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Original Article

Vitamin D3 and seizure frequency in children with epilepsy using polypharmacy

Setya Puspa Dewi Aprilyani, Tun Paksi Sareharto, Farid Agung Rahmadi, Rina Pratiwi, Alifiani Hikmah Putranti

Abstract

Background Children with epilepsy usually need vitamin D administration, primarily due to the effects of antiepileptic drugs (AEDs). The use of AEDs, particularly polypharmacy, can reduce serum 25(OH)D levels. Vitamin D improves the function of neurotransmitters furthermore boosting the seizure threshold. There has been relatively little study investigating the effects of vitamin D3 treatment on seizure frequency.

Objective To compare seizure frequency before and after administering vitamin D3 to the children with epilepsy who used polypharmacy.

Methods Sixteen children with epilepsy and polypharmacy, aged 2-18 years, from the Pediatric Neurology Clinic, Dr. Kariadi Hospital, Semarang, Central Java, were studied using a quasi-experimental approach with one group pretest-posttest. The vitamin D3 was given orally for two months with different dosages according to age and subjects' pretest serum 25(OH)D levels. Children with vitamin D insufficiency or deficiency were given therapy dosage, and the normal vitamin D status were given supplementation dosage.Seizure frequency, serum 25(OH)D levels, and vitamin D status were assessed before and after treatment.

Results Seizure frequency was significantly lower after vitamin D treatment for the entire group compared to pre- administration (P=0.019). For subjects with hypo-vitamin D levels pre-treatment, median seizure frequency was significantly decreased following normalization of vitamin D levels at one month (P=0.016) and two months (P=0.018) of vitamin D treatment. Using mean data, seizure frequency also significantly decreased at one month and at two months post-treatment.

Conclusion Vitamin D3 administration is associated with an increase in serum 25(OH)D levels, as well as a decrease in seizure frequency. Vitamin D3 administration can significantly reduce seizure frequency in epilepsy patients undergoing polypharmacy who are vitamin D deficient. **[Paediatr Indones. 2025;65:XXX; DOI: https://doi.org/10.14238/pi65.6.2025.XXX]**.

Keywords: *epilepsy; polypharmacy; hypo-vitamin D; 25(OH)D serum levels; seizure frequency*

In Indonesia, 40-50% of all instances of epilepsy occur during childhood, and percentages are on the rise.[1] There are 144/100,000 cases in the first year of life and 58/100,000 cases in the 1-10 years age group annually. At age five, the cumulative incidence was 0.45%, and at age ten was 0.66%, with 0.62% of the population having active epilepsy.[2]

The mainstay of treatment for epilepsy is the use of antiepileptic drugs (AEDs). These medications have different side effects and modes of action.[3] It is frequently necessary to take many drugs for an extended time when giving AEDs to children with epilepsy. One condition that could result from the negative effects of using AEDs is vitamin D deficiency.[4,5]

Serum 25(OH)D levels can be impacted by AEDs' effect on vitamin D metabolism through a variety of intricate mechanisms.[6] Cytochrome P-450 enzyme-inducing AED agents can reduce serum 25(OH)D levels due to increased 25(OH)D being

From the Department of Pediatrics, Faculty of Medicine, Universitas Diponegoro/Dr. Kariadi Central General Hospital, Semarang, Central Java, Indonesia.

Corresponding author: Setya Puspa Dewi Aprilyani. Department of Pediatrics, Faculty of Medicine, Universitas Diponegoro. Jl. Prof Sudarto SH. Tembalang, Semarang, Central Java, Indonesia. Email: sp.dewiaprilyani@gmail.com.

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converted into inactive metabolites.[7] A study in Spain found that levetiracetam or valproic acidsignificantly as monotherapy significantly reduced serum 25(OH) D levels.[4] Long-term use of AEDs, especially polypharmacy, can reduce 25(OH)D levels in the body. Polypharmacy was found in 47% of epileptic children in Korea.[8] The prevalence rate of epilepsy in children with polypharmacy at Dr. Kariadi Hospital in 2023 was 455/1,000 and the incidence rate was 39/1,000 per year.[9]

The neuroprotective effects of vitamin D involve the synthesis of calcium-binding proteins including parvalbumin and calbindin, as well as regulation of cellular calcium homeostasis.[10] Increased neuronal excitability in the form of the release of amino acids and stimulatory neurotransmitters due to excessive calcium levels in nerve cells has a neurotoxic effect.[11-14] The central nervous system is more excitable when there is low calcium in the CSF, which results from a vitamin D deficit. This makes the nervous system more prone to excitement and seizures. Vitamin D functions to raise the threshold for seizures in the hippocampus that are caused by hypocalcemia.[15]

A study in 13 adult patients with pharmacoresistant epilepsy showed that compared to controls, giving vitamin D3 for 90 days lowered the frequency of seizures by 30-40%.[16] Therefore, more studies are needed on vitamin D3 administration and the frequency of seizures. Our study findings are expected to enhance the care and services provided to children with epilepsy and polypharmacy.

