to greater induction of the CYP 51 A1 gene, thus cholesterol production is also increased. This mechanism contributes to the onset of atherosclerosis.

Conclusion

There was no difference between hs-CRP levels in epilepsy patients who used phenytoin for >2 years and phenytoin for less than 2 years in Dr. Soetomo General Hospital Surabaya.

Ethical Clearance: This study protocol was approved by ethical clearance Dr.Soetomo Surabaya, Indonesia teaching hospital research.

Conflict of Interest: This study protocol was approved by ethical clearance Dr.Soetomo Surabaya, Indonesia teaching hospital research.

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