

RESULTS OF A SINGLE BLIND, RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL TO STUDY THE EFFECT OF INTRAVENOUS L-CARNITINE SUPPLEMENTATION ON HEALTH-RELATED QUALITY OF LIFE IN INDIAN PATIENTS ON MAINTENANCE HEMODIALYSIS

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ABSTRACT

BACKGROUND: Carnitine insufficiency is responsible for various co-morbid conditions in maintenance hemodialysis (MHD) patients. L-carnitine supplementation is expected to improve the quality of life (QoL) of patients on MHD. **AIMS:** To study the effect of L-carnitine supplementation on QoL of Indian patients on MHD. **SETTING AND DESIGN:** This was a single (patient) blind, randomized, placebo-controlled clinical trial conducted on patients on MHD attending hemodialysis unit of the study center. **MATERIALS AND METHODS:** Twenty patients on MHD suffering from hemodialysis-related symptoms were randomly assigned to receive intravenous L-carnitine 20 mg/kg or placebo after every dialysis session for 8 weeks. SF36 (Short Form with 36 questions) score for QoL, laboratory investigations and dialysis related symptoms were recorded at baseline and after 8 weeks. Improvement in QoL, laboratory parameters and dialysis related symptoms in the two groups after 8 weeks was compared. **STATISTICAL ANALYSIS USED:** Depending on normality of data, unpaired T test or Mann Whitney U test was used for comparison of change (8 weeks-baseline) in SF36 scores and laboratory parameters observed in the two groups. **RESULTS:** L-carnitine supplementation increased total SF36 score by 18.29 ± 12.71 (95% CI: 10.41 to 26) while placebo resulted in reduction in total SF36 score by 6.4 ± 16.39 (95% CI: -16.59 to 3.73). L-carnitine also resulted in significant increase in hemoglobin and serum albumin and decrease in serum creatinine as compared to placebo. More patients were relieved of dialysis related symptoms in L-carnitine group. **CONCLUSION:** Intravenous L-carnitine supplementation improves QoL in patients on MHD.

Key words: Hemodialysis, L-carnitine, Quality-of-life.

INTRODUCTION

Although dialysis has dramatically improved survival, many patients with end stage renal disease (ESRD) remain debilitated due to multiple comorbid conditions. Studies have

suggested that insufficiency of L-carnitine and abnormalities in L-carnitine metabolism are responsible for some of these problems. Restoration of the aberrant fatty acid metabolism in ESRD patients has been thought to be the key role played by carnitine supplementation.^[1,2] Apart from loss of carnitine during the dialysis process, other factors placing ESRD patients at risk for developing carnitine deficiency include loss of renal parenchyma and reduced dietary intake of carnitine sources, such as red meats and dairy products.^[3]

Quality of life (QoL), is of particular importance in patients with ESRD. Better QoL in dialysis patients is associated with lower morbidity and mortality.^[4]

While plenty of studies have examined role of L-carnitine supplementation in co-morbid conditions, very few have studied its effect on QoL.^[5,6] Complaints like weakness, poor exercise tolerance, easy fatigability etc have implications on QoL and L-carnitine has been found beneficial in alleviation of these symptoms in maintenance hemodialysis (MHD) patients.^[5,7] It may therefore be expected that L-carnitine may be useful in improving QoL in MHD patients. Present study was designed to assess the effect of intravenous (IV) L-carnitine supplementation on QoL in Indian MHD patients.

MATERIALS AND METHODS

This was a patient-blind, randomized, placebo-controlled clinical trial. The study protocol was approved by the Institutional ethics committee.

Primary objective of the study was to assess the effect of IV L-carnitine supplementation on QoL in Indian patients on MHD. Secondary objectives were: to examine effects of L-carnitine on hemoglobin, lipid profile and laboratory kidney function parameters, to examine the effect of L-carnitine on hemodialysis-related symptoms and to assess the safety of IV L-carnitine supplementation.

ESRD patients attending hemodialysis unit of the center from January 2005 to October 2005 were screened for inclusion and exclusion criteria for enrollment in the study. Clinically stable, male and non-pregnant, non-lactating female patients, between age 18 and 65 years undergoing MHD at least twice weekly for a minimum duration of six months and having at least two of the following dialysis-related symptoms were enrolled in the trial after obtaining their written informed consent:

1. Interdialytic or intradialytic hypotension
2. Muscle cramping
3. Lack of energy/generalized weakness
4. Muscle weakness
5. Myopathy

Patients who had received L-carnitine therapy in previous 6 months or blood transfusion in previous 4 weeks, patients with history of seizure disorder, requiring/taking concomitant hypolipidemic agents and those having history suggestive of hypersensitivity to or any contraindication to L-carnitine were excluded from the trial.

