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L-Carnitine as adjunctive treatment for chronic heart failure: an Indian study with focus on SYMptoms and BIOmarker status (LC-SYMBIO)

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ABSTRACT:

Objective: This study was carried out in PMCH & other tertiary care hospitals in northwestern India during the period of January 2021 to December 2021 to evaluate L-carnitine as an adjunctive treatmentin patients of heart failure.

Background: Mitrochondrial dysfunction is a hallmark of HF syndrome, predominatly characterized by a deficit in production of myochardial adenosine triphosphate. L-C play an important role in lipid metabolism by acting as obligatory cofactor to provide enough ATP for myochardial cells.

Material & Methods: Total 109 patients of heart failure were diagnosed clinically and on echocardiographic assessment, l-carnitine a health supplement was added to standard medical therapy of CHF and primary endpoints of NYHA classification of heart failure 6 minute walktest and N-Terminal probnp level were assessed before treatment with L-carnitine and then subsequently after 16 weeks of the treatment.

Results: 63 patients improved symptomatically by at least one functional class of NYHA and 29 patients showed no response and 17 patients worsened. There was significant improvement in Weighted Mean Value (WMN) of six minutes walk distance in patients with mild limitation (more than 400mt) No significant change occurred in the WMN of N-Terminal probnp levels except in the subgroup having mild elevation (<1200pg/ml& class II NYHA)

Conclusion: As a conclusion, supplementation of L-carnitine to the conventional therapy can give successful clinical results. However, more long term multicentric RCT and Meta-analysis are required for further evaluation and establishment.

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Introduction

Chronic heart failure (CHF) is a complex syndrome characterized by decreased myocardial contractility, hemodynamic abnormality, and neuroendocrine activation.It is a global public health problem affecting estimated 26 million worldwide.[1] Currently, the neurohormonal antagonists (ACE-inhibitors, bets-blockers, angiotensin receptor blockers, and mineralocorticoid receptor antagonists) are recommended for CHF as part of optimal therapy[2, 3]

It is Levo-Carnitine (L-C) treatment has been reported to be effective in improving clinical symptoms, cardiac functions, and decreasing serum levels of BNP/NT-pro BNP of CHF patients.[4]L-carnitine (LC) is a non-protein amino acid (β-bydroxy-trimenthlyl-amino-butyric acid), that is synthesized from the essential amino acids lysine and methionine that plays an important role in supporting the body's metabolic activities. There is growing evidence that high concentrations of L-C provided beneficial effects in various diseases such as coronary artery disease, congestive heart failure.[5]

B-type natriuretic peptide (BNP) is a small protein secreted by the ventricles of the heart in response to excessive stretching of the myocytes. BNP is secreted into the blood when heart is working hard. The N-terminal fragment of BNP is a highly sensitive marker for cardiac dysfunction. An elevated NT-proBNP level frequently indicates the presence of an underlying cardiac disorder. It can even identify people with structural heart disease and cardiac dysfunction before symptoms begin. Even relatively low levels of NT-proBNP abnormalities correlate well with development of progressive atherosclerosis.[6]

Reports of carnitine leakage in the setting of cardiomyopathysupport the observation that among cardiac disease suffers, relative carnitine deficiency might exist.[7]As per Koch"s postulates, a case for causal effect regarding L-C supplementation is buttressed by observed clinical and biochemical improvements post-treatment.

Cardiac function worsening has a diverse etiology, and the clinical and molecular studies have an diversified approach that impedes the establishment of carnitine as a central theme of cardiovascular dysfunction.[8-10]The biochemical, molecular and genetic evidence has been able to stitch together a mechanistic linkage of L-C and cardiovascular ailments. There is a genetic model of cardiac disease where patients with primary carnitine deficiency (PCD) related c.95A>G mutation in *SLC22A5* have a very high propensity to suffer potentially lethal cardiac arrhythmias. Other studies have associated L-C related genes, *SLC22A4* and *SLC22A5* with ischemic heart disease.[11]Other biochemical and molecular studies have detailed the definitive pathways of L-carnitine metabolism with cardiac physiology and pathology.[11-13]

