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Original Article

The Effect of L-Arginine Oral Supplementation on the Improvement of Cardiovascular Function and Pulmonary Artery Pressure in Patients with Major and Intermedia β-Thalassemia

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Abstract

Background: Thalassemia is the most common inherited anemia in worldwide. Heart failure is the most common cause of mortality and morbidity in patients with major and intermedia β-thalassemia. This study aimed to evaluate the effect of oral administration of L-arginine on the improvement of systolic Pulmonary Artery Pressure (PAP) and cardiac function in patients with major and intermedia β-thalassemia.

Methods: This randomized clinical trial was done on 88 patients with β-thalassemia admitted to Ali Asghar Hospital, Tehran, Iran between 2020 and 2021. Echocardiography was performed for all the patients before the intervention. Afterwards, the patients were randomly divided into two groups of placebo and L-arginine. The patients underwent echocardiography after eight weeks and were compared with respect to the results.

Results: The mean blood transfusion interval was 20.21 d in the placebo group and 17.14 d in the L-arginine group (P=0.082). The results revealed no significant difference between the two groups regarding the mean levels of Hemoglobin (Hb) and ferritin, frequency of splenectomy. However, the mean PAP significantly decreased from 32.88 to 26.02 in the L-arginine group (P=0.009), but did not change in the placebo group. Nonetheless, no significant change was observed in the mean Ejection Fraction (EF) before and after L-arginine administration.

Conclusion: L-arginine administration prevented the increase of PAP and was effective in preventing cardiovascular disorders including increased systolic PAP in patients with major and intermedia B-thalassemia. However, the results have to be confirmed in further studies with larger sample sizes.

Keywords: Beta-thalassemia; L-arginine; Systolic pulmonary artery pressure; Ejection fraction; Cardiovascular function

Introduction

Beta-thalassemia is the most common inherited anemia in worldwide, caused by problems in the production of β-hemoglobin chains. There are three types of β-thalassemia including β-thalassemia minor, intermedia, and major, depending on the severity of the β-chain deficiency (1). Patients with β-thalassemia major and some patients with the intermedia form of β-thalassemia need frequent blood transfusions, which may increase iron load and deposition in sensitive organs such as the liver, heart, and endocrine glands (2). Heart involvements including Left Ventricular Dysfunction (LVD), cardiomyopathy, Right Ventricular Dysfunction (RVD), and increased Systolic Pulmonary Artery Pressure (SPAP) are the most important complications of β-thalassemia associated with physical problems, frequent hospitalizations, and even death (3). In β-thalassemia major, iron overload caused by repeated blood transfusions, coagulopathy, splenectomy, and chronic hemolysis may increase SPAP above 25 mmHg at rest or above 30 mmHg during activity (4).

Chronic hemolysis is one of the important mechanisms in enlarging the pulmonary artery. During hemolysis, arginase is released from erythrocytes and reduces the metabolism of amino acid L-arginine to L-ornithine, thereby decreasing the production of Nitric Oxide that is a potent vasodilator (5). The mean level of L-arginine, which is the necessary substrate for the production of NO, is lower in patients with β-thalassemia compared to healthy individuals, and this decrease becomes more significant with age (5). Regarding the critical role of L-arginine as a precursor for NO synthesis, reduced plasma level of this amino acid due to the higher activity of arginase may be a main mechanism for developing hypertensive pulmonary disease (6, 7). Therefore, oral administration of L-arginine may have a positive effect on reducing SPAP by increasing the serum level of this amino acid as a nitric acid substrate (7). Some studies have investigated the impact of the oral administration of L-arginine on improving the cardiac function and pulmonary artery pressure in different abnormalities (8, 9). The results revealed a significant improvement in pulmonary artery pressure after L-arginine therapy compared to the control group (10). Nevertheless, all these studies were conducted on small sample sizes in short times.

Considering the high prevalence of β-thalassemia in Iran and the associated comorbidities such as heart failure and SPAP as well as these patients' life expectancy will increase with appropriate treatments, the present study aimed to assess the effect of the oral administration of L-arginine on reducing pulmonary artery pressure and improving cardiac function in patients with major and intermedia β-thalassemia. The results can be used to improve these patients' health and quality of life.

Methods

Patient selection

This randomized double-blinded clinical trial was conducted on patients with β-thalassemia major and intermedia aged above 15 yr admitted to Ali Asghar Children's Hospital, Tehran, Iran between 2020 and 2021.

The study was approved by the Ethics Committee of Iran University of Medical Sciences and was registered in the Iranian Registry of Clinical Trials (IRCT20210220050430N1).

Before patient selection, a checklist was prepared to record data on demographic and basic clinical information including age, weight, height, gender, β-thalassemia type, blood transfusion interval, Hb and ferritin levels, and history of heart, liver, and kidney failures, diabetes, and spleen removal. Then, all parents were required to sign the informed consent forms. Patients with arterial pressure above 25 mmHg at rest were included in the study. The exclusion criteria of the study were (i) suffering from severe myocardial infarction and requiring specialized measures and treatments, (ii) having a history of cardiac medication

(iii) having severe hepatic and renal problems and diabetes, (iv) pregnancy and lactation, and (v) having received dietary supplements during the past six months.