Methods

This quasi-experimental study employed a one-group, pretest-posttest design of 16 children with epilepsy and polypharmacy aged 2-18 years, who visited the Pediatric Neurology Clinic at Dr. Kariadi Hospital Semarang, during the 8 months study period from April 1 to November 30, 2023. We used consecutive sampling to include subjects. The course of treatment entailed taking vitamin D3 for two months. Serum 25(OH)D levels were measured using an ELISA method (microplate reader by *Calbiotech Type ELx800*), vitamin D status before and after treatment, and the frequency of seizures during the previous 30 days and the 60 days of vitamin D administration wasevaluated.

A serum 25(OH)D level of less than 30 ng/mL was classified as hypo-vitamin D which is divided into two categories, insufficiency (21-29 ng/mL) and deficiency (<20 ng/mL), then a level of more than 30 ng/mL was considered normal.

Vitamin D3 dose determination was based on guidelines from the *Eastern Pediatric Epilepsy Network* (EPEN). The guidelines recommend a daily vitamin D supplementation dose of 1,000-3,000 IU should be given to infants under 6 months, 6,000 IU for 6 months to 12 years, and 10,000 IU for adolescents aged 12-18 years. Due to the risk of inducing vitamin D toxicity, which is defined by increased serum 25(OH)D levels associated with severe hypercalcemia, hypercalciuria, or nephrocalcinosis, therapy is done for 4-8 weeks at a maximum cumulative dosage of 240,000-4,500,000 IU.[17] A meta-analysis that revealed that loading doses of vitamin D <400,000 IU (or 10,000 IU/kg) did not elevate the risk of hypercalcemia or hypercalciuria, but did increase the risk of hypercalcemia.[18]

Polypharmacy in this study was defined as the concurrent use of >1 AEDs by a patient at any time. The AEDs used in this study consisted of those that affect cytochrome P-450 enzymes, namely, high dose topiramate (>5 mg/kg/day), phenobarbital, oxcarbazepine, carbamazepine, and phenytoin, as well as AEDs that do not affect the cytochrome P-450 enzymes, namely valproic acid, low dose topiramate (<5 mg/kg/day), levetiracetam, clobazam, lamotrigine, and clonazepam, or mixed (combination of both of them).

Normally distributed data on 25(OH)D levels and seizure frequency differences over the previous month were examined using paired T-test. Non-normally distributed data were analyzed by Wilcoxon test. Results with P values ≤ 0.05 with 95% confidence intervals were considered to be statistically significant. SPSS version 25.0 software was used for analyses. This research received approval from the Medical Research Ethics Commission Universitas Diponegoro Faculty of Medicine/Dr. Kariadi Hospital, Semarang.

Results

Subjects were children with epilepsy and polypharmacy

aged 2-18 years who experienced seizures. The AEDs continued to be the mainstay of treatment for all subjects' management of seizures. Sixteen patients received treatment and were available for analysis from the study's start to finish. **Table 1** displays the subjects' characteristics.

Subjects with low vitamin D levels before treatment had significant differences in seizure frequency (P=0.019), serum 25(OH)D level (P=0.001), and vitamin D status (P=0.008) (**Table 2**).

In our study, hypo-vitamin D conditions were found in 2 subjects who received a combination of AEDs that induced cytochrome P-450 enzymes, 2 subjects who received AEDs that did not induce cytochrome P-450 enzymes, and 5 subjects with mixed AEDs (**Table 3**).

A total of 9 subjects with hypo-vitamin D status and 7 subjects with normal vitamin D status before treatment experienced a reduction in seizure frequency the 1st and the 2nd month after treatment (**Table 4**).

Before treatment, 9 subjects had low vitamin D levels and 7 had normal levels. Seven subjects with hypo-vitamin D status before treatment experienced a change in 25(OH)D levels to normal after receiving vitamin D3 for two months, and two subjects experienced an increase in serum 25(OH)D levels, still, they remained below 30 ng/mL (**Table 5**).

