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Research Paper

A Study of L Carnitine Supplementation on Clinical, Systolic and Diastolic Function of Left Ventricle in Patients of Heart Failure

Medical Science

KEYWORDS : L-Carnitine, Heart failure, NYHA, Echocardiography

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ABSTRACT

Objective: This study was carried out in north-west part of Rajasthan to investigate clinical effects of supplementation of L-carnitine in patients of heart failure.

Material & Methods: Total 69 patients of heart failure were clinically assessed, NYHA classification of heart failure and standard echocardiography technique were applied before treatment with L-carnitine and at the 1st month and then subsequently on third months of the treatment.

Results: 47 patients improved symptomatically by at least one functional class of NYHA and 21 patients showed no response and 1 patients worsened. The diameter of the left ventricular end-systolic, end-diastolic and EPSS have decreased with L-carnitine treatment ($p<0.05$). 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 and myocardial fractional shortening. No significant change occurred in the diastolic function of the left ventricle.

Conclusion: As a conclusion, supplementation of L-carnitine to the conventional therapy can give successful clinical results and improvement in systolic functions of heart.

Introduction:

Cardiovascular disease is the leading cause of death worldwide[1]. Patients with larger ventricles are at higher risk of cardiac failure and death[2]. Dilated cardiomyopathy can manifest with congestive heart failure (CHF), arrythmia and sudden death[3]. L-carnitine treatment initiated early after acute myocardial infarction and continued for 12 months can attenuate left ventricular dilation during the first year after an acute myocardial infarction, resulting in smaller left ventricular volumes at 3, 6 and 12 months after the emergent event[4]. This medication is a diet supplement used to prevent and treat low blood levels of carnitine[5]. L-carnitine (LC) is a non-protein amino acid (β-hydroxy-γ-trimethyl-amino-butyric acid), that is synthesized from the essential amino acids lysine and methionine[6].

Experimental and clinical studies have shown that in the ischemic[7], infarcted[8,9] or failing myocardium[10,11], carnitine depletion occurs rapidly. Conversely, exogenous administration can restore adequate intramyocardial camitine levels with a suggested consequent beneficial effect on myocardial function[12-16].

Therefore, we have planned to search the effects of carnitine supplementation on clinical systolic and diastolic functions of the left ventricle by adding L-carnitine to the treatment of the patients with heart failure.

Materials and Methods

Totally 69 patients (21 Women and 48 men) out of 74 enrolled subjects completed follow up, 5 patients were lost in follow up or non compliance of nutrition supplement were excluded in the analysis. Remaining 69 patients, who clinically and echocardiographically were diagnosed with heart failure were selected as subjects of the study after full filling inclusion and exclusion criteria.

Inclusion Criteria:

- The subject aged≥ 40 years, men or women.
- The subject has a clinical diagnosis of CHF
- NYHA-Functional Class (FC) is Class II-IV
- The subject's USG (Echo) shows that LVEF ≤45%.
- The subject has signed the Informed Consent Form (ICF).

Exclusion Criteria:

- Subjects with medical history of heart failure caused by valvular heart disease, mechanical obstruction, pericardial disease and myocardial amyloidosis.
- Subjects with heart function Class IV that have unstable hemodynamics
- Subjects with AMI or acute pulmonary embolism.
- Subjects with uremia and did not undergo dialysis.
- Subjects with COPD.
- Subjects with anemia (Hb≤12gm%).
- Subject who is receiving other metabolism improving drugs within one month
- Subject with other severe disease and his/her life expectancy <12 months.
- Subject who is participating in other study.
- Subject who has received L-carnitine treatment within 1 month.
- Subject who is allergic to L-carnitine and its derivatives.
- Subject is receiving other cardiotoxic drugs.
- Subjects with medical history of epilepsy.
- Subject who is a drug or alcohol abuser.
- Subject with arrhythmia that the investigator thinks unsuitable to include.
- The subject who is pregnant or lactating

All of the cases who were treated with conventional heart failure therapy have taken antiplatelet agents (asprin, clopidogril),

Nitrates, ACE inhibitor or ARB, β blockers, calcium antagonist and (digitalis and antiarrhythmic drugs when required) but had no improvement in last three months of treatment. All patients were on medical treatment and refused coronary revascularization.

