Original Article *Iran J Ped Hematol Oncol. 2022, Vol 12, No 4, 220-228*

Efficacy of High Dose Vitamin D on Pulmonary Artery Pressure in Thalassemia Patients Undergoing Blood Transfusion: A Randomized Trial

Aziz Eghbali[1], Fatemeh Fadayi[2], Yazdan Ghandi[2], Vahid Falahati[2], Bahador Bagheri[3,4 *]

1. Department of Pediatrics, Aliasghar Clinical Research Development Center, Iran University of Medical Sciences, Tehran, Iran
2. Department of Pediatrics, Arak University of Medical Sciences, Arak, Iran
3. Cancer Research Center, Semnan University of Medical Sciences, Semnan, Iran
4. Center for Molecular Cardiology, University of Zurich, Schlieren, Switzerland

*Corresponding author: Dr Bahador Bagheri, Department of Pharmacology, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran. Email: bagherib@semums.ac.ir,bahadordvm@yahoo.com. ORCID ID: 0000-0003-2574-8034

Received: 17 January 2022 **Accepted:** 22 July 2022

Abstract

Background: Pulmonary arterial hypertension (PAH) may result in cardiomyopathy which is a major cause of death in thalassemia patients. Vitamin D is associated with benefits in cardiovascular disorders. Our purpose was to study effects of vitamin D on pulmonary artery pressure in thalassemia major and intermedia patients.

Materials and Methods: This randomized trial was performed on 26 patients with thalassemia major (TM) and intermedia (TI) in Amir-Kabir Hospital, Arak, Iran in 2019-2020. Patients were randomized 1:1 to intervention group (vitamin D 50,000 IU/week) and control group (received no supplement) for 20 weeks. Echocardiography was used to measure pulmonary artery pressure and assess cardiovascular function. The levels of 1,25-dihydroxyvitamin D3, ferritin, and cardiac iron content were measured in study groups.

Results: After 20 weeks, pulmonary arterial pressure (PAP), tricuspid regurgitant velocity (TRV), and pulmonary regurgitant velocity (PRV) significantly improved in the intervention group compared to the control group (P= 0.010, P= 0.003, and P= 0.001, respectively). Moreover, ejection fraction (EF) had significant increase in the intervention group compared to the control group (P= 0.008), although vitamin D supplementation had no significant impact on cardiac T2* values (P= 0.827), systolic and diastolic blood pressure (P= 0.388 and P= 0.509, respectively) and serum hemoglobin and ferritin levels (P= 0.557 and P= 0.620) as compared to the control group. However, the levels of 25-OHD3 significantly increased in the intervention group compared to the control group (P= 0.036).

Conclusion: This study showed that vitamin D 50000 IU/week can improve PAP in patients with thalassemia. Sufficient intake of vitamin D may prevent cardiomyopathies related to PAH.

Keywords: Ejection fraction, Pulmonary arterial hypertension, Thalassemia, Vitamin D

Introduction

Thalassemia is one of the most common inherited blood disorders in the world (1,2). Thalassemia is characterized by deficiency in the production of beta-globin chains. Thalassemia major is the most dangerous form of the disease which is usually presented with severe anemia (3,4). Frequent blood transfusion as a cornerstone in the treatment of thalassemia can result in iron overload. Gradually, the iron overload may damage the heart and the liver, in addition it may cause endocrine disorders.

Iron deposition can initiate the inflammatory responses within cardiomyocytes which may eventually lead to cardiomyopathy (5). Myocardial iron overload is usually the major cause of death in patients with thalassemia major. To manage the iron overload, different iron chelators like deferoxamine, deferasirox, and deferiprone are used in thalassemic patients (6). Pulmonary arterial hypertension (PAH) which is defined as an average pulmonary artery pressure above 25 mm Hg at rest or 30 mm

[DOI: 10.18502/ijpho.v12i4.10912]

