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Research Article

Vitamin D Levels in Children with Thalassemia major

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Introduction

Hemoglobinopathies are the most common inherited diseases around the world. In India, Beta Thalassemia affects over 1 lakh people and more than 8000 thalassemic children are born every year [1]. The thalassemia syndromes are a heterogeneous groupof inherited anemias characterized by defects in the synthesis of one or more of the globin chain subunits of the hemoglobin (Hb) tetramer. Clinical manifestations are diverse, ranging from asymptomatic hypochromia and microcytosis to profound anemia,which can be fatal in utero or in early childhood if untreated [2]. The mainstay of treatment of severe β thalassemia is regular blood transfusion with an attempt to maintain hemoglobin levels greater than 10g/dl. Inspite of optimal management, children with transfusion-dependent beta thalassemia have poor bone health [3]. Osteoporosis is foundin 40-80 % of well –treated thalassemic patients. The pathogenesis of low bone mass ismulti-factorial and includes defective synthesis of 25 OH vitamin D (25OH D) and/or hypoparathyroidism, effect of iron chelators, nutritional deficiency, direct iron toxicity and progressive marrow expansion [4,5].

Keywords: Vitamin D; Thalassemia Major; Calcium; Parathyroid Hormone; Alkaline Phosphatase

Material and Methods

A case control study was conducted in the Department of Pediatrics, Rajindra Hospital, Patiala and Department of Biochemistry, Government Medical College, Patiala.The study group includes 50 children in the age group of 5-18 years diagnosed with thalassemia major in the department (outdoor and indoor). The control group was comprised of 30 healthy (non thalassemia major) children of the same age group. 25 (OH)Vitamin D levels were estimated in both groups by ELISA method and then compared statistically.

Inclusion criteria:

- Age group 5 years to 18 years of either gender.
- Cases diagnosed with beta thalassemia major.

Exclusion criteria:

- Children who were less than five years of age of either gender.
- Children who were more than eighteen years of age of either gender.
- All children with liver and renal disease.
- Children with Hypothyroidism.
- Children with HIV, Hepatitis B, Hepatitis C.
- History of anticonvulsant drug intake (besides chelation therapy).
- Children with any malabsorption syndrome.

Statistical Analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 20 (SPSSInc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages and means. The statistical tests applied for the analysis were Pearson's chi-square test (χ^2), Student t-test and One-way Analysis of Variance (ANOVA). For all the tests, confidence interval and p-value were set at 95% and ≤ 0.05 respectively.

Results and Observation

The mean age of the studied thalassemia patients was 10.10 ± 3.62 years with no gender predilection. Mean (SD) Vitamin D a level in study group were 6.40 and in control group was 15.6

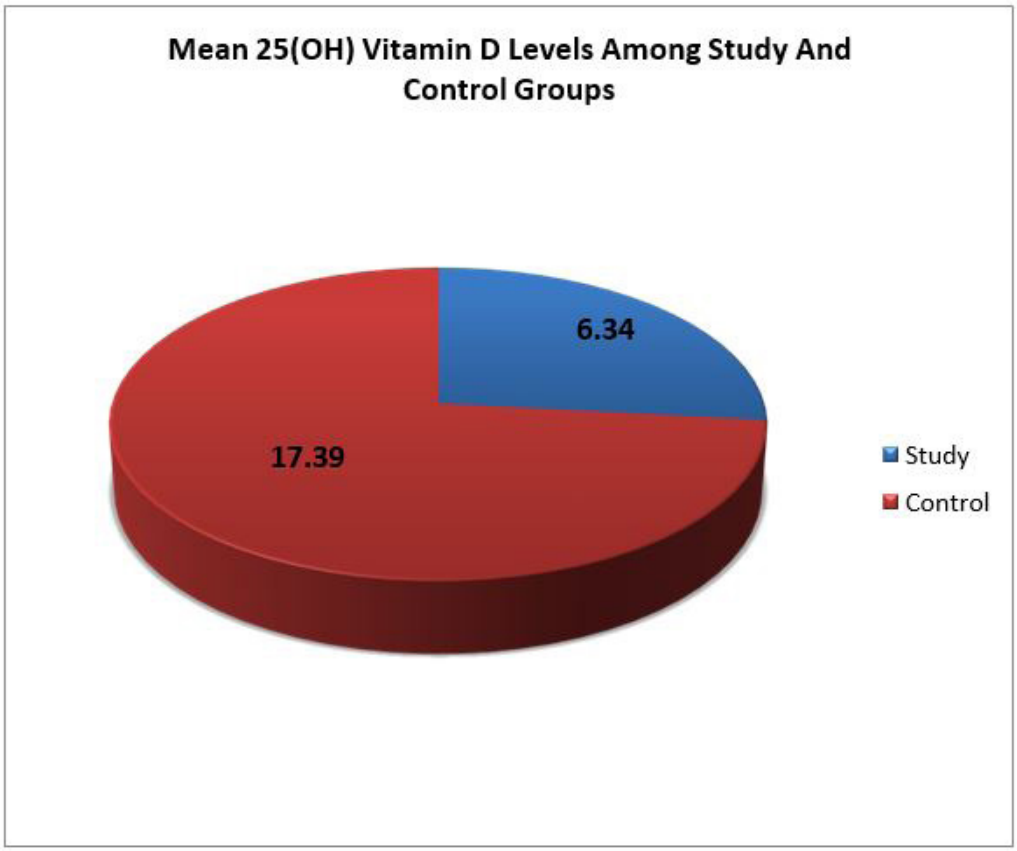
VITAMIN D STATUS	REFERENCE RANGE OF VITAMIN D
Deficient	<10 ng/ml
Insufficient	10-30 ng/ml
Sufficient	30-100 ng/ml
Intoxication	>100 ng/ml

