Therapeutic Evaluation of L-Carnitine in Egyptian Children with Dilated Cardiomyopathy

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Dilated Cardiomyopathy (DCM) represents a large subset of Congestive Heart Failure (CHF) cases. It is characterized by depressed systolic function, cardiomegaly and ventricular dilatation. Carnitine is indispensable for β-oxidation of long chain fatty acid in the mitochondria but also regulates the concentration and removal of the produced acyl groups. The aim of this study was to estimate the L-Carnitine levels in dilated cardiomyopathic patients on conventional treatment for heart failure both pre and post L-carnitine therapy and to study the effect of L-carnitine as an adjuvant therapy on clinical status, ECG and echocardiographic parameters. Fourteen patients were included in the study with dilated cardiomyopathy (7 males and 7 females) on conventional treatment for heart failure with mean age of 43.64±24.06 ms. Patients included in the study were subjected to full medical history, thorough clinical examination, plain chest X-ray PA view, electrocardiography and echocardiography. Serum carnitine level were measured to all patients at the beginning of the study and repeated three months after L-carnitine therapy. Results proved that mean serum carnitine level showed a significant increase after therapy (p<0.01). Clinically, there was significant increase in effort tolerance (p<0.01) and decrease of dyspnea (p<0.05). Ventricular systolic functions were improved as assessed by EF and FS (p<0.01), in addition to reduction of the LV dimensions (p<0.05). R wave of lead V6 was also significantly reduced (p<0.05). After therapy serum carnitine level correlated significantly with the FS, LVEF and body weight (p<0.05), no other significant correlation could be detected. The study conclude that adding L-carnitine to conventional therapy in dilated cardiomyopathic children with congestive heart failure improves cardiac systolic function, increase LVEF, FS and reduce ventricular size without any recorded health hazard.

Key words: L-Carnitine, dilated cardiomyopathy, ventricular dilation

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INTRODUCTION

Cardiomyopathy is a complex disease process that can affect the heart of a person of any age. Cardiomyopathies are conditions in which the normal muscular function of the myocardium has been altered by a specific or multiple etiologies. A patient with cardiomyopathy may have asymptomatic left ventricular systolic dysfunction, left ventricular diastolic dysfunction or both (Burger et al., 2002).

Dilated cardiomyopathy represents a large subset of Congestive Heart Failure (CHF) cases. It is characterized by depressed systolic function, cardiomegaly and ventricular dilatation (Mobini et al., 2004).

The principal biological role of levocarnitine (L-carnitine) is to facilitate the transport of fatty acids across the inner mitochondrial membrane. The molecule also is involved in modulating the cellular and mitochondrial ratio of acyl coenzyme A (CoA) to free CoA, shuttling of short- and medium-chain acyl groups from peroxisomes to mitochondria and removal of excess and unwanted acyl groups from the body (Evans, 2003).

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. When L-carnitine is given in high doses, it has been discovered that the contractility of the left ventricle is increased (Donders et al., 1998).

The aim of this study was to estimate the serum L-carnitine levels in dilated cardiomyopathic patients on conventional treatment for heart failure both pre and post L-carnitine therapy and to study the effect of L-carnitine as an adjuvant therapy on the clinical and echocardiographic parameters.

All patients enrolled in the study were subjected to the following:

- Full medical history taking.
- Thorough clinical examination and Cardiac examination, heart failure status was determined for each case and classified according to NYHA classification (Smith et al., 1993).
- Plain X-ray chest PA view.
- Electrocardiogram: Twelve lead electrocardiogram were recorded at 50 mm s⁻¹.
- Echocardiography: Two Dimensional (2D), Motion mode (M-mode), Continuous Wave (CW), Pulsed Wave (PW) and Colour Doppler echocardiographic examination using the ESAote S.P.A (Model 7250, Italy).

Z-value of echocardiography calculation: The Z-value is the standard deviation unit, a statistical value applied for standardization and normalization. In present study we used Z-value for echocardiography measurements of LAD, LVEDD and LVESD owing to great variability of body surface area among our patients.

- L-Carnitine determination by enzymatic UV test (Wieland et al., 1985): Measurement of the serum level of L-carnitine in all selected patients was done before L-carnitine therapy, after eight hours fasting by colorimetric method.
- Administration of L-carnitine (100 mg kg⁻¹ day⁻¹) to each patient in addition to conventional therapy for three months was done and then patients were reevaluated clinically, functional assessment by echocardiogram and plasma L-carnitine was also estimated.

Sample collection: Three milliliter of venous blood were drawn from each subject after fasting for eight hours (patient sampling was done before and three months after carnitine therapy). Samples were collected after parental consent and agreement to share in the study. Sample was taken in a sterile tube, sera were obtained immediately after clotting of samples, collected in sterile tubes then stored at -70°C until assay.

- Statistical analysis of the results using SPSS program, version 13 (2003). Comparison between results before and after carnitine therapy was done using logistic t-test, Cross tab/Chi-Square test and Z test. While correlation between results was done using Ranked spearman correlation test.
RESULTS

The present study included 14 patients with dilated cardiomyopathy. Seven males and 7 females. The mean age of our patients was (43.64±24.06) ms, the mean duration of illness was (23.64±20.89) ms.

