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ORIGINAL ARTICLE

Effect of L-carnitine on the physical fitness of thalassemic patients

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Abstract Poor physical fitness is a common problem among thalassemic patients. L-Carnitine plays an essential role in fatty acid β-oxidation, a process especially important in the organs that preferentially use fatty acid as a source of energy such as the myocardium and the skeletal muscles. The main objective of this study is to assess the effect of the administration of oral L-carnitine on exercise tolerance and physical fitness in patients with thalassemia major. Thirty patients followed up at the New Cairo University Children Hospital were included in this study. Clinical, laboratory, and cardiopulmonary exercise testing were performed before and after 6 months of oral L-carnitine therapy (50 mg/kg/day). The oxygen consumption, cardiac output, and oxygen pulse at maximal exercise significantly increased after L-carnitine therapy ($p<0.001$, $p=0.002$ and $p<0.001$, respectively). However, there was no significant change in minute ventilation and ventilatory equivalent of carbon dioxide ($p=0.07$ and $p=0.06$, respectively). A weak but positive correlation between the age of the patients and the degree of improvement in exercise parameters was noted. There was also significant increase in the blood transfusion intervals after L-carnitine administration ($p=0.008$). However, there was no significant change in hemoglobin concentration ($p=0.4$). L-Carnitine seems to be a safe and effective adjunctive therapeutic approach in thalassemic patients. It improves their cardiac performance and physical fitness. The younger the patients are, the higher is the degree of improvement in their exercise parameters.

Keywords L-Carnitine · Thalassemia · Physical fitness

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Introduction

Poor physical fitness is a common feature among thalassemic patients. Children with homozygous β-thalassemia have a diminished muscular mass and many of them complain of muscular weakness and myalgia [1]. The exact cause of these symptoms is still not well defined. Several factors have been implicated, including tissue anoxia, peripheral neuropathies, and abnormal calcium metabolism secondary to decreased hemoglobin and systemic hemosiderosis [2, 3]. Even though the management of β-thalassemia patients has progressed with the introduction of chronic transfusion therapy and iron chelation, the

growth retardation and the cardiopulmonary abnormalities associated with this disease remain a major problem in these patients [4, 5].

L-Carnitine (3-hydroxy-4-*N*-trimethyl-aminobutyric acid), a butyrate analogue, plays an essential role in fatty acid oxidation and glucose metabolism [6]. It is crucial to the shuttle mechanism of long chain fatty acid across the inner mitochondrial membrane to provide substrate for energy production through β-oxidation. This process is especially important in the organs that preferentially use fatty acid as a source of energy such as the myocardium and the skeletal muscle. Consequently, its inhibition leads to a decrease in cardiac function [7].

The aim of this study is to assess the effect of the administration of oral L-carnitine on exercise tolerance and physical fitness of patients with thalassemia major.

Materials and methods

Patients

Thirty patients, previously diagnosed to have homozygous β-thalassemia and followed up at the Hematology Clinic of the New Cairo University Children Hospital, were randomly selected to participate in this study after obtaining the required written consents. All the patients continued to receive the standard therapy consisting of chronic blood transfusions with Desferoxamine (20–40 mg/kg/day) as iron chelator. Patients with chest wall deformity, cardiac, muscular, metabolic, or neurological disorders were excluded.

Among the thirty patients recruited for this study, 19 were males and 11 females. Their age ranged between 10 and 20 years with a mean of 14.7±2.7 years. No adverse reactions attributed to the administration of L-carnitine were noted. All the patients completed their 6-month course and presented afterwards for evaluation.

The medical charts of the recruited patients were reviewed. Frequency of blood transfusion and chelation therapy was recorded. A complete physical exam focusing on weight, height, heart rate, liver, and spleen status was performed. The patients were evaluated before and 6 months after L-carnitine therapy was started. The drug was administered orally at a dose of 50 mg/kg/day. It was supplied to the patients free of charge by the Hematology Clinic on an outpatient basis.