There have been reports that have judged the therapeutic potential employing various study designs and largely found utility with L-C supplementation in pediatric as well as adult patients of cardiac disease.[14-17]Therefore, we have planned to search the effects of carnitine supplementation on clinical profile and biomarker level of NT-proBNP in serum of patients with heart failure which has been found by many researchers to have a dimensional value[1]

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Objective of the study

Mitrochondrial dysfunction is a hallmark of HF syndrome, predominatly characterized by a deficit in production of myochardial adenosine triphosphate. L-C play an important role in lipid metabolism by acting as obligatory cofactor to provide enough ATP for myochardial cells.This study was carried out in PMCH & other tertiary care hospitals in northwestern India during the period of January 2021 to December 2021 to evaluate L-carnitine as an adjunctive treatment in patients of heart failure.

Materials and Method

To evaluate the effect of L-carnitine in an objective manner an open label study was planned where patients of congestive heart failure (CHF) were considered candidates for inclusion into the study based upon a positive clinical diagnosis of heart failure grade II-IV.
Duration of the study was from January 2021 to December 2021.

The inclusion criteria were:

1. Age above 40years
2. Subject has significant elevation of bio marker(NTproBNP)
3. Patient in NYHA functional class II-IV
4. The patient has signed informed consent form

Exclusion criteria:

1. Patients with explained pathology causing heart failure like amylodosis, rheumatic heart, past episode of myocardial infarction, mechanical factors causing obstruction, other heart or lung diseases known to masquerade as heartfailure
2. Patients with NYHA class III or IV heartfailure
3. Patients with comorbidities like anemia (Hb < 12gm%),
4. Already on nutraceuticals during pastmonth
5. Patients with end stage disease and limited lifeeExpectancy
6. Patients participating in otherstudies
7. Pregnant and lactatingsubjects
8. Subjects with arrhythmia not controlledwell
9. Patients who have received L-carnitine during the past onemonth
10. Patients of epilepsy
11. Patients allergic to l-carnitine or it’sderivative
12. Patients with continued problem of substanceabuse.

At the time of recruitment into the study, a baseline 6-minute walk test and an echocardiographic assessment was done to confirm and document the objectivity of the clinical diagnosis of CHF and its echo-doppler correlates. The patients were informed at this time about the plan to start nutraceutical L-carnitine after 16 weeks of being on heart failure therapy. The medical history of each patient was examined, and all underwent a physical examination and a chest x-ray, ECG and Doppler echocardiography before such a diagnosis was reached. The patients were expected to stabilize on standard recommended CHF treatment regimen during initial 16 weeks from the date of recruitment. When they arrived for second visit, it was assured that the patients were compliant with the prescription. The diagnosis and grading of CHF was always made by a specialist physician as per the criteria of the European Society of Cardiology regarding clinical symptoms and Doppler echocardiography criteria. The specialist physician was "blind" to the NTpropBNP concentrations detected because analysis of NTproBNP were done at later date)

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The current study was conducted on a prospectively enrolled group of patients who had a diagnosis of congestive heart failure (CHF) NYHA class II-IV. A total of 109 patients (37 Women and 72 men) out of 115 enrolled subjects completed follow up. Overall, 6 patients were lost in follow up due to volition, noncompliance or change of residence and were excluded from the analysis. The remaining 109 patients, who clinically and by echocardiography were diagnosed with heart failure were finally recruited as subjects of the study after fulfilling inclusion and exclusion criteria.

In the printed consent form, the patients were informed that the goal of the study was to assess the effect of L-carnitine on exercise tolerance, serum pro BNP levels. The patients were given L-carnitine in dose of 2 gm per day in divided doses. Patients were asked to put their perception in terms of score ranging from 5 to 10 or 5 to1 with a score of 5 being on the day L-carnitine was started at the end of 16 week of follow up for optimal heart failure therapy. 6 minute walk test were performed according to guidelines of American Thoracic Society,2002.