Present results revealed a statistically significant higher serum carnitine level (p<0.001) after therapy than before as shown in Fig. 1.

Also present results showed clinical improvement in Cardiac Output (COP) and decrease in pulmonary congestion which presented as reduction in chest wheezing occurred after carnitine therapy (p<0.01), increased effort tolerance (p<0.01) and improved cardiac functional evaluation tested by NYHA-score (p<0.05) as shown in Table 1.

ECG findings showed significant reduction in R wave in V6 leads after carnitine therapy (p<0.05) indicating a decrease in left ventricular hypertrophy, while non significant change in other ECG parameters were noticed as shown in Fig. 2.

Table 1: Manifestations of pulmonary congestion before and after L-Carnitine therapy in children with DCM

<table>
<thead>
<tr>
<th>Item</th>
<th>Before L-Carnitine</th>
<th>After L-Carnitine</th>
<th>p-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effort intolerance</td>
<td>10</td>
<td>14</td>
<td>&lt;0.01</td>
<td>HS</td>
</tr>
<tr>
<td>Recurrent wheezing</td>
<td>11</td>
<td>4</td>
<td>&lt;0.01</td>
<td>HS</td>
</tr>
<tr>
<td>Chest</td>
<td>0.7</td>
<td>0</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
</tbody>
</table>

Table 2: Comparison between M-mode echocardiographic measurements of left ventricular dimensions presented in the form of Z score before and after carnitine therapy

<table>
<thead>
<tr>
<th>Z-score</th>
<th>Before L-Carnitine</th>
<th>After L-Carnitine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>LVEDD</td>
<td>7.10</td>
<td>2.22</td>
</tr>
<tr>
<td>LVESD</td>
<td>9.69</td>
<td>3.33</td>
</tr>
</tbody>
</table>

Table 3: Comparison between M-mode echocardiographic measurements of systolic function (LVEF and FS) before and after carnitine therapy

<table>
<thead>
<tr>
<th>Before vs after therapy</th>
<th>Before therapy</th>
<th>After therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>LVEF</td>
<td>38.07</td>
<td>9.62</td>
</tr>
<tr>
<td>FS</td>
<td>18.64</td>
<td>4.97</td>
</tr>
</tbody>
</table>

LVEF: Left Ventricular Ejection Fraction, FS: Fractional Shortening, Normal LVEF = 50-70%, Normal FS = 30-45%

Table 4: Correlation between serum carnitine levels and some Echo and clinical parameters

<table>
<thead>
<tr>
<th>Items</th>
<th>R²</th>
<th>p-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>0.45943</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>FS</td>
<td>0.48928</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
<tr>
<td>Z-score for LVEDD</td>
<td>-0.36435</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Z-score for LVESD</td>
<td>-0.28818</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Wt after therapy</td>
<td>0.60224</td>
<td>&lt;0.05</td>
<td>S</td>
</tr>
</tbody>
</table>
Results showed positive significant correlation between serum carnitine levels and each of EF, FS and weight of our patients after carnitine therapy.

**DISCUSSION**

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 ischemia and lead to sarcinemal membrane damage, a decrease has been determined in the carnitine concentration in cardiac tissue of the patients with dilated cardiomyopathy as compared to normal ones (Donder et al., 1998).

In the present study mean serum carnitine level was low at the baseline (7.1±5.95 mg L⁻¹) and it was significantly increased after carnitine therapy to (18.61±10.85 mg L⁻¹) at the end of the study (p<0.001). This was in agreement with Ergur et al. (1999) who found that the mean serum free carnitine level of children with heart failure was significantly lower than that of the healthy children (p<0.01), with significant increase (p<0.01) after L-carnitine administration. The good safety profile of propionyl-L-carnitine was an important aspect to be considered in our study group. No adverse effects were noticed throughout the study period when using L-carnitine in a dose of 100 mg kg⁻¹ day⁻¹.

Baker et al. (2005) recorded a significant increase of arterial blood levels of carnitine in patients with cardiomyopathy. They explained this phenomenon by leakage of carnitine from heart stores with subsequent cardiac tissue vulnerability to damage. Yet, they noticed no increase in venous carnitine levels. These results are as ours in the present study, as all our samples were venous in origin.

By the end of study, we found that some symptoms and signs of congestive heart failure in our patients have been significantly improved especially for higher effort tolerance (p<0.01), decrease in recurrent wheezes (p<0.01) and dyspnea grade (p<0.05) as measured by NYHA score. This was in agreement with Romagnoli et al. (2002) who have reported an improvement in exercise tolerance, life quality and functional status by adding L-carnitine to patients with dilated cardiomyopathy.

Moreover Helton et al. (2000) in their retrospective, multicenter study of pediatric patients up to 18 years of age with cardiomyopathy to evaluate the course and outcome in patients treated with and without L-carnitine (the control group), found that L-carnitine-treated patients have lower mortality and less clinical severity comparable to control patients on conventional therapy by the end of the study. L-carnitine also offers a route for removal of accumulating toxic intra-mitochondrial acyl CoA derivatives and allows for the possibility of improving the overall mitochondrial energy metabolism (Evans, 2003).