Hg during exercise is a severe and progressive condition with considerable morbidity and mortality (7,8). In thalassemia, PAH is associated with vascular contraction, vascular smooth muscle proliferation, and endothelial dysfunction which may ultimately lead to thrombosis formation (9,10). Studies in both thalassemia major and intermediate have shown that PAH is not always diagnosed although it may have a high prevalence (11, 12). It is well-known that vitamin D is associated with beneficial effects on cardiovascular function. Long-term treatment with vitamin D can regulate the vascular tone and may improve the endothelial dysfunction (13). Moreover, vitamin D deficiency is linked with decrease in nitric oxide production which is a key step in initiation and progression of the endothelial dysfunction (14). Considering the potential protective effects of vitamin D on peripheral arterial disease, this study was designed to investigate the efficacy of vitamin D on PAH in patients with thalassemia.

Materials and Methods

Study design

This randomized, open-labeled, and single center study was done in Amir-Kabir Hospital, Arak, Iran. Thalassemia diagnosis was done by normal count of red blood cell (RBC), presence of isolated microcytic anemia, electrophoresis of hemoglobin, and presences of target cells in peripheral blood smear. Thirty-two patients with thalassemia major (TM) and thalassemia intermedia (TI) aged > 10 requiring blood transfusion were included. At baseline, study patients were matched for dose of chelators. Therefore, during the study (20 weeks) no change was done on chelation treatment. Chelator doses were as follows deferoxamine: 25-50 mg/kg/day, deferasirox: 10-40 mg/kg/day, and deferiprone: 75 mg/kg/day. Volume of transfusion was about 10 ml/kg in two groups.Included subjects did not have history of vitamin D use. Study patients randomly allocated 1:1 into vitamin D 50000 IU/week (Osve Pharmaceuticals, Iran) (intervention group) and no supplement (control group) for 20 weeks. Both groups had similar protocols in blood transfusion and iron chelators. Written informed consent was taken from patients or their parents prior to trial participation. Parents or patients were trained for possible adverse effects of vitamin D and were asked to call the clinic in case of any problem. Exclusion criteria were history of hypercalcemia, severe gastrointestinal and liver disorders, chronic obstructive pulmonary diseases, sarcoidosis, restrictive lung disease, obstructive sleep apnea, chronic kidney disease, and history of drug hypersensitivity. Patients were discontinued from the study for these reasons: safety, lost to follow-up, and voluntary discontinuation.

Efficacy assessment

Changes in pulmonary artery pressure (PAP) which was measured by echocardiography (Vivid S6, GE, USA), at baseline and at 20-week of treatment were the primary end points. In addition, systolic blood pressure (SBP), diastolic blood pressure (DBP), ejection fraction (EF), tricuspid regurgitant velocity (TRV), and pulmonary regurgitant velocity (PRV). were measured and compared. Levels of 1,25-dihydroxyvitamin D3 were measured by biochemical kits (Pars Azmoon, Tehran, Iran). Cardiac T2* were measured by MR scan (1.5T Siemens, Germany). In addition, levels of ferritin were studied by ELISA (Abcam, UK).

Safety assessment

Untoward effects, CBC, physical examination, and vital signs were monitored at baseline and then monthly by physician. For assessment of side effects of the drugs, patients were weekly monitored for gastrointestinal upset, muscle pain, and confusion.

Data analysis

Chai-square (x2) and Fisher's exact tests were used to study the baseline proportions. Non parametric test

[DOI: 10.18502/ijpho.v12i4.10912]

(Wilcoxon signed rank) was used to study mean differences between groups. Two-way analysis of variance was used for subgroup analysis. $P < 0.05$ denoted as a statistical significance. Analyses were performed using SPSS software version 21.0, Chicago, USA.

Ethical Consideration

The study was approved by local Ethics Committee (IR.ARAKMU.REC.1397.148) and was registered on Iranian Registry of Clinical Trials (IRCT20190206042644N1).