At first the purpose the applications of the study were explained to the patients oral and written permission (ICF) of all patients were taken as per guidelines of ethical committee, detailed history was taken from each patient. After the physical examination required blood and urine assays were done. Serum and plasma were prepared after centrifugation (3,000 rpm, 4°C, 15 minutes). Hematological entities (serum creatinine, total cholesterol, triglyceride, low density lipoprotein-cholesterol, and high density lipoprotein-cholesterol) were measured by an automated biochemical analyzer.

The cardiac functional changes (New York Heart Association) NYHA-FC between end of the medication (3 months), 1 month and baseline are evaluated by three grade criteria (effective, no response and worsening).

- Effective - cardiac function improved by at least one class of NYHA
- No response - cardiac function remained in the same class of NYHA
- Worsening - cardiac function aggravated by at least one class of NYHA

Haemodynamic evaluations were done after the patients were in resting condition at the echocardiography lab for hour. Two dimensional M-mode and pulse & continuous Doppler echocardiograms were applied with standard techniques. The echocardiography used was GE and Philips enviser with probe of 2 - 5 Hz. All of the patients were examined from the para sternal and apical view as per the criteria suggested by American Echocardiographical society. All measurements were done at least in 6 cardiac cycles and mean values were taken.

The left ventricular end – diastolic diameters (LVDD), the left ventricular end systolic (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 diamenter (RVEDD). Aortic root (AR) and valve motion (AM) and the E-IVS distance (EPSS) were measured.

To study the diastolic functions of the left ventricular: 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 measured.

To study the systolic functions of the left ventricle, 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 of the left ventricle (VCF) were calculated from standard Formulas.

All of these parameters were measured before the patient has taken medicine and measured again on the 1st month, and then subsequently 3rd month after taking medicine. Carnitine tablets 500 mg (totally 1 g/day) were given per oral twice a day.

One-way variance analysis (ANOVA) was used in the repeated measurements to compare the first result with those on the 1st and 3rd moths after taking medicine. When a considerable difference was present between the means values and ANOVA, P<0.05 was taken as the statistical significant. Group findings were identified as means values ± standard deviation.

Results

General characteristics of the patient are given in Table 1. Mean age of the patients was 59.12 ± 9.01 years.

Table 2 shows clinical outcome of L-carnitine supplemenation. Out of 69 patients who completed study, 47 improved by at least one class of NYHA. 21 showed no response while one patient was worsened. No patient needed hospitalization for worsening heart failure and no death occurred.

Table 3 shows echocardiographical indices of LV. LVDD was 67.7+8.52 mm at the beginning it decreased to 64.4+8.46 mm on the 1st month, 61.9+6.27 mm on the 3 month, (P<0.05).The decrease between the basal value and the measurements at 3 month were significant (P<0.05).

While the basal value of LVSD was 54.43+7.56 mm, it decreased to 49.3+7.11 mm on the 1 month 48.01+7.54 mm on the 3 month after the treatment (P<0.05),There was an important difference between the basal value and on the 3 month value (P<0.05).

While the EPSS before the treatment was 9.80+2.19 mm, it was 8.50+2.11 mm on the 1 month, 7.65+1.62 mm on the 3 month (P<0.05). The difference between the basal and the 90th day value was statistically significant (P<0.05).

There was no statistical difference among the diastolic functions of the left ventricle before and after the treatment (P>0.05).

EDV was 237.08+81.95 ml before the treatment and it was found as 211.30+78.87 ml on the 1 month, 193.03+69.12 ml on the 3 month after the treatment. According to variance analysis, the decrease in the EDV was important at p<0.05 level. The decrease between the basal value and the 3 month value (P<0.05) were significant.

The basal value of the ESV was 143.38+47.39 ml, ant it was found as 114.5+41.47 ml on the 1st month, 97.24+39.28 ml on the 3 month, these values were significant at P<0.005 level according to the variance analysis. There was significant difference between the basal value and 3 month value (P<0.005).

FS prior to the treatment was 19.75+1.33% and was 23.38+1.44% on the 1 month, 25.68+1.46% on the 3 month. Increase in FS was found significant (P<0.05). There was significant difference between the basal value and 3 month values (P<0.05).

EF before the treatment was 39.57+2.7% and 45.78+2.85% on the 1 month, 49.52+2.91% on the 3 month. The increase in EF was significant at P<0.05 level according to variance analysis. There was a significant difference between the basal value and the 3 month value (P<0.05).

