TESIS

HUBUNGAN PEMBERIAN OBAT ANTI-EPILEPSI JANGKA PANJANG TERHADAP KADAR 25-HIDROKSIVITAMIN D SERUM DAN *HEIGHT VELOCITY* PADA ANAK PENDERITA EPILEPSI

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PROGRAM STUDI ILMU KEDOKTERAN KLINIK
JENJANG MAGISTER FAKULTAS KEDOKTERAN
UNIVERSITAS AIRLANGGA
SURABAYA
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TESIS

Untuk Memperoleh Gelar Magister Ilmu Kedokteran Klinik
Dalam Program Studi Ilmu Kedokteran Kinik
Pada Jenjang Megister Fakultas Kedokteran Universitas Airlangga

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SURABAYA
2019

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PADA TANGGAL : .....

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Tesis ini telah diuji dan dinilai oleh panitia penguji
pada Program Studi Ilmu Kedokteran Klinik Jenjang Magister
Fakultas Kedokteran Universitas Airlangga
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Ditetapkan dengan Surat Keputusan
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Judul Tesis : Hubungan Pemberian Obat Anti-Epilepsi Jangka Panjang terhadap Kadar 25 Hidroksivitamin D Serum dan *Height Velocity* Pada Anak Penderita Epilepsi

Menyatakan dengan sebenarnya bahwa tesis saya ini adalah asli hasil karya sendiri, bukan merupakan hasil peniruan atau penjiplakan (plagiarism) dari karya orang lain. Tesis ini belum pernah diajukan untuk mendapatkan gelar akademik. Dalam tesis ini tidak terdapat pendapat yang telah ditulis atau dipublikasikan orang lain, kecuali secara tertulis dengan jelas dicantumkan sebagai acuan dengan disebutkan nama pengarang di dalam daftar pustaka.

Demikian pernyataan ini dibuat tanpa ada paksaan dari pihak manapun, apabila pernyataan ini tidak benar, maka saya bersedia menerima sanksi sesuai dengan norma dan peraturan yang berlaku di Universitas Airlangga.

Surabaya, 1 November 2019

Chasan Ismail, dr

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Summary

THE INFLUENCE OF LONG TERM ANTIEPILEPTIC DRUGS TO 25-HYDROXY VITAMIN D SERUM LEVEL AND HEIGHT VELOCITY IN EPILEPTIC CHILDREN

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Introduction

Epilepsy is one of the pediatric neurology health problem in Indonesia with the incidence 103 new case in Soetomo academic hospital at 2013.[1)] Administration of long-term anti-epileptic drugs requires monitoring of side effects, one of them is a decreasing of serum vitamin D level.[2)] Lower of serum vitamin D level is a global health problem. Long-term administration of AED is still controversial as a risk factor for vitamin D deficiency.[3)] Vitamin D has been known to have an effect on bone growth since 1920.[4)] Deficiency or insufficiency of vitamin D in children results impaired of linear bone growth. Several studies have shown a decreasing vitamin D level due to the administration of anti-epileptic drugs that interfere with the child's height growth.[5)] Height is a complex process of chondrocyte proliferation, chondrocyte hypertrophy, and endochondral ossification of bone growth plates which are influenced by various factors, one of them is vitamin D.[6)]

Short stature is found more significantly in epileptic children who administered with long-term anti-epileptic drugs than the normal population.[7)] Short stature in children is an important problem because it can result in psychological and economic problem in the future.[8)] According to the stunting syndrome theory, a child with short stature will give birth to a baby with a low body length and head circumference, causing a decline in intelligence in the next generation.[6)] Decreasing of vitamin D level in children with epilepsy can affect the quality of the next generation in the future.[6,8)]

The aim of our study to to correlate the serum vitamin D level with height velocity in epileptic children. The study compare with healthy children also.

Methods

1. Patients

The study was carried out on 2-18 years old epileptic children who administered more than 6 months AED were included. The patients were excluded if they had overweight, obese, wasted, severely wasted, moderate malnutrition, severe malnutrition, bone mineralization disease, bad compliance of AED, and severe neurological dysfunction. Patients with vitamin D supplementation were excluded also. The family of pediatric resident was recruited as healthy children on control group. Comprehensive informed consent was obtained from a legal representative of the patient.

