ORIGINAL RESEARCH

A Prospective study on effect of antiepileptic drugs on serum vitamin D3 level in newly diagnosed epilepsy patients

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ABSTRACT

Aim: To determine the effect of antiepileptic drugs on serumvitamin- D3 levels in newly diagnosed epilepsy patients.

Material and methods: Total 65 patients (OPD/IPD) aged between 12-45 years who were newly diagnosed and matching against the inclusion and exclusion criteria were included in the study. Those who were found deficient at baseline were excluded from the study .Patients were assessed for vitamin D deficiency at further follow ups of 3rd and 6th month.

Results: We observed that vitamin D levels were found low at 3rd month as compared to baseline while after the start of vitamin D3 supplementation there was increase in the levels at 6th month as compared to 3rd month. Patients on polytherapy had greater decrease in vitamin D than on monotherapy.The total decrease in vitamin D levels in patients taking EIAEDs and combination was significantly more than in NEIAEDs at 3rd month.

Conclusion: In our study it was observed that, antiepileptic drugs leads to significant reduction in vitamin D level. So there is need to monitor serum vitamin D levels periodically during anticonvulsant therapy so that therapeutic Vitamin D should be started as early as possible which would eventually leads to better quality of life of suffering patients.

Keywords: Vitamin D, epilepsy, monotherapy, polytherapy, supplementation

INTRODUCTION

Epilepsy is defined as 'two unprovoked seizures occurring more than 24 hours apart; a single unprovoked seizure if recurrence risk is high (i.e.>60% over the next 10 years); or a diagnosis of an epilepsy syndrome'(1). Itin itself predisposes to spontaneous epileptic seizures and many neurological, cognitive and psychosocial outcomes.

The Incidence of epilepsy is 0.3%-0.5% in different populations throughout the globe and prevalence of epilepsy has been estimated at 5-10 persons per 1000(2). Data from recent studies in India reported prevalence of 3-11/1000 and incidence of 0.2-0.6/1000. In developing countries prevalence of epilepsy was higher in rural areas as compared to urban areas (3).

Antiepileptic group of drugs remain the first line in management of epilepsy. This group of drugs is classified mainly on the basis of Enzyme induction. As per enzyme inducing properties, they are classified as Enzyme Inducing Antiepileptics (EIAEDs) and Nonenzyme Inducing Antiepileptics (NEIAEDs) (4).

Researches in near past have much emphasized the association of vitamin D with epilepsy and antiepileptics.In recent studies, it has been seen that anti-epileptics may decrease serum vitamin D3 levels in epilepsy patients. AEDs activates PXR, due to which there is increase in expression of cyp24, a target gene of VDR. CYP24 is a major enzyme involved in the metabolism of 1,25(OH)2 vitamin D and thereby decreases the active form and thus lead to fall in the levels of biologically active metabolite of 1,25 dihydroxy vitamin D (5). Decreased vitamin D levels lead to lowering of intestinal calcium absorption causing hypocalcemia which further leads to development of secondary hyperparathyroidism, lowers bone mineral density and higher chances of fractures(4). Vitamin D deficiency is defined at 25(OH)D levels < 20 ng/mL, insufficiency as 21–29

ng/mL and sufficient levels as at least 30ng/mL(6).Various factors such as increased risk of falls due to disease per se and adverse effects of anti-epileptics, makes such patients at increased risk of bone problems and fractures (2-6 times) (7)

According to various studies, it is stated that hepatic microsomal enzyme inducers drugs have more negative effect on Vitamin D and bone mineral density in comparison to non inducers antiepileptics drugs. So much of the literature recommends to supplement the patients with vitamin D and calcium(4). Further it has been found that vitamin D3 itself acts as anticonvulsant and has role in seizure control(8). Considering this along with other bodily effects of lowvitamin D3 levels, it affects quality of life in such patients too.

Considering increased recognition of hypovitaminosis with use of antiepileptic drugs, we hereby attempt to determine the effect of antiepileptic drugs on vitamin D level in epilepsy patients