Intervention and measurements

After the preliminary considerations and selection of the patients based on the inclusion criteria, they were randomly divided into two groups of L-arginine (n=44) and placebo (n=44). Echocardiography was performed for all the patients to determine SPAP and Ejection Fraction (EF) at the beginning of the study. The patients in the L-arginine group received 0.1 gr/kg/day L-arginine (purchased from Zist-Takhmir Pharmaceutical Company, Iran), while those in the placebo group were prescribed 0.1 gr/kg/day of starch. The drug dosage was selected based on the previous studies (11). Both L-arginine and placebo were administrated for eight weeks. Any side effects or complications such as nausea, vomiting, headache, allergy, and itching were recorded. The patients with gastrointestinal intolerance to the drug or severe allergic reactions were excluded from the study. After eight weeks, all the patients were referred to the Hospital and another echocardiography was performed to check their EF and SPAP.

Statistical analysis

In this survey, the SPSS software, ver. 25 (IBM Corp., Armonk, NY, USA) was applied for data analysis. Quantitative data were analyzed using descriptive tests and were presented as mean ± SD. Crosstabs and chi-square tests were used to compare the two groups in terms of the percentage and frequency of each item. Additionally, paired t-test was utilized to compare the means of the quantitative data in each study group before and after the intervention. Finally, Wilcoxon test was applied to compare the means of non-parametric data before and after the intervention. $P<0.05$ was considered statistically significant.

Results

The results revealed no significant difference between the two groups with respect to mean age and height. The mean age and height were respectively 25.88 yr and 163.27 cm in the placebo group and 27.56 yr and 163.38 cm in the L-arginine group. The results also showed no significant difference between the two groups regarding the mean of weight. The mean weight was 62.09 kg in the placebo group and 60.47 kg in the L-arginine group. Additionally, there was no significant difference between the two groups concerning the mean age at diagnosis ($P=0.22$). The mean age at diagnosis was 16.79 months in the placebo group and 22.22 months in the L-arginine group. Moreover, no significant difference was observed between the two groups in terms of the frequency of gender distribution ($P=0.83$). In the L-arginine group, 47.7% of the participants were female and 52.3% were male. These measures were found to be 50% and 50%, respectively in the placebo group. The results indicated no significant difference between the two groups regarding the frequency of thalassemia ($P=0.29$). In both groups, thalassemia major was one of the most common types of thalassemia. The prevalence of thalassemia major was 84.1% and 75% in the placebo and L-arginine groups, respectively (Table 1).

Table 1: Comparison of the two groups regarding mean age, height, weight, and type of thalassemia

Variable	*Placebo*	*L-arginine*	*P-value*
Age (yr)	25.88 ± 7.73	27.56 ± 7.41	0.3
Height (cm)	163.27 ± 5.32	163.38 ± 7.42	0.93
Weight (12)	62.09 ± 8.07	60.47 ± 8.20	0.31
Thalassemia major	(%84.1) 37	(%75.0) 33	0.29
Thalassemia Intermedia	(%15.9) 7	(%25.0) 11	

The results demonstrated no significant difference between the two groups in terms of the frequency of splenectomy (*P*=0.056). Accordingly, most patients in both placebo (63.6%) and L-arginine (81.8%) groups had a history of splenectomy (Table 2).

Table 2: Comparison of the two groups regarding the splenectomy frequency

variable	*Placebo No (%)*	*L-arginine No (%)*	*P-value*
Yes	28 (63.6)	36 (81.8)	0.056
No	16 (36.4)	8 (18.2)	

The results revealed no significant difference between the two groups concerning the mean blood transfusion interval (*P*=0.082). The mean blood transfusion interval was 20.21 d in the placebo group and 17.14 d in the L-arginine groups. The results also showed no significant difference between the two groups with regard to the mean level of Hb (*P*=0.68). There was also no significant difference between the study groups regarding the mean level of ferritin (*P*=0.9) (Table 3).

Table 3: Comparison of the two groups regarding the mean interval of transfusion and mean levels of hemoglobin and ferritin

Variable	*Placebo Mean ± SD*	*L-arginine Mean ± SD*	*P-value*
Transfusion interval	20.21 ± 8.95	17.14 ± 5.49	0.082
Hemoglobin	8.17 ± 0.60	8.22 ± 0.69	0.68
Ferritin level	1080.0 ± 912.42	1100.54 ± 792.89	0.9

The results revealed no significant difference in mean SPAP between the two groups before the study (*P*=0.18). There was a significant difference in the mean SPAP after the study between the two groups (*P*=0.014). While the average SPAP in the placebo group increased from 30.04 to 30.97. The mean SPAP in the L-arginine group decreased to 26.02, but this decrease was significant (*P*=0.009).

There was no significant difference in the mean EF before the study between the two groups before (*P*=0.31) and after the study (*P*=0.22) (Table 4).

