ROLE OF L-CARNITINE IN CONGESTIVE CARDIAC FAILURE

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ABSTRACT

Objective: *To determine the effect of L- Carnitine on functional and echocardiographic parameters of patients with congestive cardiac failure (CCF).*

Material and Methods: *This double-blinded placebo control trial was conducted on 100 cases of CCF at cardiology outdoor department from March 2006 to May 2006. Subjects were randomized into group A (n=50) receiving 1 gm L-Carnitine and group B (n=50) receiving placebo. Baseline and at three months follow-up clinical and echocardiographic data of subjects was recorded.*

Results: *In L-Carnitine vs. placebo, 6 minutes walk was 400 ± 87 m vs. 360 ± 85 m (p = 0.04), NYHA class II and III improved (p= 0.7, p=0.3 respectively), LVED dimension showed no significant improvement (5.8 ± 0.7 cm vs. 5.7 ± 0.7 cm, p= 0.69), and FS improved (18.37 ± 3.4 vs.19.90 ± 6.7, p= 0.03). The 6 minutes walk and FS improved in ischemic vs. Congestive cardiomyopathy (412 ± 74 vs. 374 ± 108 meters, p= 0.3), (19.2 ± 50 % vs.15.9 ± 3.6 %, p=0.03). In ischemic cardiomyopathy 6 minutes walk improved (p= 0.001), LVED dimension increased (p=0.24), FS improved (p= 0.50) and NYHA class II (p=0.001), and III (p=0.02) improved. In congestive cardiomyopathy 6 minutes walk improved from baseline (p=0.13), FS showed no improvement (p=0.23), LVED dimension was not affected significantly (p= 0.65). NYHA class improved (p=0.05).*

Conclusion: *L- carnitine is beneficial in the treatment of congestive cardiac failure. It is more effective in ischemic as compared to congestive cardiomyopathy.*

Key Words: *L-Carnitine, CCF, Ischemic Cardiomyopathy, Congestive Cadiomyopathy, RCT.*

INTRODUCTION

L-carnitine is a naturally occurring substance. More than 90% is found in skeletal and heart muscle. It is very essential for oxidation of fatty acid and ultimately energy production particularly in ischemic myocardium.[1,2] L- carnitine is essential for long chain fatty acid from cytoplasm to mitochondria, permitting beta oxidation and producing energy in the form of ATP in heart muscles. It also enhances the oxidative utilization of glucose thus preventing lactic acid formation which is toxic to myocardial cell. L-carnitine also prevents the inhibition of nucleotide translocase, an enzyme responsible for the passage of ADP and ATP, thus improving the availability of ATP at the site of utilization. It also decreases the lipid peroxidation which suggest that it might scavange free radicls.[3, 6]

It has been observed that in the ischemic and and/or failing myocardium carnitine depletion occurs. A nonlinear correlation between myocardial free carnitine and myocardial function has been found.[7]

Present study was designed as to describe the effect of L- Carnitine on functional and echo parameters of patients with congestive cardiac failure (CCF).

MATERIAL AND METHODS

Initially one hundred adult patients diagnosed cases of congestive cardiac failure were recruited in the study due to coronary artery disease or idiopathic cadiomyopthy in New York Heart Association (NYHA) class II or III. Study was carried out at Lady reading Hospital cardiology department in out patient department from March 2006 to May 2006. This was a double-blinded placebo control study. Subjects were

CLINICAL CHARACTERISTICS OF BOTH GROUPS

Variable	Group A (L-Carnitine)	Group B (Placebo)	P value
Age	56±10	58±9.0	0.34
Male	40(80%)	32(64%)	
Female	10(20%)	18(36%)	
Systolic BP mmHg	123±24	122±20	0.80
Diastolic BP mmHg	80±7	80±5	0.79
Baseline			
LVEDD.(cm)	5.6±0.7	5.7±0.7	0.84
Fractional Shortening (%)	18.32±3.5	17.59±4.2	0.38
At three months			
LVEDD.(cm)	5.8±0.77	5.7±0.77	0.69
Fractional Shortening (%)	18.37±3.4	19.90±6.7	0.24
Angina episodes			
0 month	31(82%)	23(70%)	0.59
1 month	4(10%)	6(18%)	0.18
2 month	3(8%)	3(9%)	
3 month	0	1(3%)	0.78
Hospitalization required (p/m)	4(9%)	4(12%)	0.77
Death	3(6%)	2(4%)	0.62
Acute MI	1(2%)	0	
Diuretics	40(56.3%)	31(43.7%)	0.69
B.Blockers	29(50.9%)	28(49.1%)	0.30
ACE I	43(56.6%)	33(43.4%)	0.07
Nitrates	38(52.8%)	34(47.2%)	0.12
Antiplatlets	37(53.6%)	32(46.4%)	0.45
6 MINUTES WALK			
Baseline	331±94	297±87	0.10
3 month	400 ±87	360±85	0.07
NYHA Class Baseline			
II/ III	12(75%)/31(50%)	4(25%)/31(50%)	0.70
NYHA Class At three months			
I/ II/III	0/1/26(59.1%)/8(38.1%)	18(40.9%)/13(61.9%)	0.33

