The Efficacy of L-Carnitine Treatment in Dilated Cardiomyopathy

Abstract: This study was carried out to investigate clinical effects of treatment with the supplementation of L-carnitine in cases with dilated cardiomyopathy.

B Mode, M-Mode, and continuous Doppler echocardiograms were applied with standard techniques in totally 28 patients assessed before treatment with L-carnitine and at the 1st, 5th, 10th, 30th, and 60th days of the treatment.

The diameter of the left ventricular end-systolic and end-diastolic have decreased with L-carnitine treatment (p<0.05). While an increase was observed in the interventricular septum motion (p<0.0001); decrease was observed in the left ventricular end-systolic and end-diastolic volumes (p<0.05), and an increase was also observed in the ejection fraction, myocardial fractional shortening, and velocity of circumferential fiber shortening (p<0.05). No significant change occurred at the diastolic function of the left ventricle.

As a conclusion, supplementation of L-carnitine to the conventional therapy, dilated cardiomyopathy treatment can give successful clinical result in refractory cases.

Key Words: L-Carnitine, Dilated Cardiomyopathy, Doppler Echocardiography

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Introduction

Treatment of the patients with dilated cardiomyopathy still is one of the major problems in cardiology. Available drugs are not able to affect long-term prognosis. Although the drugs used commonly affect some of the clinical and physiopathological features, they can not affect the conditions supporting the pump-function of the myocardium (1, 2).

In recent studies, a decrease has been determined in the carnitine concentration in the cardiac tissue of the patients with dilated cardiomyopathy, when compared with the normal ones. The heart has very high concentration of carnitine and is highly dependent upon fatty acid oxidation as a source of energy. In addition to its key function as a transporter of long-chain fatty acids across the inner mitochondrial membrane, carnitine plays an important role in trapping toxic long-chain acyl CoA metabolites which may accumulate in ischaemia and leads to sarcolemmal membrane damage. Almost all of the carnitine needed for myocardium is provided from extracardiac tissues (3-9). Therefore, we have planned to search the effects of carnitine on systolic and diastolic functions of the left ventricle by adding L-carnitine to the treatment of the patients with dilated cardiomyopathy and having conventional therapy.

Materials and Methods

Totally 28 patients (7 women and 21 men), who clinically and echocardiographically diagnosed with dilated cardiomyopathy (average age was 62±10 years and age-range was 39-82 years) were selected as subjects of the study.

At first, the purpose and the applications of the study were explained to all patients. Oral and written permission of all patients were taken. Detailed history was taken from each patient. After the physical examination, required blood and urine assays were done. New York Heart association functional capacity of patients were between III and IV.

All of the cases who were treated with conventional heart failure therapy have taken digitalis, diuretic, ACE inhibitor, calcium antagonist, and antiarrhythmic drugs and had no improvement for last three months.

After the patients’-subjected to the study-
haemodynamic evaluations have done with L-Carnitine ampuls (Santa Farma-1 g) which were given intravenously twice a day. After the 10th day, L-carnitine pills (Santa Farma-1 g) were given per oral three times a day with 8 hours intervals for fifty days.

Haemodynamic evaluations were done after the patients were in resting condition at the echocardiography lab for an hour. Two dimensional M-mode and continuous Doppler echocardiograms were applied with standard techniques. The echocardiograph used was Sonolayer -SSH-60 Toshiba model, and video-records were taken with Toshiba-V 73 D model. Toshiba PSD-25RN tranducer was used in the study, and Toshiba Line scan Recorder LSR 20B in the records. The speed of the record was adjusted as 50 mm/sec. All of the patients were examined from the parasternal and apical. The criteria suggested by American Echocardiography society were used in M-Mode echocardiographic measurements. The record of the transmirtal blood velocity and continuous Doppler cursor were placed in the area where mitral valve is opened. Systolic blood velocity curve was obtained from the aortic valve by using standard techniques. All measurements were done at least in 6 cardiac cycles and mean values were taken. The records were taken at the same time with electrocardiography and phonocardiography.