MATERIAL AND METHOD

The present study was a hospital based prospective study in the Department of Psychiatry, GGSMCH, Faridkot, Punjab. Total 65 subjects aged between 12-45years registering as OPD/IPD patients and who gave the written consent were included in the study. Patients with severe medical ailment and any kind of neurological condition , history of head injury , taking drugs that effect bone metabolism or taking vitamin D supplements were excluded from the study. An informed written consent was taken from patient and their care givers reporting for treatment. The enrolled patients were subjected to the inclusion and exclusion criteria and were selected accordingly. Psychiatric interview of the subjects was conducted with the help of semi-structured Psychiatric Thesis Performa as devised by department of psychiatry. Subject's chief complaints, history of illness and symptoms severity was assessed for the first time by researcher and diagnosis of epilepsy (G40) was made as per ICD-10 criteria. As per ILAE 2017 guidelines patients were classified into generalized, partial and unknown types. Diagnosis was confirmed by consultant in the concerned department after initial assessment by the researcher. On the presenting day, the patients were subjected to the appropriate investigations like routine blood investigations (CBC, renal functional tests, liver functional tests, blood sugar level, serum electrolytes, serum calcium, Viral Markers) or to radiological investigations (NCCT Head) as and if needed to justify the inclusion and exclusion criteria or if the clinical presentation demands. The patients were then started on appropriate anti-epileptics as per clinical review. Baseline vitamin D3 level was assessed in biochemistry lab using fully automated chemiluminescence principle. A per WHO guidelines, vitamin D3 levels less than 20ng/ml are regarded as deficient and Vitamin D3 levels from 21-29ng/ml is regarded as insufficient and Vitamin D3 levels at least 30ng/ml regarded as sufficient. Those patients who were found deficient at baseline were excluded from the study.

The patients were then followed up at 3rd and 6th month, or as required. At each follow up, the patients were reassessed for serum vitamin D3 levels and quality of life. Patients found with vitamin D3 deficient levels on follow up at 3rd month and 6th month were supplemented with oral vitamin D3 till sufficient vitamin D3 level was attained.

The data was compiled and was subjected to appropriate tests. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 26 version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

RESULTS

The majority of patients in present study were in age group 31-40 years 23(35.4%), followed by 21-30years(32.3%), 11- 20 years18(27.7%) and least patients were in age group 41-50, i.e. 3(4.6%). The mean age in the study was 27.40±9.15 years. The study consisted of 35 (53.8%) male and 30 (46.2%) females. The findings of present study shows that 90.8%(59) of the total patients were on monotherapy while 9.2% were on dual or polytherapy. 40(62%) patients were on NEIAED, 19 (29%) patients on EIAED and 6(9%) patients were on combined NEIAED and EIAED therapy **(Table 1)** .

Table 2 showed that the mean vitamin D levels at baseline were 28.86±6.59, At 3 months it was 25.05±6.26 and at 6 months it was 22.74±4.76. Vitamin D was significantly less at 6 months than at 3 months which is less than baseline.**Table 3** shows that none of the patients presented vitamin D deficiency at baseline, 24.6 % by 3 months while at 6 months 18.5% had vitamin D deficiency. From baseline to 6 months total decrease in vitamin D levels in patients who were taking EIAED was 11.16 ±2.03 while on NEIAED and combination drug it was 4.15±6.07 and 3.33±5.61. The decrease in vitamin D was significantly more in patients on EIAEDs (**table 4).**

We observed from **table 5** that at the end of three months, the total decrease in vitamin D levels in patients on polytherapy was more(5.33±1.63) than monotherapy (3.66±2.87) however, this association was statistically non- significant($p>0.05$).At end on 6 months the total decrease in vitamin D levels in patients on monotherapy was significantly more (2.75 ±5.53) than in polytherapy (-2.00±4.56) and this association was statistically significant($p<0.05$).From baseline to 6 months in patients taking monotherapy, the decrease in Vitamin D levels was significantly more(6.41 ±6.08) than in polytherapy (3.33±5.61), although this association was statistically non-significant($p>0.05$).

Variable		Frequency (N)	Percent (%)
Age group	11-20 years	18	27.7
	21-30 years	21	32.3
	31-40 years	23	35.4
	41-50 years	3	4.6
Sex	Female	30	46.2
	Male	35	53.8
No. of Anti- epileptic drugs prescribed	Mono Therapy	59	90.8
	Dual/Polytherapy	6	9.2
Antiepileptic Drugs	EIAED	19	29.2
	NEIAED	40	61.5
	NEIAED+EIAED	6	9.2

Table 1: shows the basic characteristics of the study.

Intergroup comparison		Mean	Std. Deviation	t- value	p-value
Pair 1	Vitamin D at baseline	28.86	6.593	10.921	.000
	Vitamin D at 3 months	25.05	6.264		
Pair 2	Vitamin D at 3 months	25.05	6.264	3.330	.001
	Vitamin D at 6 months	22.74	4.767		
Pair 3	Vitamin D at 6 months	22.74	4.767	- 8.138	.000
	Vitamin D at baseline	28.86	6.593		

Table 2: Comparison between vitamin D levels at different time intervals in adults

Sub groups	Vitamin D Deficiency			
	Absent (>20mg/ml)		Present (<=20mg/ml)	
	N	%	N	%
Baseline	65	100	0	0
3 months	49	75.4	16	24.6
6 months	53	81.5	12	18.5