Results

Baseline Characteristics

From a total of 32 patients, 4 patients were excluded because did not meet the inclusion criteria and 2 patients were lost to follow up. Finally, 26 patients completed the study from January 2020 to June 2021 (Figure 1), 10 males and 16 females with the mean age of 23.2±7.33 years (ranged from 11-42 years). Nineteen (73.07%) patients had thalassemia major and 7 (26.93%) patients had thalassemia intermedia. Moreover, 9 (34.60%) of patients had history of splenectomy. At baseline, there were no significant differences in patients' characteristics, except the levels of vitamin D which was significantly higher in control group (P= 0.008). Baseline characteristics of subjects are shown in Table I.

Cardiac Measures

Although there were no significant differences between the intervention and control groups with respect to changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) over 20 weeks of treatments (P=0.388, P=0.509; respectively), pulmonary arterial pressure (PAP) levels were different between intervention and control groups (P= 0.01). In the intervention group, PAP decreased from 30.23±3.53 mmHg at baseline to 25.38±6.04 mmHg at 20 weeks, whereas in control group PAP increased from 29.69 ± 6.00 mmHg at baseline to 31.61±5.34 mmHg at 20 weeks. Ejection fraction (EF) significantly increased in the intervention group, compared to the control group (P=0.008). In the intervention group, there was an increase in EF from 61.92±3.92% at baseline to 64.84±5.20% at 20 weeks, whereas in the control group a small decrease was noted; 60.84±5.27% at baseline to 58.76±5.55% at 20 weeks. Of note, the between group differences were statistically significant ($P < 0.008$). However, significant reductions were noted in tricuspid regurgitant velocity (TRV), and pulmonary regurgitant velocity (PRV) compared to the control group (P= 0.003, P= 0.001, respectively). Finally, myocardial T2* had no dramatic changes in both study groups, as shown in Table II it was around 13 msec in both study groups after 20 weeks of treatment.

Serum Ferritin and Hemoglobin

There were no significant changes in the levels of ferritin in the intervention (1405.69±597.42 ng/ml at baseline to 1177.60±1547.71 ng/ml at 20 weeks) and the control group (1003.00±1004.69 ng/ml at baseline to 1408.43±1563.08 ng/ml at 20 weeks), while ferritin levels had a drop in the intervention group. As shown in Table II, no significant differences in hemoglobin levels were noted between the intervention (9.29±0.69 g/dl at baseline to 8.88±0.81 g/dl at 20 weeks) and the control group (9.44±1.11 g/dl at baseline to 8.88±2.39 g/dl at 20 weeks, P= 0.557).

1,25-dihydroxyvitamin D3

As presented in Table II, after 20 weeks of treatment the levels of 1,25-dihydroxyvitamin D3 had dramatic increases in the intervention group (17.71±7.71 ng/ml at baseline to 29.15±13.37 ng/ml at 20 weeks) versus control group (25.44±5.68 ng/ml at baseline to 19.2±9.12 ng/ml at 20 weeks, P= 0.036).

[DOI: 10.18502/ijpho.v12i4.10912]