Blood was taken from all patients during this second visit of the study and again after at the end of 16 weeks to determine the serum concentration of NTproBNP. The collected and labelled blood samples were centrifuged at 1500 RPM and stored immediately in a deep freezer awaiting biochemical analysis. Patient blood samples were taken between 08.00 and09.00 hours. The only once thawed samples were analyzed using an Elecsys 1010 analyzer (Roche Diagnostics).

The design of the study was “case control” and each of the patients served as control during the initial 16-week duration of standard CHF treatment. When the patients were started on with the nutraceutical agent L-carnitin + standard CHF treatment the status of the patients was deemed changed to “cases”. By employing this approach, it was hoped that an optimal matching of case and controls would be achieved. Thus, a focus was achieved on the potential therapeutic effect of L-Carnitine when used as adjunctive therapy to standard heart failure therapy.

The formula used to calculate the sample size (kirkwood article ref) was:

$N= \{\mu \sqrt{([\pi(1-\pi)])} + v \sqrt{([\pi^{\circ}(1-\pi^{\circ})])}\}2/(\pi-\pi^{\circ})2$

Where :

N =required minimum sample size

π =proportion of interest proposed in this study 0.7 because of variation during course of study

π° = null hypothesis proportion which is equal to 0.5

μ = one side percentage of normal distribution corresponding to 100%- the significant power (100%-85%=15%) and μ = 1.036

v=percentage of normal distribution corresponding to required two tailed significance level (5%[1.96])

The sample size comes out to be 53 which was doubled to counteract design effect.

To analyze the differences if any, T-test for independent samples and paired T test was used employing medcalc provided online statistical calculator.

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Results

The details regarding patient demographics and their clinical parameters at the time of recruitment into the study are documented in table 1.

Table 1: Patient demographics	
Gender	M:(N=72); F: (N=37)
Age	M[59.4(μ) + 8.2(σ) yrs.]; F[61.3(μ) + 4.7(σ) yrs.]
Systolic blood pressure	M[149(μ)+12(σ) mmHg]; F[134(μ)+15(σ) mmHg]
Diastolic blood pressure	M[96(μ)+6(σ) mmHg]; F[8i(μ)+8(σ) mmHg]
History of ischemic heart disease	M [22%]; F [9%]
History of hypertension	M [58%]; F [67%]
History of diabetes mellitus	M [18%]; F [24%]
History of hyperlipidemia	M [38%]; F [42%]
History of smoking or currently tobacco abuse of any type	M [38%]; F [2%]

A total number of 6 patients did not wish to continue in the study after initial recruitment and their data was not included for analysis.

In terms of perception, about 58%. (63/109) patients felt better after staring L-carnitine. The mean score of perception was reported to be 8.1+0.5 for patients who improved in terms of a change in NYHA classification of heart failure. Fo those 29 who remained stable (i.e. no change in NYHA grade) the mean perception score was 6.2+0.8. And, for those 17 with deterioration of NYHA grade of heart failure the mean perception score was 5.3+0.2.

The results of change in the level of NTproBNP during the course of study and their association with changes in NYHA heart failure classification level are shown below (table 2)

Table 2: Distribution of cases according to NYHA classification and mean serum NTproBNP 16 weeks and 32 weeks after recruitment (μ±σ)			
Heart failure as per NYHA classification	Serum NTproBNP <1200 pg/ml n=24(start) 2 (end)	Serum NTproBNP 1200-1800 pg/ml n=54(start)59(end)	SerumNTproBNP >1800 pg/ml n=31(start)26(end)
Class II (Mild)	4 (start) 15 (end)	18(start) 7(end)	2 (start) 2 (end)
Class III (Moderate)	26 (start) 17(end)	8(start) 26(end)	20(start) 16 (end)
Class IV (Severe)	0 (start) 0 (end)	11(start) 9(end)	20(start) 20 (end)
Mean Serum NTproBNP	Start 1359±356pg/ml End 1127±440pg/ml*	Start 1896±1052pg/ml End 2031±910pg/ml**	Start 4059±2453pg/ml End 4459±2134pg/ml**
Comparison of means (T-test, two tailed, independent samples)	*p<0.05	**p=non-significant	

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As evident from the results, only the group of patients which were in group that had a NYHA class II heart failure demonstrated a significant reduction in NTproBNP levels while the class III and Class IV heart failure patients failed to show any statistically significant change in NTproBNP levels. The matched pair analysis revealed that the overall reduction in NTproBNP (Start 2393+1844 vs. End 2300+1749) was not significant (p ~ 0.07)overall.