Evaluation of physical fitness

Each patient performed an incremental cycle ergometer exercise during which work load of pedaling was increased at 1-min intervals. The heart rate was continuously recorded by a cardiac monitor. The test was performed while patients were breathing room air through a pneumotachometer. The expired air was continuously sampled and analyzed. The following measurements were recorded:

- Maximal oxygen consumption (VO_2 max): the volume of oxygen consumed at maximal exercise.
- Minute ventilation (Ve): the volume of air respired per minute.
- Ventilatory equivalent for CO2 (Ve/VCO_2).
- Oxygen pulse (O_2 pulse): the ratio of VO_2/heart rate.
- Cardiac output calculated from oxygen consumption and heart rate according to Striger et al. (1997) [8].

All measurements were expressed as percentage of normal predicted values for each subject according to Wasserman et al. [9]. The size of workload increment was adjusted for each subject according to his/her age, height, and weight so that he/she would reach his/her maximal exercise level in around 10 min.

$$Work\ load\ increment\ (watt/minute) = \frac{Predicted\ VO_2\ max - VO_2\ of\ unloaded\ pedaling}{100}$$

VO2 of unloaded pedaling = 150+6×weight in kilogram [9].

Statistical methods

The mean and standard deviation were calculated for the numerical data. Student's *t* test (paired *t* test) was used to compare numerical data between groups. Coefficient of correlation (*R*) was used to assess the degree of correlation between different variables.

Results

A significant increase in VO_2 max, cardiac output and O_2 pulse was noted after 6 months of L-carnitine therapy ($p<0.001$, $p=0.002$ and $p<0.001$, respectively), while no significant changes were found in minute ventilation or in ventilatory equivalent of carbon dioxide ($p=0.07$ and $p=0.06$, respectively) (Table 1 and Fig. 1). There was a weak but positive correlation between the age of patients and the percentage change in VO_2 max, cardiac output, and O_2 pulse ($R=0.49$, 0.49, and 0.43, respectively).

A significant increase in the interval of blood transfusion was also observed after therapy ($p=0.008$). However, there was no significant change in hemoglobin concentration ($p=0.4$) (Table 2).

Table 1 Cardiopulmonary exercise parameters before and after 6 months of L-carnitine therapy

Parameter[a]	Before therapy	After therapy	*P* value
VO_2 max	39.1±11.6	56.7±17.1	<0.001
Cardiac output	56.6±12.1	73.2±15.1	0.002
O_2 pulse	3.8±1.0	5.4±1.6	<0.001
Minute ventilation	56.0±15.9	60.0±16.8	0.06
Ve/V_{CO2}	26.6±2.7	27.4±2.7	0.07

[a] Expressed as percent of predicted value

Table 2 Clinical and laboratory parameters before and after 6 months of L-carnitine therapy

Parameter	Before therapy	After therapy	*P* value
Interval of blood transfusion (days)	28.6±9.3	37.3±14.9	0.008
Hemoglobin (g/dl)	7.8±0.8	7.3±1.0	0.4

Discussion

Even though the prognosis of thalassemic patients has improved with the introduction of chronic blood transfusion therapy with iron chelation, most of them still complain of the cardiac and muscular complications of the disease [1, 4]. L-Carnitine, due to its crucial role in the oxidation of fatty acids, the main energy source for the myocardium and skeletal muscle, may have a role in limiting these complications [10].

VO_2 max represents the highest oxygen consumption attainable for a given form of exercise [11]. It is affected by many factors including age, sex, physical activity, weight, and height. Reduction of VO_2 max occurs in conditions that impair oxygen flow to the tissues such as anemia, cardiac, and pulmonary diseases [9]. In addition to the chronic anemia, thalassemic patients are known to suffer form cardiac dysfunction and reduced pulmonary function tests, secondary to iron deposition from repeated blood transfusions [12]. As a result, these patients tend to have low VO_2 max. This was shown in our study because the baseline VO_2 max of the recruited patients was 39.1±11.6% their normal predicted value. VO_2 max appears not to be directly related to the degree of anemia and pulmonary function because the increase in VO_2 max after L-carnitine therapy was not associated with a significant change in the hemoglobin level, minute ventilation, and ventilatory