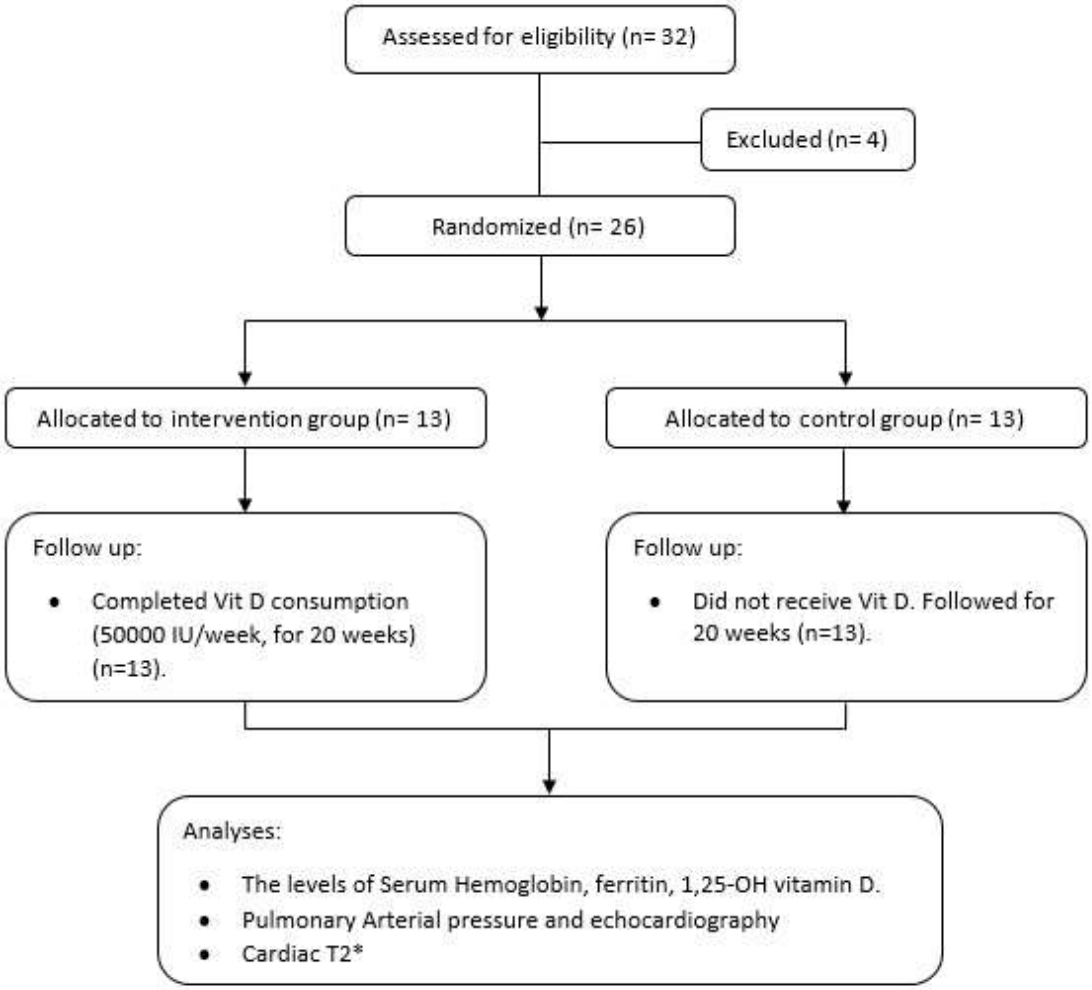

Figure 1. Consort diagram detailing the study subjects

[DOI: 10.18502/ijpho.v12i4.10912]

Table I: Baseline characteristics of study patients in the intervention and control groups

Characteristic	Values	*P* value*
Mean age (years)	23.2±7.33 (11-42)	-
Gender		
Male	10 (38.50%)	-
Female	16 (61.50%)	
Type of thalassemia		
Thalassemia major	19 (73.07%)	-
Thalassemia intermedia	7 (26.93%)	
History of splenectomy		
Yes	9 (34.60%)	-
No	17 (65.40%)	
1,25-OH vitamin D (ng/ml)		
Intervention	17.71 ± 7.71 (7.30 - 29.32)	*0.008*
Control	25.44 ± 5.68 (19.90 - 38.02)	
Ferritin (ng/ml)		
Intervention	1405.69 ± 597.42 (521 - 2590)	*0.226*
Control	1003.00 ± 1004.69 (120 - 4000)	
Hemoglobin (g/dl)		
Intervention	8.88 ± 0.81 (7.70 - 10.20)	*0.155*
Control	9.44 ± 1.11 (7.5 – 11.5)	
SBP (mm Hg)		
Intervention	101.15 ± 8.69 (90 - 120)	*0.132*
Control	106.92 ± 10.11 (90 -125)	
DBP (mm Hg)		
Intervention	62.69 ± 5.25 (55 - 70)	*0.201*
Control	65.38 ± 5.18 (60 - 70)	
PAP (mm Hg)		
Intervention	30.23 ± 3.53 (25 - 39)	*0.783*
Control	29.69 ± 6.00 (22 - 46)	
EF (%)		
Intervention	61.92 ± 3.92 (55 – 70)	*0.560*
Control	60.84 ± 5.27 (50 – 70)	
Cardiac T2* (msec)		
Intervention	13.75 ± 2.57 (8.90 – 16.50)	*0.776*
Control	13.47 ± 2.49 (9.10 – 17.10)	
TRV (m/sec)		
Intervention	2.24 ± 0.18 (1.90 - 2.53)	*0.500*
Control	2.17 ± 0.30 (1.72 – 3.00)	
PRV (m/sec)		
Intervention	2.57 ± 0.30 (1.87 – 2.95)	*0.560*
Control	2.65 ± 0.31 (2 – 3.40)	