A total of 80 patients had a change in their judged NYHA class at the end of 16th week of optimal heart failure therapy and L-carnitine. Out of these patients with a changed NYHA class 63 patients experienced an improvement and 17 patients did show a decline in their NYHA class.

The NYHA class of congestive heart failure agreed reasonably with the results obtained by the conduct.

Table 3: Distribution of cases according to NYHA classification and mean distance covered during a 6 minute walk test at 16 weeks and 32 weeks after recruitment($\mu \pm \sigma$)

Heart failure as per NYHA classification	Mild limitration (400 plus meters) n=30(start) 49 (end)	Moderate limitation (300-400 neters) n=35(start) 31(end)	Severe limitation (>220 meters pg/ml) n=44(start) 29(end)
Class II (Mild)	6 (start) 12 (end)	14(start) 10(end)	4 (start) 2 (end)
Class III (Moderate)	26 (start) 34(end)	6(pre) 15(post)	22(start) 10(end)
Class IV (Severe)	0 (start) 0 (end)	9 (start) 8 (end)	22 (start) 18(end)
Results of 6 min walk test	Start 344±30 meters End 384±46 meters *	Start 251±50 meters End 270±43 meters**	Start 211±67 meters End 225±48 meters **
Comparison of means (T-test, two tailed, independent samples)	*p<0.05	**p=non-significant	

The majority of the patients in subgroup with mild limitation (more than 400 mts) experienced a significant improvement of their distance covered during 6-minute walk test indicating the positive adjunctive effect of the efficacy of nutraceutical agent L-carnitine.

Discussion

The overall clinical grading of heart failure improved by at least one NYHA class for about 58%of the of the patients and the overall trend for L-carnitine adjunctive therapy was of improvement in clinical and biochemical status. Similar results were reported by Beniwal S et al[15] and Song et al.[17]The movement of patients across NYHA grades of heart failure (from IV to III) was perhaps the cause for non-significant change in NTproBNP in the group with grade III heart failure. The patients with NYHA class IV heart failure usually have an exponential rise in NTproBNP levels (due to very high ventricular wall tension) which probably persist at higher level for some time even when patient moves to NYHA class III. However, our subgroup analysis might be an indication that L-carnitine might be able to help in physiological reduction of ventricular wall tensions for patients still in early classes of heart failure. It can be speculated that the reduction in standard deviation of NTproBNP also indicates a distinct physiological mechanism of ventricular wall tension reduction. Similar results were reported by various other study groups.[16-18]

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The psychical effects of a muscle building nutraceutical might have contributed somewhat to an increase in patient satisfaction. But, it appears that L-carnitine has induced its effect largely through a mechanistic physiological change that has probably resulted in a positive outcome for patients. An overall statistically non-significant reduction in NTproBNP serum concentration is not with much clinical relevance without the subgroup analysis. (Table 2) Our results affirm our contention that the trend for the adjunctive therapeutic role of L-carnitine is positive. The possible indicators for existence of a physiological mechanism of action of L-carnitine are the overall reduction in NTproBNP, overall improvements in patient perception score and a meaningful overall reduction in NYHA class of heart failure for majority of the patients experiencing a class change.

Conclusion

To summarize, L-carnitine was not able to enable an overall statistically significant decrease in NTproBNP levels, but in subgroup analysis patients having NTproBNP (<1200pg/ml NYHA II) had statistically significant reduction with standard therapy along with Leo-Cartinine. There was significant improvement in Weighted Mean Value (WMN) of six minutes walk distance in patients with mild limitation (more than 400mt) . In terms patient perception patients with all grades of heart failure were more likely to respond favorably to treatment by nutraceutical agent L-carnitine. Theclinical utility of L-carnitine is reasonable and itssupplementation to the conventional therapy can give successful clinical results which, however, needs evaluation through more long term multicentric RCT and Meta-analysis.

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