Discussion

Carnitine is a physiologic compound (a quaternary amine) that plays an essential role in the production of myocardial energy at the mitochondriai level. It reduces the ischemia induced increase in long-chain fatty acid concentration and thus mitigates its deleterious functional effects[17,18].

Carnitine deficiency within the myocardium can be primary or secondary to various conditions, including acute ischemia[7-8] and chronic cardiac failure[10]. Experimental and clinical studies have shown that in situations characterized by its deprivation, exogenous administration of carnitine exerts a beneficial functional effect as expressed by improved cardiac performance[12,13] and tolerance to myocardial ischemia[14-16].

Gülçin et al[19] have reported that LC might be a good antioxidant. The lack of plasma and myocardial carnitine causes heart failure has been shows 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. Ghidini et al[20] have reported that improvement occurred in the symptoms and findings of the patients with heart failure by adding L-carnitine to their treatment. In our study 47 out of 69 subjects had improvement in symptoms of heart failure. Donder et al[21], reported that patients felt better after L-carnitine treatment. It was observed that their exercise tolerance and life quality was also improved.

Tripp et al[22] observed a decrease in the LVDD and LVSD after they had applied L-carnitine. treatment to the patients with dilated cardiomyopathy for 2 months. Donder et al[21], reported significant decrease in LVDD and LVSD with L-carnitine treatment for 2 months. In our study significant decrease was observed at LVDD, LVSD and EPSS with L carnitine treatment at 3 months ($p<0.05$).

Webber et al[23] reported that LVEF improved of 30% to 69% by 5 months. Donder et al has reported that LVEF improved from 44% to 51.48% by 60th day[21]. While in our study LVEF improved from 39.50 to 49.52% by 3 months.

Regarding the safety of LC supplementation, Singh and Aslam[24] Indicated that there are some side effects, such as mild nausea and vomiting after LC supplement at a dose of 2000 mg/d, but in three divided doses, supplementation might not cause any side effects. In the present study, we administered LC to heart failure patients at a dose of 1000 mg/d in two divided doses (500 mg/bid), and there were no clinically significant changes in the subjects' vital signs, serum chemical values, or hematological values. During L-carnitine supplementation one patient complained of itching, two patients complained of abdominal discomfort. Additionally there were no serious adverse events, no withdrawals due to adverse events and no cardiovascular event or death report during the study. Therefore, we suggest that a dose of 1000 mg/d is safe for patients with heart failure.

Conclusion:

As a conclusion, supplementation of L-carnitine to the conventional therapy can give successful clinical results and improvement in systolic functions of heart but there are some limitations of the present study that should be mentioned. First, the number of participants was small. Second, this study was designed using daily LC supplements for 3 months only. Larger and longer intervention studies are needed to understand and establish the beneficial effects of a high dose of LC in patients with heart failure.

Table - 1 : General Characteristic of Subjects

	No. of patients (n = 69)
Gender (male / female)	48 / 21
Age (years)	59.12 ± 9.01
Systolic BP	129.3 ± 5.10
Diastolic BP	78.4 ± 4.62
Waist circumference	90.7 ± 10.4
Waist hip ratio	0.92 ± 0.1
BMI (Kg/m^2)	24.3 ± 2.1

Table No. 2 Clinical effects of Levocarnitine supplementation in patients of Heart failure

N=69	One month	3 months
Effective	35	47
No response	34	21
Worsening	0	1

Table No. 3 Effects of Levocarnitine supplementation on Echocardiographic indices

Mean Value	Basal	1st Month	3rdMonth	P value
LVDD (mm)	67.70+8.52	64.4+8.46	61.9+6.27	<0.05
LVSD (mm)	54.43+7.56	49.3+7.11	48.01+7.54*	<0.05
EPSS (mm)	9.80+2.19	8.50+2.11	7.65+1.62*	<0.05
EDV (mm)	237.08+81.95	211.30+78.87	193.03+69.12*	<0.05
ESV (mm)	143.38+47.39	114.5+41.47	97.24+39.28	<0.005
EF (%)	39.57+2.7	45.78+2.85	49.52+2.91	<0.05
FS (%)	19.75+1.33	23.38+1.44	25.68+1.46	<0.05

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