Table 4: Comparison of the two groups regarding the echocardiographic results

Variable	*Placebo Mean ± SD*	*L-arginine Mean ± SD*	*P-value*
Mean SPAP before the study	30.04 ± 3.67	32.88 ± 4.33	0.18
Mean SPAP after the study	30.97 ± 3.90	26.02 ± 2.62	0.014
P-value	0.63	0.009	
Mean EF before the study	55.02 ± 1.08	55.02 ± 1.08	
Mean EF after the study	55.00 ± 1.07	55.00 ± 1.12	0.31
P-value	0.49	0.98	0.22

Discussion

This study aimed to assess the effect of L-arginine administration on the improvement of cardiovascular function and SPAP in patients with thalassemia in comparison to the placebo group. The results revealed no significant difference between the two groups regarding mean age, height, weight, and sex distribution. Approximately half of the patients in both placebo and L-arginine groups were male. Additionally, most patients in both groups had thalassemia major. In this study, the effect of L-arginine administration on the function of the left ventricular systolic system and increased pulmonary artery pressure was evaluated. L-arginine administration did not exert any effects on the left ventricular systolic system's function. In other words, no significant change was observed in the mean EF before and after L-arginine administration. Although no significant change was detected in pulmonary artery pressure in the placebo group before and after the study, this measure decreased significantly from 32.88 to 26.02 in the patients receiving L-arginine.

L-arginine administration prevented the increase of pulmonary artery pressure and had an effective role in preventing cardiovascular disorders such as increased pulmonary artery pressure in the patients with thalassemia. However, insufficient L-arginine uptake by heart cells is an important and probable cause of heart failure in these patients (11-13). Therefore, despite the administration of L-arginine, no significant improvement was observed in the patients' cardiac function, which could be due to the lack of effective absorption by cardiac cells. Iron overload and oxidative stress also lead to endothelial cell damage and disruption of NO production (14). To support this hypothesis, L-arginine uptake by heart cells was significantly lower in patients with congenital heart failure than in normal individuals (15). These results may indicate an association between decreased L-arginine and the incidence of heart problems.

However, several studies have evaluated the effect of L-arginine administration on the improvement of myocardial function, pulmonary artery pressure, and quality of life in patients with heart failure, and conflicting results have been obtained. For example, a study evaluated the effect of L-arginine (8 g/day) on the improvement of pulmonary artery pressure and Right Ventricular Function (RVF) in 15 patients with heart problems over two months (7). L-arginine administration significantly reduced the mean pulmonary artery pressure from 56.3 to 44 mmHg. A significant decrease was also observed in systolic and diastolic blood pressure. Therefore, L-arginine administration not only improved the RVF by increasing the EF, but it also significantly reduced pulmonary artery pressure in patients with heart problems. These results were somewhat in line with those of the present research findings. The only difference was that no significant change was found in EF in this study, but the decrease in the mean pulmonary artery pressure was evident, which indicated the protective effect of L-arginine on preventing pulmonary artery hypertension in patients with thalassemia.

In a recent clinical trial, the effect of L-arginine (3 g/dl) was evaluated among 50 patients with heart problems (9). L-arginine consumption significantly improved EF, Left Ventricular Failure (LVF), diastolic failure, and LVD. A significant increase was also found in the patients' quality of life at the end of the study compared to the baseline.

The effect of L-arginine administration on EF improvement was explored in 53 patients undergoing coronary artery surgery with EF <35% (6). L-arginine administration significantly improved Left Ventricular Diastolic Function (LVDF) and EF by increasing the levels of antioxidants and decreasing cellular peroxidation. These results were somewhat inconsistent with those of the present research. In this study, there was no significant change in the mean EF after L-arginine administration, associated with the lack of effective uptake by cardiac cells in patients with thalassemia. Nonetheless, the decrease in the mean

pulmonary artery pressure improved the RVF and prevented right ventricular hypertrophy.
In another study, the effect of L-arginine administration was investigated on improving cardiac function in patients with congenital heart defects (8). L-arginine administration decreased the mean blood pressure from 102 to 89 mmHg and increased cardiac output from 4.1 to 4.7l/min without no change in heart rate. There was also a slight but not significant increase in the mean EF. Similarly, the present study findings revealed no significant change in the mean EF after L-arginine administration. Nonetheless, a significant decrease was observed in pulmonary artery pressure.
The effect of L-arginine and sildenafil administration on the improvement of pulmonary pressure was assessed in 60 children with thalassemia with a mean age of 10 yr. L-arginine and sildenafil equally led to a reduction in pulmonary pressure in the children with thalassemia (16).

Conclusion

L-arginine administration had no effects on the left ventricular systolic system's function, but resulted in a significant reduction in the mean pulmonary artery pressure from 32.88 to 26.02 mmHg. This indicated that L-arginine administration prevented the increase of pulmonary artery pressure and had an effective role in preventing cardiovascular disorders such as increased SPAP among the patients with thalassemia. However, insufficient uptake of L-arginine by heart cells is one of the important and probable causes of heart failure in patients with thalassemia, which requires further studies on larger sample sizes.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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