The left ventricular end-diastolic diameters (LVDD), the left ventricular end-systolic diameters (LVSD), the left ventricular diastolic posterior wall thickness (LVDPWT) and its motion (LVDPWM), interventricular septum thickness (IVST) and its motion (IVSM), the left atrium diameter (LAD), the right ventricular end diastolic diameter (RVEDD), aortic root (AR) and valve motion (AM) and the E-IVS distance were measured.

Having studied the diastolic functions of the left ventricle; total mitral flow (MVM), the mean and peak flow velocity of the early diastolic filling (EVM- EVP), the mean and peak flow velocity of the late diastolic filling (AVM, AVP), peak velocity rate of the early diastolic on that of the late one (E/A) have been studied.

Just about to study the systolic functions of the left ventricle were aortic peak flow velocity (AoVP), aortic

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<th>Table. Some parameters before and after L-carnitine treatment</th>
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<td>LVDD: left ventricular end-diastolic diameter (mm), LVSD: left ventricular end-systolic diameter (mm), IVSM: interventricular septum motion (mm), EDV: End-Diastolic Volume (ml), ESV: End-Systolic Volume (ml), EF: Ejection Fraction (%), FS: Fractional Shortening (%), Vcf: Mean circular shortening velocity (Circ/sec), MVM: total mitral flow (m/sn), EVM: The mean flow velocity of the early diastolic filling (m/sn), EVP: The peak flow velocity of early diastolic filling (m/sn), AVM: The mean flow velocity of the late diastolic filling (m/sn), AVP: The peak flow velocity of the late diastolic filling (m/sn). p: Variance analysis, P Value, (*): Statistically significant ones according to Tukey’s HSD.</td>
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mean flow velocity (AoVM), the left ventricular end-diastolic volume (EDV), the left ventricular end-systolic volume (ESV), stroke volume (SV), cardiac output (CO), ejection fraction (EF), fractional shortening (FS) and the mean circular fractional shortening acceleration of the left ventricle (Vcf) were calculated from standard formulas (9-11).

All of these parameters were measured before the patient has taken medicine and measured again on the 1st, 5th, 10th, 30th and 60th day after taking medicine. For the first ten days, carnitine ampul 12 mg was given as intravenously to the patients twice a day in the morning and evening. For later days, carnitine tablets 1 mg (totally 3 g/day) were given per oral three times a day.

One-way variance analysis (ANOVA) was used in the repeated measurements to compare the first result with those on the 1st, 5th, 10th, 30th and 60th days after taking medicine. When a considerable difference was present between the means values and ANOVA, Tukey’s HSD test was applied. Group findings were identified as means values±standard deviation. P<0.05 was taken as the statistical significancy.

Results

Some clinical characteristics of the study and of the control group were shown in the table.

While the LVDD was 75.21±9.38 mm at the beginning, it decreased to 74.90±9.62 mm on the 1st day, 73.57±8.56 mm on the 5th day, 73.20±7.61 mm on the 10th day, 72.00±8.69 mm on the 30th day, 73.06±6.17 mm on the 60th day (p<0.05). According to Tukey’s HSD, the decrease between the basal value and the measurements on the 10th, 30th and 60th days were significant (p<0.05).

While the basal value of LVSD was 61.03±9.56 mm, it decreased to 61.43±9.56 mm on the 1st day, 58.97±7.81 mm on the 5th day, 59.97±6.87 mm on the 10th day, 57.94±11.77 mm on the 30th day, and 57.35±7.54 mm on the 60th day after the treatment (p<0.05). According to Tukey’s HSD, there was an important difference between the basal value and the 30th day value (p<0.05), between the basal value and the 60th day value (p<0.05), and between on the 1st day value and that on the 60th day (p<0.05).

