EFFECTS OF VITAMIN D SUPPLEMENTATION ON THE ELECTROCARDIOGRAPH RECORDS OF PATIENTS WITH BETA THALASSEMIA MAJOR: AN OPEN-LABEL RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Background

Cardiac disease is believed to be the leading cause of death in thalassemia major. Iron cardiomyopathy is the primary cause of death in thalassemia major patients. Monitoring cardiac function with electrocardiography is essential in thalassemia major patients, however, diastolic and systolic dysfunction are later signs of iron overload.

Objectives

This study aimed to investigate the pleiotropic effect of vitamin D supplementation on the electrocardiograph records and cardiac risk variables in patients with beta thalassemia major.

Patients and Methods

Forty-six patients of beta thalassemia major were recruited in an open label, randomized clinical trial, from the Thalassemia Center of the General hospital in the Sulaimani city, Kurdistan Region. Oral dose of vitamin D of 100,000 IU ampoule was administered to the patients every two weeks for eight weeks as add on therapy. Electrocardiography (ECG), serum vitamin D levels, serum ferritin, body mass index (BMI), waist circumference and blood pressure were determined before (at baseline) and after eight weeks of vitamin D treatment.

Results

Vitamin D3 supplements significantly prolonged PR period, QTcB interval, JTc interval and T-Pe duration in the electrocardiograph records. Additionally, a significant increase in body mass index and blood pressure were observed after supplementation with vitamin D. Furthermore, serum vitamin D was significantly increased and serum ferritin was significantly reduced after 8 weeks of supplementation with vitamin D.

Conclusions

Vitamin D supplement of 100,000 IU every two weeks causes risk when prescribed to patients with beta thalassemia major, since it impairs cardiac conduction.

Keywords: *Thalassemia, Vitamin D3, Electrocardiography.*

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INTRODUCTION

Beta-thalassemia is a group of hereditary disorders of hemoglobin synthesis characterized by the absence or reduction in one or more of the beta globin chains of hemoglobin [1]. the absence or reduction of globin chain synthesis may produce an imbalance among the subunits of hemoglobin. Beta-thalassemia as a result of reduced synthesis of the beta globin chains of hemoglobin results in different outcomes ranging from severe anemia to clinically asymptomatic individuals. Beta thalassemia patients suffering from severe anemia usually need regular blood transfusions that will result in an iron overload condition [2].

Iron overload results in iron accumulation in different organs, particularly in the heart where it leads to iron overload cardiomyopathy. This is the primary reason of mortality in patients with beta thalassemia [3]. Many approaches have been applied to detect cardiac iron status, because clinical assessment is unreliable to observe early stages of cardiomyopathy due to iron overload in thalassemia major patients. These consist of the indirect cardiac iron evaluation including serum ferritin, echocardiogram, and electrocardiogram (ECG) also the direct but invasive evaluation such as myocardial biopsy and liver biopsy [4]. A normal ECG does not exclude a risk of significant arrhythmia formation in patients with iron overload. In a retrospective analysis of 27 transfusion-dependent thalassemia patients who utilized annual 24 hour electrocardiographic monitoring, two patients developed significant clinical symptoms secondary to cardiac arrhythmias during one year of follow-up [5].

Torsades de pointes (TdP) is a severe life-threatening polymorphic ventricular tachycardia associated with QT interval prolongation [6]. The QTc interval is an independent predictor of mortality in patients associated with left ventricular hypertrophy. It has been discovered that mortality is highest in patients with QTc interval $\geq$ 500 msec [7]. Measurement of QT interval in electrocardiograph (ECG) record has drawn attention because of its prolongation associated with the risk of serious cardiac arrhythmias, such as torsade de pointes, and may be associated with ventricular arrhythmia and sudden cardiac death [8]. The value of the QT interval measurement is limited because increase of QRS duration is contributed to QT prolongation. Therefore, measurement of the JT interval has been considered as a more suitable parameter of ventricular repolarization than the QT. Furthermore, the JT interval measurement is independent of QRS duration, and it is believed that the JT interval better represents the specific repolarization time than does the QT interval [9]. Tpeak-Tend interval, which is the interval between the peak and the end of T wave on electrocardiogram (ECG), is recognized as an index of transmural dispersion of ventricular repolarization [10].