2. Methods

This study is a prospective cohort study. The study were conducted from August 2018 to July 2019. Ethical Committee in Health Research Soetomo General Hospital Surabaya approved this study with the ethical clearance number

0259/KEPK/V/2018. In every patient, height velocity and serum level of 25-hydroxyvitamin D was measured.

3. Measurement of Serum 25-Hydroxyvitamin D Level

The serum 25-hydroxyvitamin D level from peripheral blood were measured using an enzyme-linked fluorescence assay (ELFA) method with VIDAS® reagents. Vitamin D status is determined based on serum 25-hydroxyvitamin D level according to the Endocrine Society (deficiency <20ng/ml, insufficiency 20-29ng/ml, and deficiency >29ng/ml).

4. Height Velocity Examination

The height was examined by same pediatricians based on the Indonesian Ministry of Health protocol. Height velocity was measured with twice examination during 6 months and converting to z score by Barcelona Longitudinal Study 1995-2017.

5. Statistical Analysis

SPSS ver. 21.0 was used for statistical analysis. Chi-square was applied to evaluate data comparison between groups. Saphiro-wilk test was used for normality data. The 25-hydroxyvitamin D level were correlated with height velocity by using pearson test. Epileptic and healthy children groups were compared also by using anova and t test. Statistical significance was considered with p-value of <0.05.

Results

The study was participated by 46 children. Two children were excluded because of technical difficulty on blood taken samples and insufficient of blood sample volume. There were 2 groups, epilptic and healthy children groups. Each group has 22 samples. There was no difference in age, sex, milk consumption, mother education, and serum calcium level between groups. There was significant difference of hemoglobin level between groups. The hemoglobin level was Z score based on American Academy of Pediatrics. The distribution data was normal based on shaphiro-wilk test (p>0.05). The characteristic of subject are showed in table 1.

Table 1. The Characteristic of Subject

Characteristic	Epileptic Children	Healthy Children	p*
Mean age (year ± SD)	8.5 ± 3.87	8.2 ± 3.79	0.429
Sex (boy : girl)	15:7	15:7	0.627
AED (n/ %)			-
Phenitoin	5/ 23	0	
Phenobarbital	1/ 4	0	
Valproat acid	5/ 23	0	
Phenitoin + phenobarbital	6/ 27	0	
Phenitoin + valproic acid	1/ 4	0	
Phenobarbital + valproic acid	4/ 19	0	
Milk consumtion per day (n)			0.326
< 200 ml	9	4	
200 - < 500 ml	6	8	
500 - < 1000 ml	7	9	
≥ 1000 ml	0	1	
Mother graduation (n/ %)			0.533

Junior school	6/ 27	3/ 14	
Senior high school	11/ 50	13/ 59	
University	5/ 23	6/ 27	
Mean duration of AED (month ± SD)	13.5 ± 5,67	0	-
Mean hemoglobin level (Z score ± SD)	-1.5 ± 0.93	-0.8 ± 1.91	0.016
Mean serum calcium level (mg/dl ± SD)	9.0 ± 0.55	9.4 ± 0.49	0.342

* Statistic with chi-square test

The serum 25-hydroxyvitamin D level was measured in Clinical Pathology Laboratory of Soetomo General Academic Hospital. There were a significant difference in serum 25-hydroxyvitamin D level and vitamin D status of epileptic children compared with healthy children group ($p < 0.05$). The results of serum 25-hydroxyvitamin D level and height velocity both of groups are showed in table 2. The vitamin D status both groups are showed in table 2.

