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Original Article

# Serum Vitamin D levels in Children Receiving Sodium Valproate as Antiepileptic Medication in Uttar Pradesh, India

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## Abstract

**Introduction:** Epilepsy is a common problem among children. Most of these children are under sodium valproate therapy. Valproate is known to cause fluctuations in serum vitamin $D_3$ level. The present study aimed to assess impact of sodium valproate on serum vitamin $D_3$ levels in ambulated epileptic rural children.

**Methods:** A prospective study was conducted from January 2020 to June 2024 at a tertiary care centre in North India. Ambulatory children with epilepsy aged one to 18 years receiving sodium valproate monotherapy for more than six months were included. Children on valproate were cases and healthy volunteer children taken as controls. Data were analysed using SPSS v21 on Windows-10.

**Results:** 130 children were enrolled. Vitamin $D_3$ levels were significantly lower in children on valproate therapy compared to the controls. Mean levels in cases and controls were 14.98 + 2.19 ng / ml cf. 25.90 + 3.14 ng / ml respectively ($P < 0.001$). There was a strong negative correlation of duration of anti-epileptic drugs (AED) and vitamin $D_3$ levels (Pearson's correlation value of < .0001). Further, after vitamin $D_3$ supplement of 60000 IU weekly for six weeks, 10% children did not achieve levels of 20 ng / ml (defined as cut off for deficiency).

**Conclusions:** Study suggests that children on prolonged sodium valproate medication are at significant risk of vitamin $D_3$ deficiency; vitamin $D_3$ levels should be monitored and vitamin $D_3$ supplementation considered. Vitamin $D_3$ levels estimation after supplementation is important as repeat supplementation may be needed.

## Introduction

Vitamin $D_3$ is a member of broad family of steroid hormones signalling via nuclear and membrane-associated receptors. Besides bone mineralization, vitamin $D_3$ is also involved in functions like cardiovascular health, tumor prevention, immunological functioning and glucose metabolism. Vitamin $D_3$ levels vary substantially in different subsets of population as well as among populations from different geographical regions.[1-3]

Many factors affect the vitamin $D_3$ levels in blood. One such factor is antiepileptic drugs.[4,5] Epilepsy is common in children and anti-seizure medications [ASMs] need long term use. Their adverse effects include influence over bone mineralization due to impact on vitamin $D_3$ metabolism. Pathogenetic mechanism appears to be based

on decreased active levels of vitamin $D_3$ which could be due to ASMs inducing hepatic cytochrome P450 enzymes, resulting in its conversion to inactive metabolites in the liver microsomes.[4] Hypocalcaemia can be caused by decreased absorption from the stomach as a result of hypovitaminosis $D_3$ causing increase in circulating parathyroid hormone and secondary hyperparathyroidism causes accelerated bone turnover, which raises serum alkaline phosphatase levels.[5]

However, less attention has been paid to interaction between ASMs and vitamin $D_3$. Not many studies are available on this subject.[6] Due to lack of awareness, it is not a common practice to supplement vitamin $D_3$ in children with antiepileptic drugs — United Kingdom had only 3% of paediatric neurologists using prophylactic vitamin $D_3$ medication for infants on anticonvulsants.[7,8] In low resource countries like India, it is even less and no information in African children could be found.[7] There is a need for more studies particularly from patients with rural and resource constrained background, malnutrition which are more likely to suffer the vitamin $D_3$ deficiency. Also, studies of vitamin $D_3$ therapy in children with epilepsy have been limited by lack of stratification with regard to confounding factors such as duration of treatment and response to supplementation with vitamin $D_3$.

Present study was conducted to assess prevalence of vitamin $D_3$ deficiency among rural North Indian children receiving sodium valproate monotherapy for seizure control and also to find any correlation between duration of sodium valproate therapy and serum vitamin $D_3$ levels. Vitamin $D_3$ supplementation was attempted in these children and response to supplementation was analysed.