PATIENTS AND METHODS

The ethical scientific committee of the University of Sulaimani in Sulaimani-Kurdistan Region gave approval to the study according to the guidelines that fulfill the requirement of postgraduate research and the International Continuous Medical Education. Each medicine or device that was used for the patients was safe and without side effects, and the patients were allowed to withdraw from the study at any time they wished.

The authors informed the parents/guardians of patients about the study design, and the medicines used in the study. An informed consent was signed by the parents/guardians of patients before initiating the study.

Patients attending the Thalassemia Center in Sulaimani General Hospital, Kurdistan Region, with a diagnosis of beta thalassemia major, were enrolled into the study. The patients were transfused on regular basis and were being treated with iron chelating agents.

Enrolled patients were children and teenagers aged between 6-18 years. The criteria of inclusion were transfusion-dependent children and adolescents with beta-thalassemia major not receiving vitamin D containing supplements. The diagnosis of beta-thalassemia was based on the hemoglobin electrophoresis that indicates beta thalassemia trait commonly has reduced or absent HbA, elevated levels of HbA2, and increased HbF [11].

The criteria of exclusion included pregnancy, end stage renal failure, acute blood loss for any cause, chronic liver disease and malignancy. A total number of fifty patients fulfilled the above criteria were enrolled in this open labelled clinical trial, four patients were lost in follow up, a total of forty-six patients were included in the final data analysis.

Demographic data such as age, gender, body weight, height, and medical history was recorded by thorough history from parents/guardians and from patient's medical record. Moreover, systolic and diastolic blood pressures were recorded at two settings, before and

after vitamin D supplementation. All the patients were treated with the same therapeutic iron chelating regimen plus vitamin D3 oral ampoule as an add-on-therapy 100,000 IU/every two weeks (Dibase, 100,000 IU/ml solution for intramuscular and oral use, Abiogen Pharma, Pisa-Italy) for eight weeks, which is equal to a total of four doses. The patients were regularly transfused monthly and were being treated with iron chelating agents.

After 12 hours of overnight fasting, a blood sample was obtained by venipuncture from each patient before blood transfusion at baseline and after initiation of the eight-weeks commencement with vitamin D supplement. The blood sample was kept in plain tubes and allowed to clot before centrifuging at (3000 rpm, for 20 min) to obtain the serum for the determination of serum vitamin D (measured by Cobas e411) and ferritin levels.

Systolic and diastolic blood pressures were obtained in the supine or seated position by auscultation using a brachial cuff, after allowing the patient to rest for 5 minutes.

Anthropometric measurements included weight (kg), height (m) and waist circumference (cm) measurements. The waist circumference was measured at the midpoint between the lower margin of the last rib and the top of the iliac crest, using a stretch resistant tape. The waist to height ratio was calculated. Body mass index (BMI; kg/m^2) was calculated according to the equation: weight (kg) / height^2 (m).

An electronic 12-lead electrocardiograph (ECG) record (using Cardimax FX-7102 instrument) was performed for each patient on admission into the study. Two ECG records were obtained for all patients, one before commencing vitamin D treatment and the second after 8 weeks of vitamin D treatment. ECG was performed by advising the patient to remove any jewelry before starting the procedure. Moreover, the patient/guardians of the patient was informed to remove the upper parts of their clothes to expose the chest. Then the patient lay down with arms positioned at the side of the body with legs not crossed. Ten leads were placed at exact anatomical areas on the patient to the best optimal quality data. Prior to the placement of the leads, the electrode area of the patient's skin was cleaned with alcohol and gauze to remove any dirt. The four limb lead electrodes were applied to the extremities; starting with the right leg. The right leg electrode was applied to the inner leg about 5 cm above the ankle followed by the left leg electrode, the right arm and the left arm electrode. The lead wires were attached to the four extremities. The patient's chest was palpated to locate the suitable sites for the precordial leads. The lead wires were attached to the connectors in the corresponding chest positions. The patient was asked to relax, breathe normally and not to speak while the tracing is recorded.

The corrected QT interval (Bazett's) is automatically printed in the ECG record. The corrected QTc interval was determined using the following formula:

Bazett's formula (QTc): QTc = $QT/\sqrt{RR}$

Corrected J-T (J-Tc) was determined using the following formula:

J-Tc = QTc/QRS

The results expressed as number, percentages and Mean ± SD. The data were analyzed by using two-tailed paired t-test taking the p-value of ≤ 0.05 as a lowest level of significance. All the data were analyzed using Microsoft Excel 2010 program for Windows and SPSS (Microsoft Cooperation, Redmond, USA).