Twenty enrolled patients were randomly assigned, 10 each to L-carnitine or placebo group using a computer generated

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randomization chart for simple randomization in blocks of 4 (www.randomization.com). Patients assigned to L-carnitine group received injection L-carnitine 20 mg/kg administered as IV bolus slowly through venous catheter over a period of 2-3 minutes at the end of every hemodialysis session for eight weeks. Patients from placebo group received 5 ml normal saline IV at the end of every hemodialysis session for eight weeks. To ensure blinding of patients, L-carnitine ampoules were broken and filled in syringe for injection in the absence of patients. The patients were able to visualize only the syringe, fluid from which was injected into the venous catheter. As L-carnitine and normal saline injections are not apparently distinguishable, the patients remained blind of the medication received. The attending staff was strictly instructed not to reveal identity of the medication to the patient. Generation of allocation sequence, assignment of enrolled patient to the appropriate treatment and compliance of patient blinding were all done by the attending resident and/or the nephrologists in charge.

Concomitant intake of hypolipidemic agents was not allowed during the study. Use of furosemide, blood transfusion and iron supplements were decided by the needs of the patient and recorded in the CRF. Patients continued to receive the anti-hypertensive therapy that they were receiving before entry into the study. Dietary restrictions in the form of salt restriction to less than 4 gm per day, fluid restriction according to urine out-put, a low protein diet and no consumption of fruits were advised to all the patients.

Increase in total SF-36 (Short Form with 36 questions) QoL score after eight weeks of treatment as compared to baseline value was the primary efficacy end-point. The SF-36 scoring system involves a questionnaire of 36 questions, 35 of which are compressed into eight multi-item scales:

1. Physical functioning: Ten items (questions)
2. Role-physical: Four items
3. Bodily pain: Two items
4. General health: Five items
5. Vitality: Four items
6. Social functioning: Two items
7. Role-emotional: Three items
8. Mental health: Five items

The scales were assessed quantitatively, each on the basis of answers to two to ten multiple choice questions and a score between 0 and 100 was then calculated, higher score indicating a better state of health. The first five scales make up the "physical health" dimension and the last five form the "mental health" dimension. The scales vitality and general health are parts of both dimensions. The questionnaire was first explained to the patients and they were asked to mark their answers at appropriate places at baseline and after eight weeks. The questionnaire was also translated into Marathi for patients not conversant with English. The Marathi version was back-translated into English. This back-translated version was complied with the original English version and necessary changes were made in the Marathi text to obtain the final Marathi version of the questionnaire. For convenience of calculation, the pre-designed Microsoft Excel based program for assessment of SF-

36 score that performs automatic scoring of the scales upon entry of scores for individual questions was used.^[8] Scores for individual questions were entered into the Excel sheet at baseline and after eight weeks.

Increase in hemoglobin, improvement in cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, laboratory kidney function parameters and hemodialysis related symptoms after eight weeks as compared to baseline were the secondary efficacy endpoints. These were recorded at baseline and after eight weeks of treatment. Blood samples for all the investigations were collected pre-dialysis.

Any drug-induced side effects as experienced by patient during the course of treatment were recorded in the case report form.

Random blood sugar was also measured at baseline and after eight weeks.

For statistical analysis, data for all the parameters was first subjected to test of normality (Graphpad InStat version 3.06, Sep 2003). Data showing normal distribution was analysed by using parametric tests and that showing non-normal distribution was analysed using non-parametric tests. Accordingly difference between the two groups for change (baseline versus 8 weeks) in hemoglobin, blood urea nitrogen, total cholesterol, LDL cholesterol, HDL cholesterol, scores of bodily pain, general health, vitality, social functioning, mental health, overall mental health and the total SF 36 score was compared by using students two-tailed

unpaired T test (Microsoft Excel, Windows 98) while difference between the two groups for change (baseline versus 8 weeks) in serum albumin and serum triglycerides and the scores of physical functioning, role physical, role emotional and overall physical health was compared by using Mann-Whitney U test (Graphpad InStat version 3.06, Sep 2003). Baseline values of the two groups were compared to detect homogeneity of the two groups. Unpaired T test or Mann-Whitney U test was used for comparison of age, duration of hemodialysis, number of units of blood transfused and baseline SF-36 component and total scores and Fisher's Exact test was used to compare male: female ratio between the two groups. A responder rate analysis was also done. Increase in total SF-36 score after eight weeks by atleast 10 was considered as response. Difference in proportion of responders in the two groups was compared by using Fisher's Exact test. For all statistical tests a p value of less than or equal to 0.05 was considered as significant. Sample size of ten patients in each group assuming baseline standard deviation of 10 units in total SF-36 score was calculated to yield power of at least 80% at 5% significance level to detect a difference between the two groups of at least 18 units of difference (from baseline) in the total SF-36 score. Sample size was calculated using Compare2 version 1.09, part of WINPEPI suite.^[9]