## Methods

This prospective study was conducted at Subharti Medical College and Chhatrapati Shivaji Subharti Hospital, Meerut, Uttar Pradesh, India which is a tertiary care centre in North India catering to rural population. Out-patient department (OPD) cases were enrolled from January 2020 to June 2023 and followed-up till June 2024 or till completion of valproate therapy whichever was earlier. Children with seizures aged one year to 18 years on sodium valproate monotherapy for more than 6 months were included. A time interval of six months from the initiation of therapy was taken so that the body stores which might have been adequate prior to treatment would not affect the results. Children on multiple ASMs, steroids, thiazides, bisphosphonates, anticancer drugs, anti-hypertensive drugs, and those with malabsorption and renal diseases were excluded.

Serum was separated by centrifuging at room temperature. Vitamin $D_3$ and sodium valproate levels were analysed using chemiluminescence method. Cases with vitamin $D_3$ deficiency were prescribed with vitamin $D_3$ supplementation of oral preparation 60,000 IU weekly for six weeks and vitamin $D_3$ levels re-assessed after four to six weeks of the last dose of vitamin $D_3$. If vitamin $D_3$ levels were still insufficient, a second course of weekly 60,000 IU of vitamin $D_3$ were administered and reassessment of vitamin $D_3$ levels was again done after four to six weeks. All cases were reassessed at 18 - 24 months after starting ASM while planning cessation of ASM and lastly after 6 - 12 months of closure of ASM. High dose short course of vitamin $D_3$ supplementation was preferred over continuous vitamin $D_3$ supplementation for better compliance and monitoring, total dose administered being as per the recommendations.[5,9] Vitamin $D_3$ levels are often laboratory specific, but most studies have taken 20 ng / ml as cut-off for deficiency. Hence, levels of a value $< 20$ ng / ml was taken deficient, 20 – 29 ng / ml as insufficient and a value of $> 30$ ng / ml was regarded sufficient.[10,11] Children were divided into two groups—cases who were on ASM and controls who were matched normal children. Valproic acid (VPA) was used in doses of 20.5 to 36.3 mg / kg of body weight of child (Mean 28.1 + 3.7). Serum VPA levels were measured with mean value 78.9 mcg / ml + 11.3 (Range 43.8 to 111.1 mcg / ml)

Sample size was calculated using formula

$$\text{Sample size} = \frac{z^2 \times p\,(1-p) / e2}{1 + \{z^2 \times p\,(1-p) / e2\, N}$$

where z is Z score (1.96 for 95% confidence limit)

p is proportion of population (taken as 50%),

e is margin of error (5%) and

N = population surveyed (75 which is the number of cases in OPD being treated with sodium valproate monotherapy).

Based on the above, minimum sample size calculated was 63.

All data were entered in excel sheet and analysed using SPSS v21 operating on Windows-10. Demographic details of the patients are represented as frequency and percentage; continuous variables using mean and standard deviation. Mean difference between the two continuous variables was analysed using the unpaired student t-test and P-value of $< 0.05$ was considered statistically significant. Informed written consent was obtained from both parents in each patient. If consent was denied, child was not enrolled. Study was approved by institution's ethics committee (SMC/PG1/2020/265).

## Results

A total of 143 individuals were initially enrolled in the present study. Of these, 73 were cases and 65 were controls. Of the 73 cases, eight children dropped out. Thus, a total of 65 cases and 65 controls were finally included in the study and their results analysed. Demographic details of children, serum valproate levels and duration of treatment are shown in Table 1.

**Table 1:** Demographic details of the patients included

| Parameter | Group | Mean | SD | P value |
|---|---|---|---|---|
| Age (years) | Case | 13.11 | 1.83 | > 0.05 |
| | Control | 12.89 | 1.72 | |
| Weight (kg) | Case | 39.12 | 7.37 | > 0.05 |
| | Control | 40.86 | 5.96 | |
| Gender (nos.) | Male | 68 (52.3%) | | |
| | Female | 62 (47.7%) | | |
| Serum valproate level (µg / ml) | Case | 119.02 | 7.63 | |
| Duration of AED (months) | Case | 19.02 | 3.54 | |

Vitamin $D_3$ levels in cases and controls are depicted in Tables 2 and 3. Significantly lower vitamin $D_3$ levels in children on sodium valproate were found (Table II).