RESULTS

The study included 46 beta thalassemia major patients with the mean age of 10.9±3.7 (6–18) years, 24 were males and 22 were females. Body mass index was 15.9±2.5. The demographic statistics are shown in (Table 1).

Vitamin D3 supplements significantly prolonged PR period (From 131.8±22.5 to 140.8±23.4) (p= 0.049), QTcB interval (from 258.9±36.2 to 272.5±42.0) (p= 0.018), JTc interval (from 210.8±37.5 to 224.0±42.4) (p= 0.031) and T-Pe duration (from 53.3±17.5 to 61.3±16.3) (p= 0.009) in the electrocardiograph records after vitamin D supplementation for 8 weeks (Table 2). Systolic (from 102.3±9.1 baseline to 106.3±7.0, p<0.001), diastolic (from 61.7±4.5 baseline to 63.7±3.6, p= 0.003) and mean blood pressure (from 75.2±5.4 baseline to 77.9±4.0, p<0.001) was significantly increased. Body mass index (from 15.8±2.5 to 16.3±2.6, p<0.001) and waist circumference (from 63.2±6.7 to 63.8±6.6, p=0.001) were significantly increased (Table 3). Serum vitamin D level was significantly increased (from 15.70±7.52 to 60.98±67.78, p<0.001), and serum ferritin was significantly reduced (from 1681.9±1273.3 to 1519.2±990.93, p=0.046).

Table 1. Characteristics of patients.

Characteristics	Results
Sex (Male: Female)	24:22
Age (year)	10.9±3.7
Residency	
Urban	27
Rural	19
History of splenectomy	7
Body weight (kg)	29.0±8.7
Height (cm)	133.7±12.2
Body mass index (kg/m2)	15.9±2.5

The results are expressed as number, and mean ± SD

Table 2. Effect of vitamin D on the electrocardiograph records of patients with thalassemia.

Electrocardiograph findings	Before treatment (n=46)	After treatment (n=46)	p-value
Heart rate (beat/min)	98.3±13.9	94.2±20.0	0.201
PR period (ms)	131.8±22.5	140.8±23.4	0.049*
QTcB interval (ms)	258.9±36.2	272.5±42.0	0.018*
TQ duration (ms)	466.6±99.6	467.4±100.2	0.965
QRS duration (ms)	48.1±8.4	48.5±8.3	0.795
QRS dispersion (ms)	12.8±5.3	11.1±4.3	0.054
JTc interval (ms)	210.8±37.5	224.0±42.4	0.031*
JT index	107.9±11.6	112.0±13.0	0.087
T-Pe duration (ms)	53.3(1).±17.5	61.3±16.3	0.009*
T-Pe /QTcB ratio	0.212±0.082	0.228±0.067	0.201

The results are expressed as mean ± SD. P value was calculated by using two-tailed paired student's t-test.

Table 3. Effect of vitamin D supplementation on the cardiac risk variables of thalassemia patients.

Determinants	Before vitamin D treatment (n=46)	After vitamin D treatment (n=46)	p-value
Age (year)	11.0±3.7	11.0±3.7	1.000
Weight (kg)	29.0±8.8	29.9±8.8	<0.001
Height (cm)	133.9±12.2	134.0±12.2	0.183
Body mass index (kg/m2)	15.8±2.5	16.3±2.6	<0.001
Waist circumference	63.2±6.7	63.8±6.6	0.001
Waist to height ratio	0.472±0.036	0.474±0.037	0.001
Systolic blood pressure (mmHg)	102.3±9.1	106.3±7.0	<0.001
Diastolic blood pressure (mmHg)	61.7±4.5	63.7±3.6	0.003
Mean blood pressure (mmHg)	75.2±5.4	77.9±4.0	<0.001

The results are expressed as mean ± SD. P value was calculated by using two-tailed paired student's t-test.

Table 4. Effect of vitamin D supplementation on the laboratory biochemical tests of thalassemia patients.

Biochemical tests	Before treatment (n=46)	After treatment (n=46)	p-value
Serum vitamin D (ng/ml)	15.70±7.52	60.98±67.78	<0.001
Serum ferritin (ng/ml)	1681.9±1273.3	1519.2±990.93	0.046

The results are expressed as mean ± SD. P value was calculated by using two-tailed paired student's t-test.