Table 3: Comparison between vitamin D deficiency at different follow up

Vitamin D at different time Intervals	EIAED (n=19)		NEIAED (n=40)		EIAED+ NEIAED (n=6)		f-value	p- value
	Mean	SD	Mean	SD	Mean	SD		
Vitamin D at Baseline	33.16	4.62	27.38	6.72	25.17	4.75	7.144	0.002
Vitamin D at 3 months	26.68	4.82	25.05	6.77	19.83	4.31	2.889	0.063
Vitamin D at 6 months	22.00	3.94	23.23	5.36	21.83	2.48	0.537	0.587
Difference between 3 months from Baseline	6.48	1.26	2.33	2.42	5.33	1.63	27.119	0.000
Difference between 6 months from 3 month	4.68	2.43	1.83	6.32	-2.00	4.56	3.993	0.023
Difference between 6 months from baseline	11.16	2.03	4.15	6.07	3.33	5.61	12.691	0.000

Table 4: Association of Vitamin D with type of drug

Vitamin D at different time interval	Number of drugs	N	Mean	Std. Deviation	t-test	p- value
Vitamin D at baseline	Monotherapy	59	29.24	6.67	1.453	0.151
	Polytherapy	6	25.17	4.75		
Vitamin D at 3 months	Monotherapy	59	25.58	6.21	2.203	0.031
	Polytherapy	6	19.83	4.31		
Vitamin D at 6 months	Monotherapy	59	22.83	4.95	0.485	0.629
	Polytherapy	6	21.83	2.48		
Difference between baseline and 3 months	Monotherapy	59	3.66	2.87	-1.396	0.168
	Polytherapy	6	5.33	1.63		
Difference between 6 months and 3 months	Monotherapy	59	2.75	5.53	2.03	0.047
	Polytherapy	6	-2	4.56		
Difference between baseline and 6 months	Monotherapy	59	6.41	6.08	1.186	0.24
	Polytherapy	6	3.33	5.61		

Table 5: Association of Vitamin D with number of drugs

Discussion

In present study we observed that the mean age in the study was 27.40±9.15 years. The study consisted of 35 (53.8%) male and 30 (46.2%) females. In present study we observed that mean vitamin D levels at start of treatment was 28.86±6.59(21-47), at 3 months it was 25.05±6.26 and at 6 months it was 22.74±4.76.Thus mean vitamin D levels at 6 months were found to be lowest than at 3 months than at baseline because already patients were on anti- epileptics that further decrease vitamin D levels. No doubt we started with supplementation at first follow up at 3 months but they were only started in patients with deficient Vitamin –D levels(<20ng/ml) whilepatients having insufficient levels(21-29ng/ml)/optimal levels(≥30ng/ml) were not given supplementation thus their levels further decrease that lead to minimum mean levels of vitamin D at 6 months.

We observed that at the end of three months, the total decrease in vitamin D levels in patients taking EIAEDs(6.48±1.26) andcombination(5.33±1.63) was significantly more than in NEIAEDs(2.33±2.42) and At end on 6 months, the total decrease in vitamin D levels in patients taking EIAEDs (4.68 ±2.43) was significantly more than in NEIAEDs(1.83±6.32) and this association was statistically significant. The patients on combination drugs had a net increase in vitamin D levels which could be due to supplementation(-2.00±4.56) and From baseline to 6 months total decrease in vitamin D levels in patients on patients who were taking EIAEDs was 11.16±2.03, while on NEIAEDs it was 4.15±6.07 and on combination of both it was 3.33±5.61, the decrease in vitamin D levels was significantly more in patients on EIAEDs.Similarly conducted by teagarden et al. (9) found in their study that Vitamin D3 deficiency was higher in EIAEDs (54%) than NEIAEDs (37%). In contrast Wu et al.(10) reported that there was a similar risk ofdeveloping vitamin D deficiency with both EIAEDs and NEIAEDs and study by Chaudhry et al(11) also found that both EIAEDs andNEIAEDs were significantly associated with deficiency of vitamin D levels which was dissimilar to our study .Thus, there has been a lot of debate on whether the enzyme inducing properties of AEDs are to blame. Initial studies reported an association of reduced bone mineral density and increased fracture risk with mainly enzyme inducing AEDs (EIAEDs). However, recent studies have found no difference between EIAEDs and NEIAEDs in their action on 25-hydroxyvitamin D status. There was a similar risk of developing vitamin D deficiency with both EIAEDs and NEIAEDs.

We observed that at the end of three months, the total decrease in vitamin D levels in patients on polytherapy was more(5.33±1.63) than monotherapy (3.66±2.87). However, study conducted by Dr.DevhutiGodhani et al.(12) in which total of 90 patients were taken out of which30 were on mono-therapy while 30 on polytherapy therapy and 30were taken as control. Study found that 26% were found deficient in vitamin D which were on monotherapy compared to 43% on poly therapy which was in concordance with our study.

Conclusion

In our study it was observed that, antiepileptic drugs leads to significant reduction in vitamin D levels over 6 months of follow ups. So there is need to monitor serum vitamin D levels periodically during anticonvulsant therapy so that therapeutic Vitamin D should be started as early as possible which would eventually leads to better quality of life of suffering patients.

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