While the basal value of LVSM was 4.78±1.73 mm, it was 5.50±2.22 mm on the 1st day, 5.80±2.19 mm on the 5th day, 5.17±2.17 mm on the 10th day, 5.82±1.59 mm on the 30th day, and 6.65±1.62 mm on the 60th day (p<0.0001). According to Tukey’s HSD, the difference between the basal and the 60th day value was statistically significant (p<0.0001).

There was no statistical significance among the posterior-wall thickness of the left ventricular end-diastolic, posterior-wall motion of the left ventricular, right ventricular diastolic diameter, and interventricular septum thickness before and after the treatment (p>0.05).

There was no statistical significance between the pre and post L-Carnitine treatment values of the MVM, EVM, EVP, AVM, and AVP (p>0.05) and the AoVM and AoVP (p>0.05).

EDV was 465.34±164.84 ml before the treatment and it was found as 462.44±168.95 ml on the 1st day, 433.22±144.87 ml on the 5th day, 428.24±124.65 ml on the 10th day, 424.13±163.60 ml on the 30th day, and 421.07±106.91 ml on the 60th day after the treatment. According to Variance analysis, the decrease in the EDV was important at p<0.05 level. According to Tukey’s HSD, the decrease between the basal value and the 30th day value (p<0.05), between the basal value and the 60th day value (p<0.05), and between on the 1st day value and that on the 30th day value (p<0.05), and between on the 1st day value and the 60th day value (p<0.05) were significant.

The basal value of the ESV was 252.58±103.57 ml, and it was found as 260.92±117.39 ml on the 1st day, 228.73±153.77 ml on the 5th day, 222.12±75.02 ml on the 10th day, 220.90±94.43 ml on the 30th day, and 207.32±82.76 ml on the 60th day. These values were significant at p<0.005 level according to the variance analysis. According to Tukey’s HSD, there was significant difference between the basal value and the 10th day value (p<0.005), between the basal value and the 30th day value (p<0.005), between on the 1st day value and the 30th day value (p<0.005), between on the 1st day value and the 60th day value (p<0.005), and between the 1st day value and the 60th day value (p<0.005).

EF before the treatment was 44.99±7.13 %, and 46.57±7.90 % on the 1st day, 48.07±8.35 % on the 5th day, 48.04±6.29% on the 10th day, 49.98±12.10% on the 30th day, and 51.48±8.70% on the 60th day. The increase in EF was significant at p<0.05 level according to variance analysis. According to Tukey’s HSD, there was a significance between the basal value and the 30th day value (p<0.005), and between the basal value and the 60th day value (p<0.005), and between the 1st day value and the 30th day value (p<0.005), between the 1st day value and the 60th day value (p<0.005).

FS prior to the treatment was 18.23±3.53% and was 19.65±4.48% on the 1st day, 19.88±4.46% on the 5th day, 19.69±3.42% on the 10th day, 21.21±6.38% on
the 30th day, and 21.62±4.61% on the 60th day. Increase in FS was found significant (p<0.05). Tukey’s HSD was significant between the basal values and the 30th and 60th day values (p<0.05).

Vcf was found 0.81±0.20 circ/sec at the beginning and 0.84±0.24 circ/sec on the 1st day, 0.85±0.32 circ/sec on the 5th day, 0.88±0.17 circ/sec on the 10th day, 0.90±0.23 circ/sec on the 30th day, and 0.92±0.21 circ/sec on the 60th day after the treatment. There was a significance at p<0.05 level according to variance analysis. Increase in Vcf was significant between the basal values and the 30th and 60th day values (p<0.05) according to Tukey’s HSD.

Significant change could not be found between the values of the stroke volume and cardiac output before and after L-carnitine treatment (p>0.05).

During L-carnitine application, one patient complained from itching, two patients had headache, two patients had distension in stomach, and two patients had constipation. These conditions have not required to stop the therapy.