Table 1

randomized into either group A or B, each containing 50 patients. Group A received 1 gm L-Carnitine while group B received placebo. Patients in both groups already receiving anti failure therapy were instructed to continue medication. Baseline clinical data of all subjects were recorded. Baseline echocardiograph and distance measured in meters in 6 minutes walk was recorded. Follow up visits were scheduled at 30, 60 and 90 days. At each visit 6 minutes walk, NYHA class, angina episodes and need for hospitalization .At the end of 90 days echocardiography was done. Data was analyzed on SPSS V.10.Chi square test used for categorical variables. Independent t-test and paired t- test was used for continuous variable. P value of 0.05 deemed significant.

RESULTS

Clinical characteristics (table 1):

One hundred adult diagnosed patients of CCF were initially recruited in the study. Twelve cases were excluded from the study because they did not come for the first month follow up. At the end of study 66 patients data was available for analysis. The mean age of subjects was 56 ± 10 years as compared to placebo 58 ± 9.0 years (p=0.43). Male were 40(80%); female were 10(20%) in the L carnitine group. Mean systolic blood pressure was 123 ± 23 vs. 122 ± 20 in L carnitine as compared to placebo (p= 0.80). Majority of the subjects were already on diuretic, beta-blocker, ACEI, nitrates and antiplatelets. The difference for drugs being used was not significant

(Table 1). Three patients died in L-carnitine group while 2 patients died in placebo group. All died at home because of sudden cardiac arrest. The numbers of anginal episodes were steadily decreased from baseline in L-Carnitine and placebo group. No significant side effects were observed in the patients.

The 6-minute walk, echo parameter and NYHA Class:

The 6 minutes walk was more covered in L-Carnitine group from baseline when compared with placebo at end of three months 400 ± 87 vs. 360 ± 85 metes (p= 0.04).

The NYHA functional Class showed improvement relative to baseline in both the groups. The trend for improvement was more in L-Carnitine group but not significant (p=0.33) (table-1). The end diastolic dimension in patients taking L-carnitine did not differed as compared to placebo 5.8 ± 0.7 cm vs. 5.7 ± 0.7 cm (p= 0.69). Fractional shorting did not show improvement at the end of 3 months when both groups were compared at 3 months follow up (p=0.24) (table-1).

L-Carnitine in ischemic vs. congestive cardiomyopathy:

The 6-minute walk, echo parameter and NYHA Class (table-2):

In sub group analysis the effect of L-carnitine was compared among ischemic and congestive cardiomyopathy. The 6 minutes walk was more achieved (74 meters) in ischemic cardiomyopathy as compared to congestive cardiomyopathy at the end of three months relative baseline (412 ± 74 vs. 374 ± 108 meters) (P= 0.30). The difference made for improvement in NYHA class was seen in ischemic and congestive cardiomyopathy group, but not significant (p=0.3). The left ventricular end diastolic dimension was not affected significantly by L-carnitine at the end of three months of therapy. The fractional shorting was significantly improved in ischemic vs. congested cardiomyopathy (19.2 ± 50 % vs. 15.91 ± 3.6 %) (p=0.03) (table 2).

L-Carnitine in ischemic cardiomyopathy:

The 6-minute walk, echo parameter and NYHA Class (table-3):

The effect of L-crnitine within the ischemic cardiomyopathy on 6 minutes walk was beneficial, improving total distance covered at the end of three months as compared to baseline. (319 ± 90 meters vs. 412 ± 74 meters)(p= 0.001).The end diastolic dimension increased by 2mm but not significant trend at the end of the study (5.6 ± 0.64 cm vs. 5.8 ± 0.67 cm)(p=0.24). The fractional shorting was improved at the end of the study (18.5 ± 3.2 % vs. 19.2 ± 5.0 cm) (p= 0.50). The number of patients with NYHA II improved and the numbers of patients with NYHA class decreased significantly at the end of three months (p=0.02). Table-3