Table 2. The Mean of Serum 25-Hydroxyvitamin D Level and Height Velocity

Characteristic	Epileptic Children	Healthy Children	p*
Mean of 25-OHD level (ng/ml ± SD)	21,5±8,41	34,3±10,09	0.000
Height velocity (z score ± SD)	-0.35±1.733	0.59 ±1.384	
p**	0.004	0.024	
Coeficient of correlation**	0.550	0.425	

Statistic with *t test ** Pearson correlation test

Table 3. The Vitamin D Status

Characteristic	Epileptic Children	Healthy Children	p
Vitamin D status (n/ %)			0.001*
Sufficient	2/ 9	14/ 64	
Insufficient	14/ 64	5/ 23	
Deficient	6/ 27	3/ 13	

Statistic with * Anova test

Discussion

Low level of vitamin D are one of the health problems in children. Previous study examined serum 25-hydroxyvitamin D level at 48 districts in Indonesia to determine the prevalence of vitamin D deficiency and insufficiency in the children population. Vitamin D insufficiency occurs in 38.76% of children. While vitamin D deficiency occurs in 1.08% of children.[9)]

This study showed vitamin D status in healthy children found 64% of children with sufficiency, 23% of children with insufficiency, and 13% of children with deficiency. In epileptic children, there were 9% of children with sufficiency, 64% of children with insufficiency, and 27% of children with deficiency. Vitamin

D insufficiency and deficiency are higher in children with epilepsy who get long-term AED compared to the normal population in the previous study.

There are still differences of opinion regarding the decrease in vitamin D level in children with epilepsy who get long-term anti-epilepsy drugs. Several studies have concluded that there is an association between anti-epileptic drug administration and serum 25-hydroxyvitamin D level. However, other studies have produced different conclusions which state that there was no association between anti-epileptic drug administration and serum 25-hydroxyvitamin D level.[10)]

In this study, there were significant differences of serum 25-hydroxyvitamin D level between epileptic and healty children group. This study avoid counfounding factors serum 25-hydroxyvitamin D level by strict of exclusion criteria. There was not significant difference of subject characteristic also exept the hemoglobin level.

Fong compared serum 25-hydroxyvitamin D level in epileptic children that AED long-term administration with healthy children in Malaysia. The study proved that there was significant difference between epileptic and healthy children group.[3)] Vitamin D level are influenced by several factors, one of them is the process of vitamin D degradation. Long-term administration of anti-epileptic drugs activates pregnane x receptors which increase the enzyme activity of CYP24A1 and CYP3A4. The increasing of CYP24A1 and CYP3A4 enzymes activity result higher vitamin D catabolism became an inactive substance. Several studies have suggested that anti-epileptic drugs affect the activity of enzymes CYP24A1 and CYP3A4.[11)] Anti-epileptic drugs increase CYP3A4 activity. This process will increase vitamin D catabolism, thereby reducing vitamin D level in the blood.[12)]

Babayigit study gave different results. The study compared serum 25-hydroxyvitamin D level in epileptic and healthy children. Data found that administration of long-term AED in epileptic children was not significant difference with healthy children. It suspected that compensation of vitamin D catabolism preserve the serum 25-hydroxyvitamin D level still normal. [10)]

Lee compared height velocity between epileptic and healthy children. There was significant difference both groups. Epileptic children had lower height velocity than healthy children.[13)] But, Nettekoven study concluded there was not significant difference of height velocity between epileptic and healthy children.[14)] In this study there was significant difference of height velocity between epileptic and healthy children. A significant correlation of serum 25-hydroxyvitamin D level with height velocity both groups were noted in this study.

Some study showed lower of vitamin D level result hypocalcemia because of bowel absorbtion decreasing, hypocalcemia stimulate the phosporus excretion also. Hypocalcemia and hypophospatemia reduce linear bone growth. Other study concluded lower insulin like growth factor (IGF)-1 as a result of lower serum 25-hydroxyvitamin D level. IGF-1 has significant roles of linear bone growth in ephypisial plate.[15)]

Several limitations of this study must be considered. Epileptic children was only demonstrated in a limited number of patients. Ideally, to better understand the clinical aplication, should be initially AED treatment comparison. In conculsion, epileptic children with long-term AED have lower level of serum 25-hydroxyvitamin D and height velocity than normal population.

Conflicts of Interest

No potential conflict of interest in this study was reported.

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Recomendation

We should study 25-hidroksivitamin D before and after treatment, IGF-1, bone mass density, and vitamin D suplementation.