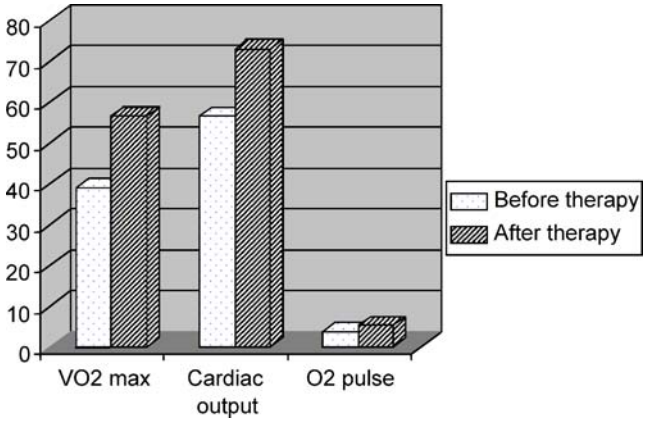

Fig. 1 Cardiopulmonary exercise parameters before and after 6 months of L-carnitine therapy

equivalent for CO_2. On the other hand, the increase in VO_2 max can be attributed to the improvement in cardiac function demonstrated by an increase in cardiac output and O_2 pulse. In fact, two separate studies demonstrated, using echocardiography and multiple gated cardiac blood pool imaging (MUGA), significant improvement in the cardiac function of thalassemic patients after L-carnitine therapy [13, 14]. Furthermore, there is evidence that giving L-carnitine decreases the shortness of breath and improves the exercise capacity and VO_2 max of patients with heart failure [15, 16].

The cardiac complications seen in thalassemic patients are probably the resultant of chronic hypoxia and iron overload. Cardiac hypoxia interferes with the metabolism of free fatty acids by reducing their transport into the mitochondria and inhibiting their β-oxidation. This leads to the accumulation of oxidative intermediates, such as long chain acyl CoA esters, that impair cardiac mechanical and metabolic function [17]. Iron overload causes an increase in lipid peroxidation, damages the mitochondrial membrane in addition to the lysosomes, thus releasing their enzymatic contents. As a result, fibrosis of the myocardium and its conductive system occurs [18]. Moreover, the hypoxia and hemosiderosis reduce myocardial L-carnitine level. Thus, exogenous carnitine administration would improve the cardiac metabolic functions [19, 20], as was shown in our patients. This improvement can also be ascribed to an increase in overall glucose utilization [21]. Furthermore, L-carnitine improves oxidative metabolism of skeletal muscles, increases pyruvic acid consumption and decreases lactic acid production. Therefore, In addition to decreasing myalgia, this medication may indirectly improve cardiac performance as a result of a lower myocardial oxygen demand at submaximal exercise [20, 22]. Because the improvement in cardiac function after L-carnitine therapy was higher in younger patients, it might be important to start this therapy at an early age.

In this study, a significant increase in blood transfusion interval after L-carnitine therapy was also noted. This was previously reported [14, 23] and can be explained by the protective effect of L-carnitine on the red blood cells from oxidative stress and the stabilization to their membranes where latent peroxidative damage has occurred [24, 25]. The autooxidation of globin chains and iron overload were

the suggested mechanisms for the increased oxidative stress. The counteracting effect of antioxidants on lipid peroxidation and their protective effect against oxidative damage of erythrocytes in β-thalassemia patients were previously demonstrated [26]. However, in our study, there was no statistically significant change in hemoglobin concentration after L-carnitine therapy.

In conclusion, L-carnitine seems to be a safe and effective adjunctive therapeutic approach in thalassemic patients. It improves their cardiac performance and physical fitness. Moreover, the younger the patients are, the higher is the degree of improvement in their exercise parameters.

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