Table 1: The results were inferred with reference to following ranges:

Age (Years)	Study Group		Control Group	
	Mean 25 (OH) Vitamin D level	Std. Deviation	Mean 25 (OH) Vitamin D level	Std. Deviation
5-9	7.16	6.36	18.90	6.35
10-14	6.11	3.86	15.63	4.15
15-18	4.03	3.36	20.14	11.74
F-value	0.805		0.135	
p-value	0.453		0.275	
Significance	NS		NS	

Table 2: Age wise distribution mean 25 (OH) vitamin D levels among study and controlgroups

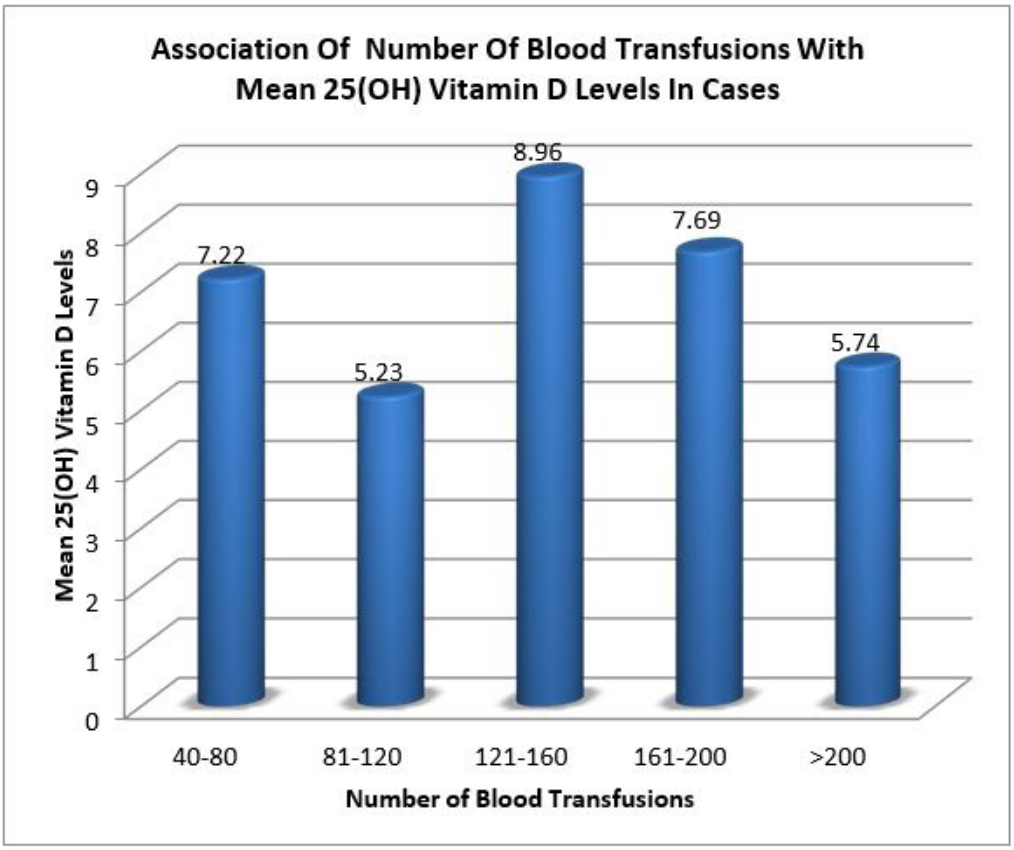
Graph 1: Mean Vitamin D Levels among study and control groups