Discussion

L-carnitine is an essential co-factor having a major role in the oxidation of the fatty acids which are the most important energy producing pathway of the heart in human and animal (3, 5, 8).

The role of L-carnitine in energy production from fatty acid oxidation is obvious. L-carnitine takes part in the shuttle mechanism whereby long-chain fatty acids are transformed to acyl carnitine derivatives and transported across the inner mitochondrial membrane. This is impermeable to long-chain fatty acids and to their CoA esters. Across the membrane, the acyl carnitine is reconverted to carnitine and to acyl CoA, which undergoes beta-oxidation. This interesting action of L-carnitine is essential in heart free fatty acid metabolism. L-carnitine has a role not only in energy production, but also, has a role, in energy delivery from the mitochondrium to the cytosol (6, 12, 13).

When long-chain acyl CoA metabolites accumulate, they cause damage in sarcolemmal membranes. Myocardial contractility decreases, and arrhythmia occurs. L-carnitine ensures the long-chain acyl CoA, which might cause deterioration in cell-membranes, and hydroxy peroxides might lead to toxic effects and these toxic effects could be eliminated with carnitine (6, 15).

Skeletal and cardiac muscles are largely dependable on fatty acids as substrates. Muscle and cardiac tissues need enough carnitine concentrations, so they can do their normal functions, but muscle and cardiac tissues are not capable of synthesizing carnitine. Both are dependable to adequate carnitine concentration (16).

The lack of plasma and myocardial carnitine causes dilated cardiomyopathy has been shown in human and animal models. When L-carnitine is given in high doses, it has been discovered that the contractility of the left ventricular is increased (5-7, 17, 18). Ghidini et al. (19) have reported that improvement occurred in the symptoms and findings of the patients with heart failure by adding L-carnitine to their treatment. Our patients with dilated cardiomyopathy told us that they felt better after L-carnitine treatment. It was observed that their exercise tolerance and life quality was also improved.

In our study, significant decrease was observed at LVDD and LVSD with L-carnitine treatment (p<0.05). Tripp et al (20) also observed a decrease in the LVDD and LVSD after they had applied L-carnitine treatment to the patients with dilated cardiomyopathy for 2 months.

Schiovani et al. (21) identified a specific increase in the IVSM after they had applied L-carnitine treatment to the patients with ischemic cardiomyopathy. After L-carnitine treatment, we identified an increase in interventricular septum motion. We think increase in the interventricular septum motion is due to carnitine’s improving the myocardial energy metabolism and removing off the toxic long- chain acyl CoA metabolites from the environment that may cause deterioration in myocardial contractility and functions. That matter has not been clarified specifically yet (6, 14, 15).

Carnitine has not made a considerable change in parameters related to the left ventricular diastolic functions. In the literature, we could not find any information about the effect of L-carnitine on the left ventricular diastolic functions.

In our study, EF increased after the carnitine treatment. While EF before the treatment was 44.99±7.13%, it was 51.48±8.70% on the 60th day (p<0.05). Waber et al (22) have identified that EF in patients with cardiomyopathy has risen from 39% to 75% after one month treatment and to 69% after five months therapy. Increase in EF can be explained with L-Carnitine’s rising energy production and removing off the long chained fatty acids that have toxic effects on myocardium.

In our study, while the myocardial FS before the treatment was 18.23±3.53%, it increased to...
21.62±4.61% on the 60th day (p<0.05). Chapoy et al. (23) have mentioned that after 3 months therapy, the myocardial FS in the patients with cardiomyopathy has risen to 31% while it was 18% before the treatment. Chapoy et al. (23) informed that a significant improvement was present in Vcf of the patients with dilated cardiomyopathy after L-carnitine treatment. [We also have determined an improvement in Vcf values (p<0.05).]

In conclusion, we suggest that L-carnitine can be added to the treatment of the patients with dilated cardiomyopathy in whom no more improvement has occurred with standard treatment.

References