There was a significant reduction in the frequency of seizures in subjects with hypo-vitamin D status before and after treatment during continuous

Table 1. Characteristics of children with epilepsy and polypharmacy

Characteristics	(N=16)
Median age (range), months	77.5 (30-184)
Gender, n	
Male	11
Female	5
Nutritional status, n	
Overweight	2
Normal	10
Wasted	3
Severely wasted	1
Epilepsy types, n	
Focal	5
Focal to bilateral	1
General	10
Number of AEDs used	
2	3
3	7
4	4
5	2
Characteristics of AED combinations, n	
AEDs that affected cytochrome P-450 enzyme	2
AEDs that did not affect cytochrome P-450 enzyme	6
Mixed	8
Duration of AED therapy, n	
≥1 year	15
<1 year	1
AED therapy changes*, n	
Yes	2
No	14
Sun exposure >60 minutes per day, n	
Yes	16
No	0

*AED therapy changes was reduction or addition of doses and types of OAEs or discontinuation of certain OAEs during the study.

observation (P=0.016 at the 1st-month post-treatment and P=0.018 at the 2nd-month post-treatment) (**Table 5**). We noted that the serum vitamin D levels of 7 of these subjects became normalized after treatment.

No patients experienced clinical signs of vitamin D poisoning, such as nausea, vomiting, diarrhea, constipation, or severe hypercalcemia (serum calcium levels >2.6 mmol/L) during the study. Calcium examination results were within normal range for all subjects before and after treatment. Analysis of serum calcium levels before and after treatment was not significant, with (P=0.173). This investigation did not find any consequences of vitamin D poisoning that were associated with hypercalcemia.

Table 2. Analysis of characteristics of children with epilepsy and polypharmacy before and after treatment (N=16)

Variables	Before treatment	After treatment	P value
Median serum 25(OH)D (range), ng/mL			
Hypo-vitamin D	21 (13.9-26.4)	82.5 (23.1-155.4)	0.008*
Normal	47.5 (31.1-90.8)	62.3 (22.5-110.7)	0.128
Median seizure frequency at 1st-month post-treatment (range), times	17 (1-552)	7.5 (0-284)	0.019*

Significant (P<0.05); *Wilcoxon

Table 3. Proportion of AED combination to vitamin D status

Characteristics	(N=16)
Combination of AEDs that induced cytochrome P-450 enzymes, n	
Hypo-vitamin D	2
Normal	0
Combination of AEDs that did not induce cytochrome P-450 enzymes, n	
Hypo-vitamin D	2
Normal	4
Mixed	
Hypo-vitamin D	5
Normal	3

Table 4. Changes in seizure frequency after administration of vitamin D3 (N=16)

Seizure frequency	The 1st month post	The 2nd month post
Normal vitamin D status pre-treatment (n=7)		
Reduced	6	5
Not reduced	1	2
Hypo-vitamin D pre-treatment (n=9)		
Reduced	6	9
Not reduced	3	0

Table 5. Analysis of changes in vitamin D status and seizure frequency before and after 60 days of vitamin D treatment

Vitamin D status		Seizure frequency				
		Before treatment	After treatment			
Before treatment	After 2nd month of treatment	The 1st month post			The 2nd month post	
		Median (range)	Median (range)	P value*	Median (range)	P value*
Hypo-vitamin D (n=9)	Normal (n=7)	12.0 (1-552)	1.0	0.016**	0.0 (0-136)	0.018**
	Hypo-vitamin D (n=2)	11.5 (3-20)	15.0 (0-30)	0.655	3.5 (0-7)	0.180
Normal (n=7)	Normal (n=6)	19.0 (8-67)	11.0 (1-48)	0.043**	6.0 (0-30)	0.058
	Hypo-vitamin D (n=1)	3.0 (3-3)	1.0 (1-1)	-	0.0	-

*Significant (P<0,05); **Wilcoxon

Discussion

Sixteen subjects, ranging in age from 30 to 184 months (median 77.5 months), participated in this study. Most cases of hypo-vitamin D were seen in subjects older than 5 years of age. Our findings were consistent with a French study that found the prevalence of vitamin D insufficiency to be higher among all children aged ≥5 years (67-71%) and lowest in toddlers (10-35%). Their median serum vitamin D concentration was 90.2 nmol/L in 0 to18-month-olds, 56.7 nmol/L those aged 18 months to 5 years, 39.05 nmol/L in those aged 5-10 years, and 32.45 nmol/L in those aged 10-15 years.[19]

Serum 25(OH)D levels in healthy and epileptic children dropped from infancy to adolescence, according to a Chinese study. They reported median serum 25(OH)D levels declined by 1-1.5 times from infancy to adolescence in both healthy and epileptic children. However, children in excellent health had serum 25(OH)D levels that were substantially higher than those in children with epilepsy.[20]

In the hypo-vitamin D group, 2 subjects were overweight, 5 were normal, and 2 were wasted. Previous research on the incidence and risk factors for vitamin D insufficiency in children with epilepsy reported that hypo-vitamin D in the general population, particularly in those with epilepsy undergoing treatment, was connected to obesity. The chance of hypo-vitamin D increased up to 1.179 times (95%CI 1.047 to 1.329) with every BMI point increase. This might be due to the volumetric dilution of vitamin D in fat tissue, serum, the liver, and bigger muscles.[21]