L-Carnitine in ischemic congestive cardiomyopathy:

The 6-minute walk, echo parameter and NYHA Class (table-4):

The effect of L- carnitine within the

EFFECTS OF L-CARNITINE IN ISCHEMIC VERSUS DILATED CARDIOMYOPTHY

Variable	Ischemic cardiomypathy (n=30)	Congestive cardiomypathy (n=13)	P value
6 minutes walk (m) (baseline)	320 ± 90	356 ± 104	0.29
6 minutes walk (m) (3 months)	412 ± 74	374 ± 108	0.30
LVEDD (cm) (baseline)	5.6 ± 0.72	5.8 ± 0.67	0.40
LVEDD (cm) (at 3 months)	5.8 ± 0.67	5.7 ± 0.98	0.93
Fractional Shorting (baseline)	18.8 ± 3.5	17.40 ± 3.18	0.27
Fractional shorting (%)	19.2 ± 50	15.91 ± 3.6	0.03
NYHA Class (Baseline)			
II	9(75%)	3(25%)	
III	21(67.7%)	10(32.3%)	0.7
NYHA Class (3 months)			
I	1(4.2%)		
II	19(73.1%)	7(26.9%)	
III	4(50%)	4(50%)	0.33

Table 2

EFFECTS OF L-CARNITINE IN ISCHEMIC CARDIOMYOPATHY

Variable		Baseline	After treatment	P value
6 minutes walk (m)		319±90	412±74	<0.001
End diastolic dimension (cm)		5.6±0.64	5.8±0.67	0.24
Fractional Shortening (%)		18.5±3.2	19.2±5.0	0.50
NYHA Class	I	0	1	0.02
	II	9	19	
	III	21	4	

Table 3

congestive cardiomyopathy on 6 minutes walk was improved from 352 ± 104 meters at baseline to 374 + 108 meters at end of three months (p=0.13). The fractional shorting decreased relative to the baseline at three months of follow up although not significant (17.1 ± 3.4 % vs. 15.91 ± 3.5 %) (p=0.81). The end diastolic dimension decreased at the end of three months of carnitine therapy but not significantly (5.8 ± 0.8 cm vs. 5.7 ± 0.9cm) (p=0.23). The NYHA class improved in majority of the cases and class III dysponea decreased significantly (p=.05){table 4}.

DISCUSSION

The fatty acid oxidation process constitutes the main source of energy in the contractile mechanism of cardiac muscle cells[8]. A very important role in this process is played L-carnitine, which promotes the transfer of acyl CoA to the mitochondria[9].

The results obtained by administering L-carnitine to elderly patients suffering from congestive heart failure confirm the clinical and experimental data reported by other investigators[3,10].

In our patients significant improvement in distance covered during six minutes walk was observed in carnitine group as compared to placebo. All patients had improved NYHA class in our study. However echocardiographic parameters did not change in the two groups. Similar findings were observed by Akira Kobayashi in his study[11]. Since L-carnitine has neither appositive ionotropic nor a vasodilator effect, it may be difficult to exert an improvement of cardiac kinetic parameters due to treatment with L-carnitine. Although small improvement was seen in improving ejection fraction (p=0.01) in single blind design study by Anand, but the author used initially i/v bolus dose (30mg/kg) followed by higher oral dose (1.5 gm/day) as compared to our study (1gm/day)[12]. It is now apparent that various defect s of myocardial energy metabolism may be present in chronic heart failure. Endomyocardial biopsies taken from the hearts of patients with chronic heart failure have shown a correlation between a decrease in the ATP concentration and impairment of myocardial contraction and relaxation.[13]

Ours is the first study in which we compared the beneficial effects of L-carnitine in ischemic versus idiopathic dilated crdiomyopathy and it was observed that L-carnitine improved the exercise capacity, fractional shorting significantly in ischemic cardiomyopathy. L- carnitine improved the NYHA class and LV dimension did not gone worse although statistically not significant in CCF due to ischemic cardiomyopathy. Pauly Daniel reported similar observation in his placebo control with 1-3 months of follow up in CCF due to ischemic cardiomyopathy[14]. In his trial there was small increase in LV dimension over the time, like

EFFECTS OF L-CARNITINE IN IDIOPATHIC DILATED CARDIOMYOPATHY

Variable		Baseline	After treatment	P value
6 minutes walk (m)		352+104	374+108	0.13
End diastolic dimension (cm)		5.8+0.8	5.7+0.9	0.81
Fractional Shortening (%)		17.1+3.4	15.91+3.5	0.23
NYHA Class	II	3	7	0.05
	III	10	4	