	Study group		Control group	
Mean 25 (OH)vitamin D level	**Mean**	**Std. Deviation**	**Mean**	**Std. Deviation**
	6.34	5.09	17.39	6.04
Median	5.78		14.9	
Range	0.19-26.01		9.31-32.63	
t-test	-8.747			
p-value	0.001			
Significance	S			

Table 3: Mean 25 (OH) Vitamin D Levels among study and control groups

Graph 2: Association of number of blood transfusion with mean 25 (OH) Vitamin DLevels among study group



Number of Blood Transfusions	Study Group		Control Group	
	Mean 25(OH) Vitamin D	Std. Deviation	Mean 25 (OH) Vitamin D	Std. Deviation
40-80	7.22	6.01	-	-
81-120	5.23	4.84	-	-
121-160	8.96	7.16	-	-
161-200	7.69	4.58	-	-
>200	5.74	3.82	-	-
F-value	0.617		-	
p-value	0.653		-	
Significance	NS		-	

Test applied: One-way ANOVA

Table 4: Association of number of blood transfusions with mean 25 (OH) Vitamin DLevel among study group

Table 4 In the present study mean 25 (OH) Vitamin D levels were compared with number of blood transfusions. The mean 25 (OH) vitamin D of the children who were given blood transfusion between 40-80 times was 7.22, between 81-120 mean 25 (OH)vitamin D level was 5.23, between 121-160 mean 25 (OH) vitamin D level was 8.96, between 161-200 mean 25 (OH) vitamin D level was 7.69 and the children who were transfused more than 200 times their mean 25 (OH) vitamin D level was 5.74. Oneway analysis of variance revealed that the mean difference for 25 (OH) vitamin D levels between the groups was statistically non-significant (p=0.653) respectively.

Duration of Beta Thalassemia Major (Months)	Study Group		Control Group	
	Mean 25 (OH) Vitamin D	Std. Deviation	Mean 25 (OH)Vitamin D	Std. Deviation
Less than or equal to105	7.16	6.36	-	-
More than 105	5.75	3.95	-	-
t-test	0.963		-	
p-value	0.05		-	
Significance	S		-	

Test applied: Test applied: student t-test

Table 5 In the present study while analyzing the association of duration of beta Thalassemia major with mean 25 (OH) vitamin D levels, it was observed that the mean value of 25 (OH) vitamin D levels among those who have beta thalassemia major for less than or equal to 105 months (7.61) showed almost 1.5 times the level than those who have thalassemia major for more than 105 months (5.75). Student t-test analysis revealed that the mean difference for 25 (OH) vitamin D levels between the groups wasstatistically significant (p=0.05) respectively.

Table 5: Association of duration of Beta Thalassemia major with mean 25 (OH) vitaminD levels among study group

Discussion

Thalassaemias are a group of hereditary disorders of hemoglobin (Hb) derived from animbalanced production of either alpha or beta globin chains [6]. The clinical spectrum varies from asymptomatic carrier state to more serious state, which require regular blood transfusions [7].

BETA THALASSEMIA MAJOR AND MEAN 25 (OH) VITAMIN D LEVEL

In accordance with one of the main aims of the present study we evaluated the serum 25 (OH) Vitamin D levels in beta thalassemia major patients who formed the study group and compared them to healthy children taken as control group. In the present study, it was observed that the mean value of 25 (OH) vitamin D levels among study group (6.38) was approximately thrice less than that of controls (17.39). That the meandifference for 25 (OH) vitamin D levels between the groups was statistically significant (p=0.001). This was found in agreement with the findings of a hospital based case control study conducted by Akhouri and Neha 2017 [8], in which 60 patients of beta thalassemia major (aged from 8 months to 12 years) were compared with 60 sex and age matched children serving as control group. Vitamin D (25 hydroxycholecalciferol) were estimated for all patients & controls. 25 (OH) vitamin D deficiency was present in 82% of the patients and in 47% of the controls. Difference in mean vitamin D levels between cases and controls was statistically significant ($p<0.05$). Similar reports were found in studies conducted by Fahim et al (2013) [9]. It has been postulated that it is dueto iron overload leading to hepatic dysfunction which leads to defective 1 alpha hydroxylation of vitamin D and so decreased serum levels of vitamin D has been observed.