Of our 16 subjects, 9 (56.25%) had hypo-vitamin D [25(OH)D serum levels <30 ng/mL. Similarly, previous studies investigated the connection between children's serum 25(OH)D levels and epilepsy. Vitamin D deficiency was significantly higher in 100 children with epilepsy (45%) than in the control group (24%).[22] A cross-sectional study in 138 Thai pediatric epilepsy patients from 2018 to 2019 had similar findings; 71% (n=98) of patients had low vitamin D levels where 23.2% (n=32) had vitamin D deficiency, and 47.8% (n=66) had vitamin D insufficiency.[11] Furthermore, a study in Itali in 2014-2016 indicated that epileptics had significantly lower serum 25(OH)D levels than the control group (P<0.001). Only 25% of 160 patients with epilepsy showed normal 25(OH)D levels; whereas 41.9% had a vitamin D insufficiency, and 33.1% had a vitamin D deficiency (P<0.001).[23]

For two months in our study, vitamin D3 was given orally at different dosages based on subjects' pretest serum 25(OH)D levels and age. We found that mean and median serum 25(OH)D levels in epileptic children with polypharmacy were significantly higher at 2 months post-vitamin D supplementation than prior to supplementation (**Table 2**). Our findings were consistent with a prior investigation carried out in 2017 at Dr. Cipto Mangunkusumo and Bekasi Hospital that examined vitamin D level profile and supplementation therapy in 51 children with epilepsy. A study in Bekasi discovered that vitamin D supplementation for three months resulted in a statistically significant increase in 25(OH)D levels (P=0.001).[24] A study in China examined serum vitamin D status and AED therapy and found that in epileptic children, vitamin D supplementation of 100-800 IU/day significantly raised their serum 25(OH)D levels from 45.29 to 52.52 nmol/L, with an increase of as much as 16% (P<0.0001). After taking vitamin D supplements, the percentage of seizure-free patients rose from 49% to 76% (P<0.001).[20]

A significant decrease in the frequency of seizures occurred in the hypo-vitamin D group, which had serum 25(OH)D levels above 30 ng/mL after administering vitamin D3 for two months. Previous studies have elucidated the mechanism by which vitamin D could reduce seizure frequency. The impact of vitamins B12 and D in children with epilepsy was examined in a 2015 study; 50,000 vitamin D2 units and 200 mg/kg vitamin B12 twice a day were administered to epileptic patients who suffered from refractory seizures. Their IL-β, IL-6, IL-8, macrophage inflammatory protein-1β (MIP-1β), and monocyte chemoattractant protein-1 (MCP-1) significantly decreased. After therapy, the location of epileptic activity in the left and right temporal lobes decreased, resulting in a decrease in seizure intensity.[25]

In 2022, a retrospective analysis including 524 epileptic participants reported a 40% decrease in the incidence of seizures in those with elevated serum 25(OH)D levels, which could be achieved by sun exposure or supplementation.[26] A study in Semarang revealed that taking 5,000 IU of vitamin D per day for 42 days significantly affected TNF-α levels

(P=0.001), which in turn significantly affected the frequency of seizures (P=0.002). The two variables showed significant positive associations (P<0.001 and r=0.661).[27] Another study suggested that in individuals with drug-resistant epilepsy, addressing the vitamin D3 deficiency could significantly lower seizure frequency by 40% (P=0.04). To treat vitamin D insufficiency, their subjects with serum 25(OH) D level of < 30 ng/mL were given an oral dose of vitamin D3 (40,000-200,000 IU loading), followed by a daily maintenance dose of 2000-2600 IU for 90 days. Previous study claimed that vitamin D's anticonvulsant qualities derive from its capacity to reduce inflammation as an immunomodulator in its active form.[13]

Vitamin D3 can improve neurotransmitter function through both genetic and non-genomic mechanisms. Epidemiological and case-study evidence has connected vitamin D3 with seizures. These findings support the use of vitamin D3 as a viable therapy for epilepsy, whether taken alone or in conjunction with presently existing AEDs.[3]

In summary, patients with polypharmacy epilepsy are susceptible to hypo-vitamin D. Vitamin D3 administration is associated with an increase in serum 25(OH)D levels, as well as a decrease in seizure frequency. The limitation of this study is the small number of samples, only 16 subjects, but all of the subjects follow the study to the end. As a result, further research with larger sample sizes is required to determine how much dosage should be given to polypharmacy epilepsy patients in order to reduce seizures. Hopefully, this study may be considered as an adjuvant therapy for polypharmacy epilepsy patients.

Conflict of interest

None declared.

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