Table 4

in our study, positive effect on symptoms of heart failure. Although these effects were more pronounced in CCF due to ischemic cardiomyopathy versus idiopathic dilated cardiomyopthy but there was overall beneficial effect of L-carnitine in improving exercise capacity, LV dimension, FS, and improving the NYHA class even in idiopathic dilated cardiomyopathy. These positive effects of L-carnitine can be explained on the basis that ischemic myocardium is more deficient of carnitine as compared to myocardium of idiopathic dilated crdiomyopathy and when given exogenously produces beneficial effects[3,15]. Moreover L-carnitine increases blood flow in ischemic myocardium; prevent the accumulation of toxic metabolites during ischemia[8,16].

CONCLUSION

The drug proved completely devoid of side effects with the result that patient's compliance was optimal. L-carnitine appears to be beneficial therapeutic agent in the treatment of congestive cardiac failure in conjunction with traditional pharmacological therapy for heart failure. This is a short-term study; a longer follow up study is required to see the long term beneficial effects because certain parameters their was beneficial trend towards improvement.

REFERENCES

1. Camici P, Marracinni P, Lorenzoni R. Metabolic markers of stress induced ischemia. Circulation 1991; 83(Suppl III): 118.
2. Opiele LE. Role of carnitine in fatty acid metabolism of normal and ischemic metabolism. Am Heart J 1979; 97: 375-88.
3. Spagnoli LG, Corsi M, Villaschi S, Palmieri G, Maccari F. Myocardial carnitine deficiency in acute myocardial infraction. Lancet 1982; 1: 1419-20.
4. Bohles H, Noppeney T, Akcetin Z. The effect of preoperative L-Carnitine supplementation on myocardial metabolism during aorta bypass surgery. Curr Ther Res 1990; 39: 429-35.
5. Goa KL, Brogoten RN. L-Carnitine: A preliminary review of its pharmacokinetics and its therapeutic use in ischemic cardiac disease and primary and secondary carnitine deficiencies in relationship to its role in fatty acid metabolism. Drug 1987; 34: 1-24.
6. Siliprindi N, Di Ilisa E, Toninello A. Biochemical derangements in ischemic myocardium: The role of carnitine. G Ital Cardiol 1984; 14: 804-8.
7. Regitiz V, Shug AL, Flece E. Defective myocardial carnitine metabolism in congestive heart failure secondary to dilated cardiomyopathy and to coronary hypertensive and valvular heart disease. Am J Cardiol 1990; 65: 755-60.
8. Roberto F, Merli E, Cicchitelli G, Mele D, Faucili A, CeconiC. Therapeutic effects of L-carnitine and propionyl-L-carnitine on cardiovascular disease: a review. Ann NY Acad Sci 2004; 1033: 79-91.
9. Lango R, Smolenski RT, Narkiewiaz M, Suchorzewska J, Lysiak-Szydlowska W. Influence of L-carnitine and Hs derivatives on myocardial metabolism and function in ischemic heart disease and during cardio pulmonary bypass. Cardiovasc Res 2001; 51: 21-9.
10. Vick JA, De Felice S. Role of carnitine in congestive heart failure and myocardial hypoxia. Pharmacologist 1974; 16: 224-227.
11. Akira K, Yoshinor M, Noboru Y. L carnitine treatment for congestive heart failure-experimental and clinical study. Jap Circ J. 1992; 56: 86-94.
12. Anand I, Chandra SY, Degiule F, Pasini E, Mazzoletti A, Confortini R, et al. Acute and chronic effects of propionyl L carnitine on hamodynamics exercise capacity and hormones in patients with congestive heart failure. Cardiovasc Drug Ther 1998; 12: 291-99.
13. Bashore TM, Magorien DJ, ketterio J, Shaffer P, unverferth DV. Histologic and biochemical correlates of left ventricular chamber dynamics in man. J Am Coll Cardiol 1987; 9: 734-40.
14. Pauly Daniel F, Pepine CJ. The role of L-carnitine in myocardial dysfunction. Am J Kidney Dis 2003-41: 535-43.
15. Suzuki Y, Kamikawa T, Yamazaki N. protective effects of L-carnitine of ischemic heart. In: Fronkel RA, McGarry JD (eds): Carnitine Biosynthesis, Metabolism, and functions. Academic Press, New York, 2000, 341-352.
16. Retter AS. Carnitine and its role in cardiovascular disease. Heart Dis 1999; 2: 108-13.

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