**Table 2:** Comparison of serum vitamin $D_3$ levels between cases after six months of AED and controls

| | Group | Mean | SD | P-value |
|---|---|---|---|---|
| Vitamin $D_3$ level (ng/ml) | Case | 14.98 | 2.19 | < 0.001 |
| | Control | 25.90 | 3.14 | |

**Table 3:** Comparison of the vitamin $D_3$ deficiency among the cases and control

| | Vitamin $D_3$ Deficiency (< 20 ng / ml) | | Sufficient vitamin $D_3$ (> 20 ng / ml) | | Chi-square (P value) |
|---|---|---|---|---|---|
| | Nos. | % | Nos. | % | |
| Case | 63 | 96.9% | 2 | 3.1% | < 0.001 |
| Control | 1 | 10.7% | 64 | 89.3%* | |

16.9% (11 cases) had levels > 30 ng / ml. None in the case group had levels > 30 ng / ml

There was a strong negative correlation between duration of AED and vitamin $D_3$ levels. (P < 0.001) (Figure1).

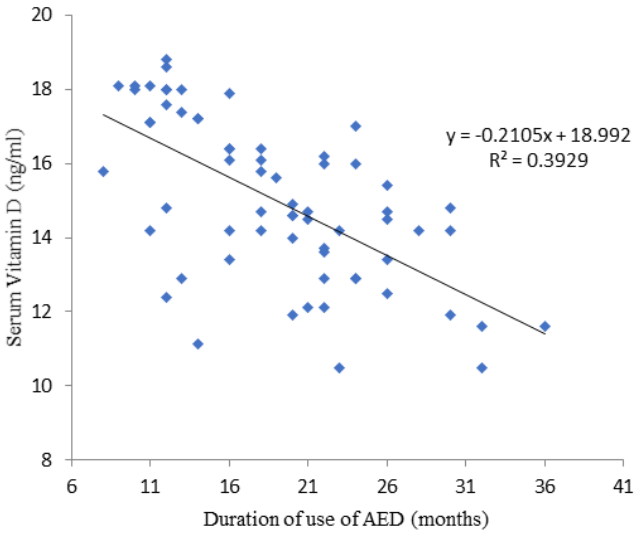


**Figure 1:** Correlation of duration of AED (months) with vitamin $D_3$ levels (ng / ml)

Table 4 shows the results after six weeks supplementation of vitamin $D_3$ at dose of 60000 IU weekly for six doses and 10% children could not achieve levels of > 20 ng / ml and a second course of six weeks was repeated whereafter all children achieved above deficiency levels.

**Table 4:** Serum vitamin $D_3$ level post supplementation of vitamin $D_3$ to cases

| | Group (cases) | Mean | SD | P-value |
|---|---|---|---|---|
| Vitamin $D_3$ level (ng/ml) | Before supplementation | 14.98 (10.50 – 18.80) | 2.19 | 0.001 |
| | After supplementation with vitamin $D_3$ | 27.34 (18.36 – 35.21) | 4.26 | |

## Discussion

Observers agree about a potential risk of vitamin $D_3$ deficiency in children on anti-epileptic drugs including valproic acid. However, frequency and severity are not uniform. This depends not only on the inherent vitamin $D_3$ level status before starting treatment, dietary intake, and exposure to sun light of the children included in the study but also on the criteria used to define. The last variable makes it often difficult to compare various studies.

In the present study, mean levels were 25.9+3.14 ng/ml among controls. Only one child was deficient with 19.8 ng / ml level of vitamin $D_3$ and 16.9% (11 cases) had levels above 30 ng / ml to be counted as sufficient. Community-based Indian studies of the past decade done on apparently healthy controls reported prevalence ranging from 50% to 94%.[12,13] Hospital-based studies have reported an overall vitamin $D_3$ deficiency to be 40-93%.[14] Most studies have been in pregnant or