Mean ± Standard deviation, Frequency (% of total or minimum- maximum provided) is given either in range or percentage.

SBP: systolic blood pressure; DBP: diastolic blood pressure; PAP: pulmonary arterial pressure; EF: ejection fraction; TRV: tricuspid regurgitant velocity; PRV: pulmonary regurgitant velocity, msec: millisecond

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Table II: Serum 25-OHD, ferritin, hemoglobin, and echocardiography parameters after follow up, in the intervention and control groups.

Parameter	Intervention group (n=13)	Control group (n=13)	*P* value*
1, 25-OH vitamin D (ng/ml)	29.15 ± 13.37 (11.58 - 57.63)	19.2 ± 9.12 (7.02 - 40.47)	*0.036*
Ferritin (ng/ml)	1177.60 ± 1547.71 (528 - 2309)	1408.43 ± 1563.08 (263 - 6317)	*0.620*
Hemoglobin (g/dl)	9.29 ± 0.69 (8.20 - 10.30)	8.88 ± 2.39 (2.55 – 11.4)	*0.557*
SBP (mm Hg)	103.84 ± 10.43 (90 - 120)	107.69 ± 11.83 (90 - 130)	*0.388*
DBP (mm Hg)	65.76 ± 4.93 (60 - 70)	67.3 ± 6.65 (60 - 80)	*0.509*
PAP (mm Hg)	25.38 ± 6.04 (18 - 38)	31.61 ± 5.34 (24 - 45)	*0.010*
EF (%)	64.84 ± 5.20 (59 - 77)	58.76 ± 5.55 (45 - 66)	*0.008*
Cardiac T2* (msec)	13.85 ± 2.44 (9.10 – 17.10)	13.64 ± 2.35 (8.90 - 17)	*0.827*
TRV (m/sec)	1.91 ± 0.36 (1.41 - 2.65)	2.37 ± 0.30 (1.87 – 3.00)	*0.003*
PRV (m/sec)	2.43 ± 0.30 (2.13 – 3.09)	2.82 ± 0.23 (2.45 – 3.35)	*0.001*

Mean ± Standard deviation, (minimum - maximum); SBP: systolic blood pressure; DBP: diastolic blood pressure; PAP: pulmonary arterial pressure; EF: ejection fraction; TRV: tricuspid regurgitant velocity; PRV: pulmonary regurgitant velocity, msec: millisecond

Discussion

In this randomized trial we assessed the impact of vitamin D consumption on pulmonary artery hypertension in patients with β-thalassemia. Our study confirms that 20-week treatment with high dose vitamin D (50000 IU/week) was effective to improve PAP in transfused patients with thalassemia. Thalassemia, as an inherited disorder with the highest prevalence in Mediterranean and Southeast Asia, is usually accompanied by multiple cardiac complications, including PAH mainly due to frequent blood transfusion (15). Although the pathophysiology of PAH in thalassemia is not clear, it might be related to chronic anemia, hemolysis, or oxidative stress. Multiple lines of evidence suggest a link between vitamin D deficiency and PAH through activation of renin-angiotensin-aldosterone system (RAAS) which affects cardiovascular system (16). Of note, vitamin D may improve brachial artery flow-mediated dilatation (17). In current investigation, we found that vitamin D significantly reduced pulmonary arterial pressure (PAP), tricuspid regurgitant velocity (TRV), and pulmonary regurgitant velocity (PRV). Previous studies reported a high prevalence of PAH (ranging between 10% and 78.8%) in patients with β-thalassemia major (TM) and intermedia (11,12). Demir M et al. reported that pulmonary artery systolic pressure was significantly higher in patients with vitamin D deficiency compared to the control group and also a significant relation between vitamin D deficiency and pulmonary artery hypertension was revealed (18). However, experimental studies indicated that vitamin deficiency can lead to endothelial dysfunction and increase anti-apoptotic factor which can eventually induce