25 (OH) Vitamin D and Age Distribution

In the present study it was observed that among the study group the mean value of 25(OH) vitamin D levels deceases as the age advances in study group i.e. among 5-9 years old children was (7.16) followed by 9-14 years old children (6.11) and >14 years old children (4.03). As the age advances, the cumulative numbers of blood transfusions taken by the patients were more due to repeated blood transfusions. As the number of blood transfusions increases, chances of iron overload increases thus decreasing 25 (OH) vitamin D levels. This was found in accordance with study conducted by HazarikaD et al 2016 [10].

25 (OH) Vitamin D and Number of Blood Transfusions

In the present study, mean 25 (OH) vitamin D level was observed and it was compared with the number of blood transfusions taken by the children under study group. It was observed that mean 25 (OH) vitamin D level was below the normal level in all

the children under study group who are on repeated blood transfusions. When the relationship of 25 (OH) vitamin D level with the number of blood transfusions was compared, it was found non-significant. Mean value of 25 (OH) vitamin D was 7.22 in children who had taken 40-80 blood transfusions, it was 5.23 in children who had takenbetween 81-120 blood transfusions, 8.96 among 121-160 blood transfusions, 7.69 among 161-200 blood transfusions and 5.74 among children who had taken >200 blood transfusions. This can be explained that certain other factors play role in regulation of vitamin D levels other than number of blood transfusions. This was in accordance to thestudy done by Hadeer AA et al (2019) [11], which stated that Vitamin D deficiency in patients with thalassemia is caused by decreased intake, lower sun exposure, defectiveskin synthesis; associated with jaundice, impaired absorption, or defective 25 hydroxylation of vitamin D in the liver due to hepatic siderosis.

25 (OH) Vitamin D and Frequency of Blood Transfusion

In our study, we have divided the study group children into five categories depending upon their frequency of blood transfusion. The mean value of 25 (OH) vitamin D levels was observed to be 6.37 in children who were getting transfused every 6-10 days, mean 25 (OH) vitamin D of 6.43 in children who were transfused every 11-15 days, 6.07 in children who were transfused every 16-20 days, 7.32 in children who were transfused every 21-25 days and mean value of 4.69 in children who got transfused every 26-30 days interval. It was found that there was no correlation of 25 (OH) vitamin D level in relation to frequency of blood transfusion. This can be due to the effect of other parameters that affect vitamin D levels in thalassemic children requiring blood transfusion like their socioeconomic status, nutritional status, outdoor activity, intake ofvitamin D supplementation, in addition to iron overload and iron chelation therapy. Thiswas according to study conducted by RK Marwaha et al (2005), Akhouri MR et al (2017), Seema P et al (2008), Soliman A et al (2013) [12-15].

25 (OH) Vitamin D and Duration of Thalassemia Major

In the present study it was observed that as the duration of beta thalassemia major increases with age in patients, their 25 (OH) vitamin D levels decreases. This is in accordance to the study conducted by Ellen B. Fung et al (2011) [16]. This can be explained on the basis that as the duration of thalassemia major increases with age in the patients their cumulative number of blood transfusions increases, which thus causesiron overload and decreased 25 (OH) vitamin D levels. In our study it was found that thepatients who had taken more than 105 blood transfusions when compared with children who had taken lesser than 105 blood transfusions, the difference in their mean 25 (OH) vitamin D levels were significantly lower. This study was comparable to the study conducted by Shruti Dhale et al **(2019)** [17] in which they concluded that the levels of 25 (OH) vitamin D are deficient among β-thalassemia major patients on repeated blood transfusion.

Conclusions

The present study concluded that the serum25 (OH) vitamin D levels in patients of β thalassemia major who have received repeated blood transfusion is statistically significantly lower compared to age and sex matched controls. It might be due to iron overload in patients receiving repeated blood transfusion which alters the function of theendocrine glands involved in maintaining the normal levels. It was also concluded from the study that as the age of the children diagnosed with beta thalassemia major advances,their 25 (OH) Vitamin D levels decreases. This can be due to increase in number of bloodtransfusions received by these children.

Recommendations

It is recommended that it is vital to check the serum 25 (OH) Vitamin D levels in patientswith beta thalassemia major receiving repeated blood transfusions. Annual evaluation ofbone mineral status is also recommended in thalassemia major patients. It is importantto emphasize that treatment of thalassemia patients should include supplementation withvitamin D and iron chelation therapy. Adequate nutritional support should be given to thechildren with beta thalassemia major. It is also recommended to have adequate sunlightexposure to these children.

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