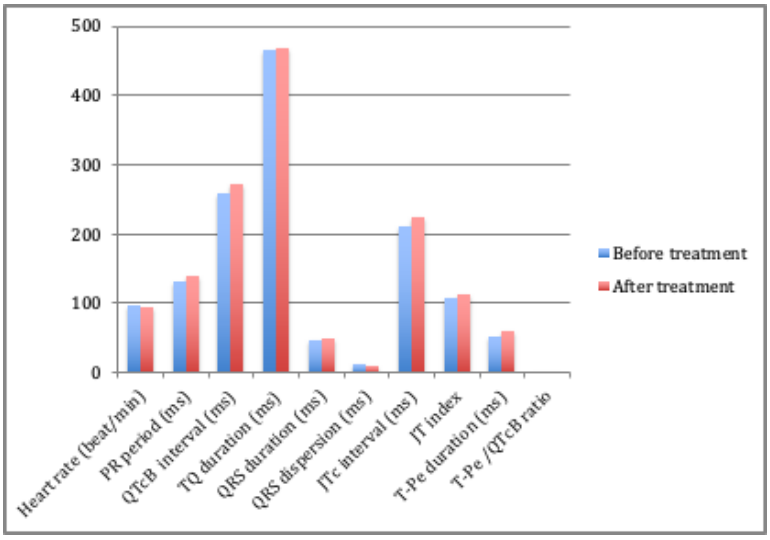

Figure 1 .Effects of vitamin D supplement on cardiac risk variables.

DISCUSSION

The results of the current study demonstrates that vitamin D can increase the blood pressure in thalassemia patients, although significantly elevated, but still within the normal range. This finding is consistent with previous works on animals that showed vitamin D supplementation was associated with higher blood pressure (Santos et al., 2014; Santos et al., 2011) [12, 13]. A study reported that a single dose of vitamin D3 (300,000 IU) did not reduce blood pressure in the patients with type 2 diabetes [14]. Daily supplementation of vitamin D3 (1,000-5,000 IU) has not proven the effect on blood pressure [15]. Even though numerous interventional studies have been conducted, the impact of vitamin D supplement on reducing blood pressure in human is still controversial [16].

Regarding the effects of vitamin D on the electrocardiographic parameters, the results demonstrated a significant prolongation of four ECG parameters, PR period, QTcB interval, JTc interval and T-Pe duration. Ulger et al. revealed that even though there were no clinical or echocardiographic manifestations of cardiac disease, QTc intervals were prolonged in beta thalassemia major patients when compared to the control group [17]. This finding is consistent with our results that the QTc interval was significantly higher in these patients after taking vitamin D supplement in comparison to baseline data, which explains the negative effects of vitamin D on the heart in these patients. QTc and JTc dispersion are useful electrocardiographic markers of sudden cardiac death risk and are increased in some conditions [18]. A previous study reported that beta thalassemia major leads to significant changes in ventricular repolarization, and the use of QTc dispersion and JTc dispersion, as simple electrocardiographic parameters for distinguishing the sudden cardiac death risk in beta thalassemia major patients, should be applied in daily clinical practice [19]. The findings of this study indicated that the JTc interval was significantly prolonged post vitamin D supplementation. JTc interval is a more appropriate

measure of ventricular repolarization than the QT, it represents the specific repolarization time than does the QT interval [20].The PR interval is defined as the time required for an electrical impulse to be conveyed from the sinus node down the atrioventricular node to the Purkinje fibers, and therefore, it represents the atrioventricular conduction. PR prolongation without structural heart disease or conduction disturbances has been considered as a benign condition [21].

The Tpeak-Tend interval (Tpe), the interval from the T-wave peak to the end of the T wave measures transmural dispersion of repolarization, related to arrhythmogenesis [22]. A prolonged QT and Tpe interval are predictors of ventricular arrhythmia and sudden cardiac death. Some authors consider that a prolonged Tpe is a more desirable predictor of sudden cardiac death compared to a prolonged QT interval [12]. Concerning the electrocardiographic parameters, these results indicate the harmful effects of using vitamin D supplement in beta thalassemia patients. Such supplement should be used with caution and under monitoring in these patients.

In conclusion, our results suggest prolongation of four ECG parameters of PR period, QTcB interval, JTc interval and T-Pe duration. As well as elevation of blood pressure in beta thalassemia major patients after using vitamin D supplements. This indicates the harmful effects of using vitamin D supplement at the dose of 100,000 IU every two weeks in beta thalassemia patients. Such supplement should be used with caution and under monitoring in these patients.

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