[DOI: 10.18502/ijpho.v12i4.10912]

pulmonary vascular dysfunction (19). In agreement with our finding, a study by Mirdamadi demonstrated that correcting vitamin D deficiency in patients with pulmonary hypertension significantly improved the size of the right ventricle (20). In this study, we showed that vitamin D supplement could significantly improve ejection fraction (EF). A study conducted by Hiradfar et al. indicated a positive correlation between levels of vitamin D and EF and also cardiac T2* in transfusion-dependent thalassemia patients (21). In addition, vitamin D deficiency can induce secondary hyperparathyroidism which may lead to movement of non-transferrin bound iron (NTBI) into the myocardium and myocardial iron overload possibly through calcium channels (22,23). However, vitamin D is associated with an increase in left ventricular ejection fraction (LVEF) in patients with advanced heart failure aged ≥ 50 years (24). In line with mentioned investigations and due to clinical implications of nutrients like iron and vitamin D on cardiopulmonary function, recent studies have provided more data about protective roles of vitamin D. A cross sectional study by Rahayuningsih showed that vitamin D deficiency was associated with a greater risk for PH in children with cardiac septal defect. In this study, vitamin D deficiency was more prevalent in female children and it may require more intervention to reduce this risk (25). A quite recent meta-analysis performed by Mokhtari revealed that there was an inverse correlation between vitamin D levels and systemic blood pressure. It showed a consistency between vitamin D levels and hypertension meaning that optimal levels of vitamin D may lead to reduce the likelihood of hypertension and prehypertension (26). A prospective study by Mendoza showed that infants suffering from bronchiolitis and increased pulmonary pressure had low levels of vitamin D (below 20 ng/mL) (27). Another study confirms that adult patients with thalassemia in particular those who are transfusion dependent have decreased bone mineral density and also vitamin D levels. Disregarding PAH, low levels of vitamin D may lead to several complications for such patients and it stresses the importance of endocrinopathties in thalassemia (28). A work by Yozat demonstrated that vitamin D deficiency is associated with impaired myocardial function especially cardiac contractility in patients with thalassemia and they showed that 3-month therapy with vitamin D could improve the cardiac contractility (29). Overall, patients with thalassemia needs different drugs added to iron chelators in order to secure an improved life quality and reduce the disease complications. Like vitamin D, we showed previously that pantoprazole could be added to iron chelators to reduce the ferritin levels and possibly the associated negative outcomes of thalassemia (30).

Lack of thalassemia patients who were heavily iron overloaded was our limitation. The investigation was not blinded and we did not use placebo due to lack of producer support. For this reason the present findings should be confirmed in double-blinded trials with larger sample sizes which are placebo or drug- controlled. In addition, Chronic vitamin D therapy may have some harms that should be addressed and thoroughly investigated by in the future studies.

Conclusion

The present study showed that vitamin D 50000 IU/week can improve PAP in patients with thalassemia. Sufficient intake of vitamin D may prevent cardiomyopathies related to PAH.

Acknowledgments

This study was supported with a grant of vice chancellor of research of Arak University of Medical Sciences. The authors are thankful to staff of Amir Kabir Hospital for their assistance with this project.

Conflict of interest

The authors declare no conflict of interest.

[DOI: 10.18502/ijpho.v12i4.10912]

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[DOI: 10.18502/ijpho.v12i4.10912]

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[DOI: 10.18502/ijpho.v12i4.10912]