lactating women, old people above 60 years of age as also on cord blood depicting maternal status.[14] Hospital based studies from different parts of India including Kolkata, Chandigarh, Pune, Delhi for urban children one to 16 years age group reported deficiency in 27 - 50% cases.[15-19] Kadam found 34% of undernourished girls in Pune to be with levels < 9 ng / ml.[15] Choudhary from Delhi reported 34.5% children to be deficient;[17] while Marwaha had 27% of upper socioeconomic and 42% of lower socioeconomic group children with levels < 9 ng / ml.[16] Basu from Kolkata reported median levels to be 19 ng / ml, 52% children were deficient, 24 % insufficient and 22% having levels above 30 ng / ml.[18] Angurana from Chandigarh reported 40% deficiency, 26% having insufficient and 34% children in three months to 12 years group having sufficient vitamin $D_3$ levels.[19] We had < 2% healthy children with values less than 20 ng / ml and none below 10 ng / ml while 17% had levels above 30 ng / ml. Probable reason for marginally better vitamin $D_3$ levels in controls could be the rural background of these children with better exposure to sun light and lesser of air pollution as compared to those in cities.

Among the children on sodium valproate monotherapy for a minimum of six months, vitamin $D_3$ deficiency was 100% (Mean levels 14.98 ng / ml, range 10.5 - 18.80). High risk of vitamin $D_3$ deficiency is also reported in studies from South India.[6,20-21] Sreedharan et al from Kerala, India reported 60.7% of patient receiving carbamazepine and 35.7% on valproate had low 25 (OH)HCC levels (< 20 ng / mL).[6] Chaudhuri et al from Hyderabad, India documented 25-hydroxyvitamin D (≤ 20 ng / mL) significantly higher deficiency among epileptics (44%) compared to control subjects (20%) but found risk higher with valproate than carbamazepine.[20] Ramya reported 75.5% deficiency (< 20 ng / ml).[21]

A negative correlation of duration of ASM and vitamin $D_3$ levels has been reported in few studies.[20-23] It was very strong ($P < 0.001$) in the present study. The exact duration of ASMs that cause vitamin $D_3$ insufficiency is not defined and further studies on this aspect are suggested. Cansu et al showed vitamin $D_3$ levels were considerably lower after 18 months of taking ASMs.[22] Ramya et al also documented a linear relation between the vitamin $D_3$ level and the duration of anticonvulsant use.[21] Chaudhuri et al reported a mean exposure length of 25.2 months.[20] The present study also observed a continuous decline in serum vitamin $D_3$ levels with increasing duration of treatment. After 18 months of valproate therapy, levels were often 12 - 13 ng / ml and most cases had values closer to 10 – 12 ng / ml after 24 months of therapy. This is significantly greater than prior data and could be due to increased exposure to sunlight in rural India which was the cohort in our study.

This study reinforces the deleterious effects of ASMs on bone mineral metabolism and is consistent with current global literature. Supplementing with vitamin $D_3$ may aid in the prevention and correction of these problems. But vitamin $D_3$ levels vary depending on diet and sunlight exposure and excessive therapeutic intake can be harmful as well. Despite the fact that vitamin $D_3$ hypervitaminosis is uncommon in children, continuous administration of vitamin $D_3$ supplements increases risk of vitamin $D_3$ toxicity and it may be asymptomatic in epileptic children. There are studies recommending vitamin $D_3$ therapy combined with ASM in children.[19,20] Vitamin $D_3$ supplementation even before starting antiepileptic medicines has also been advocated.[19] However, information on the length of therapy, the significance of diet / exercise is still insufficient. Even supplementation may not always raise the vitamin $D_3$ levels as was the case in the present study where 10% children could not achieve above deficiency levels. Hence, monitoring of vitamin $D_3$ levels with or without monitoring bone mineral density is very much needed when contemplating supplementation with vitamin $D_3$. The present study does have some limitations. One limitation is that VPA levels before starting treatment were not assessed and, secondly, we did not estimate bone density. Pretreatment vitamin $D_3$ levels were not assessed as patients when enrolled were already on valproate treatment.

## Conclusions

This study identifies that ambulant children on long term sodium valproate therapy are at significant risk of vitamin $D_3$ deficiency. Consequently, influence on bone health needs to be addressed by treating physicians. Regular monitoring of vitamin $D_3$ levels in blood should be done. Routine supplementation of vitamin $D_3$ for children on AED should be considered. However, length of therapy, the significance of diet / exercise, sunlight exposure necessitates to standardize the therapeutic protocols locally.

**Conflict of Interest:** None

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