In the present study, out of 14 patients with congestive heart failure, 4 patients moved to a lower NYHA class and the overall condition of all patients improved except for one patient who moved to a higher NYHA class due to the bad condition from the start and young age (< one year) (EF>35%).

In 1992 similar findings were found by Kojibashi et al. (1992) who reported that (55%) of their patients with congestive heart failure moved to a lower NYHA class and the overall condition was improved in (60%) after treatment with L-carnitine. This was explained by the ability of L-carnitine to reverse the inhibition of adenine nucleotide translocase and thus can restore the fatty acid oxidation mechanism which constitutes the main energy source for the myocardium.

Reduced R wave in V6 lead means decrease in LV ventricular size which was confirmed by Echocardiography dimension reduction.

In present study, significant improvement was observed at LVESD on the 90th day (p<0.01). Also LVEDD was significantly decreased (p<0.05) after carnitine therapy.

Similar findings were previously reported by Donder et al. (1998) who observed a decrease in the LVEDD and LVESD (p<0.05) after L-carnitine treatment to patients with dilated cardiomyopathy, but their cases were adults and elderly with mean age of 62±10 years.

Anand et al. (1998) studied the effect of L-carnitine on hemodynamics, hormone levels, ventricular function, exercise capacity and peak oxygen consumption in patients with chronic congestive heart failure (NYHA II and III) in which acute administration of L-carnitine (IV bolus, 30 mg kg⁻¹ body weight) followed by chronic administration (1.5 mg day⁻¹) for one month was done, they found significant (p<0.01) reduction in the left ventricular dimensions in the treated group and concluded that propionyl-L-carnitine reduces ventricular size and increases exercise capacity in patients with congestive heart failure, but the drug has no significant effects on hemodynamics or neurohormone (norepinephrine, dopamine and aldosterone) levels.

This study revealed also that the EF improved after carnitine treatment. As mean EF before the treatment was 38.07±9.02%, it became 42.71±11.86% on the 90th day of therapy (p<0.01). This was in agreement with (Donder et al., 1998) who found that EF was increased
after the carminite treatment from 44.99±7.13 to 51.48±8.70% on the 60th day (p<0.05). In the present study, the myocardial FS before treatment was 18.64±4.97% and increased to 21.36±6.75% on the 90th day of therapy (p<0.01).

Similar findings were also found by Donder et al. (1998) who found an increase of the FS from 18.23±3.53 to 21.62±4.61% with L-carnitine therapy for 2 months (p<0.05) and Chapoy et al. (1980) who mentioned that after 3 months therapy, the myocardial FS in patients with cardiomyopathy has risen to 31% while it was 18% before the treatment.

An explanation of the positive effect of L-carnitine on EF and FS may be due to L-carnitine’s rising energy production and removing of the long chain fatty acids that have toxic effects on the myocardium (Donder et al., 1998).

In general, patients with newly diagnosed dilated cardiomyopathy either improve, enter in a fulminant acute fatal course or proceed to chronic form of cardiomyopathy. All our patients were cases with chronic cardiomyopathy who were receiving the conventional therapy for long time. For the past ten months, they showed no improvement in their myocardial functions. Hence, the improved EF, FS, LVEDD, LVESD and the significant decrease of R wave in V6 lead of ECG were not part of the improved natural course of the disease or due to the conventional therapy.

El-Beshlawy et al. (2004) investigated the effect of L-carnitine therapy on cardiac function in cardiomyopathy affecting thalassemia major patients. Echocardiographic studies revealed no significant changes in systolic and diastolic functions after L-carnitine therapy (p>0.05), but analysis of the data taken by Multi-gated Equilibrium Radionuclide Angiography (MUGA), however, showed a significant increase of diastolic function after 6 months of L-carnitine therapy. Moreover the systolic function showed a significant increase in the left ventricular ejection fraction (p>0.0001).

The present study revealed a positive correlation between serum carminite level and FS, EF and weight gain (p>0.05) after L-carnitine therapy. In contrast, we were not able to demonstrate any significant correlation between serum level of L-carnitine and other clinical or echocardiographic parameters.

In conclusion, L-carnitine can be safely added to the patients with dilated cardiomyopathy in whom no improvement has occurred with standard treatment. L-carnitine supplementation showed clinical improvement of the chronic heart failure symptoms and myocardial contractility in patients with primary dilated cardiomyopathy.

The present study suggest that measurement of L-carnitine should be a part of routine workup in dilated cardiomyopathy patients as its deficiency may be the cause. Addition of L-carnitine as an adjuvant therapy to treatment of those patients may have an additional improvement of cardiac symptoms and function. Study the effect of L-carnitine on a large scale of patients and for longer periods to assess the effect of increasing the duration of therapy on the degree of improvement and to see effect of carnitine therapy on morbidity and mortality of cardiomyopathic patients.

Other studies are needed for the correlation of serum carminite and cardiac carnitine since the later is better predictor of cardiac performance.

REFERENCES