RESULTS

The study was initiated in January 2005 and completed in November 2005. Twenty six patients were screened. Six patients did not

fulfill the inclusion/exclusion criteria. Twenty patients were finally enrolled in the study. All the enrolled patients from both the groups completed the study duration of eight weeks. Data of all the twenty patients was included for analysis (See flow chart in appendix II). All patients followed the dietary restrictions. Patient demographics and baseline characteristics are depicted in [Tables 1, 2 and 3]. There was no significant difference in demographics, baseline SF-36 total and component scores and other baseline parameters of the two groups except serum creatinine which was significantly higher in the L-carnitine group. During the study duration of 8 weeks, all patients received furosemide 100 mg twice daily orally, six patients each from both the groups received ferrous fumarate 300 mg once daily and the remaining four patients each from both the groups received ferrous fumarate 200 mg once daily. Two patients from L-carnitine group received two doses each and one patient received three doses of subcutaneous (SC) erythropoietin 2000 IU. In the placebo

group, two patients received two doses each of erythropoietin 2000 IU, one patient received three doses of 2000 IU and one patient received two doses of erythropoietin 4000 IU.

All participating patients were able to answer the SF-36 questions independently. Results of QoL scores and laboratory parameters in the two groups are shown in [Table 2 and Table 3] respectively. The total SF-36 QoL score increased by 18.29 ± 12.71 in L-carnitine group while it decreased by 6.4 ± 16.39 in the placebo group. As compared to placebo, L-carnitine resulted in significantly greater increase in the total SF-36 score, the overall physical health score, overall mental health score and the scores of the components physical functioning, general health, vitality social functioning and mental health. The scores for role physical, bodily pain and role emotional also followed similar trend but significant difference between L-carnitine and placebo was not observed. Nine out of ten (90%) patients turned out to be

Table 1: Patient demographics and baseline characteristics

Particulars	L-carnitine	Placebo
Age (years: Mean \pm SD)	40.30 \pm 13.58	47.30 \pm 11.69
Sex (M/F)	10:0	8:2
Duration of hemodialysis (Months: Mean \pm SD)	9.20 \pm 2.25	9.6 \pm 2.50
Associated conditions (Number of patients)		
Hypertension	05	05
Diabetes mellitus with hypertension	02	03
Tuberous sclerosis	-	01
Chronic pyelonephritis	01	01
Chronic glomerulonephritis	02	-
Blood transfusion over the study duration of 8 weeks (Number of units: Mean \pm SD)	2.2 \pm 2.13	3.30 \pm 1.41
Time since last blood transfusion (Days: Mean \pm SD)	36.50 \pm 7.05	37.60 \pm 8.18
Con-comitant anti-hypertensive treatment	-	01
Nifedipine 10 mg BD	05	01
Nifedipine 20 mg BD	02	01
Nifedipine 10 mg plus Atenolol 50 mg BD	02	04
Amlodipine 5 mg plus Atenolol 50 mg BD	01	03
Losartan 50 mg plus hydrochlorothiazide 12.5 mg OD		

Abbreviations: M-Male, F-Female, SD-Standard deviation

Table 2: Effect of L-carnitine versus placebo on various components of and total SF36 scores in MHD patients

Parameter	Baseline		After 8 weeks		Difference (8 weeks -baseline) with 95% CI*		Median & IQR for difference†		P value
	L-carnitine	Placebo	L-carnitine	Placebo	L-carnitine	Placebo	L-carnitine	Placebo	
PF	29.50 \pm 17.70	35.00 \pm 25.27	56.00 \pm 23.06	30.50 \pm 21.00	26.50 \pm 20.28 (13.92 - 39.07)	-4.50 \pm 31.66 (-24.1 - 15.12)	32.5 (12.5)	-2.5 (43.75)	0.02
RP	35.00 \pm 21.08	42.50 \pm 16.87	50.00 \pm 11.78	47.50 \pm 7.90	15.00 \pm 21.08 (1.93 - 28.06)	5.00 \pm 19.70 (-7.22 - 17.22)	0 (25)	0 (0)	0.33
BP	30.90 \pm 19.80	35.80 \pm 16.27	48.60 \pm 22.80	39.20 \pm 17.03	7.70 \pm 133.01 (-2.76 - 38.16)	3.40 \pm 24.29 (-11.65 - 18.45)			0.28
GH	24.50 \pm 16.23	35.90 \pm 23.51	46.50 \pm 17.92	29.20 \pm 19.71	22.00 \pm 22.90 (7.80 - 36.19)	-6.70 \pm 22.38 (-20.57 - 7.17)			0.01
Vitality	28.50 \pm 17.48	43.00 \pm 26.58	39.50 \pm 23.97	24.00 \pm 16.63	11.00 \pm 30.62 (-7.98 - 29.98)	-19.00 \pm 32.30 (-39.01 - 1.01)			0.04
SF	47.50 \pm 24.15	56.25 \pm 22.24	61.25 \pm 12.43	35.00 \pm 11.48	13.75 \pm 30.30 (-5.03 - 32.53)	-21.25 \pm 25.71 (-37.19 - -5.30)			0.01
RE	20.00 \pm 28.10	36.66 \pm 18.92	50.00 \pm 28.32	46.66 \pm 17.21	30.00 \pm 36.68 (7.26 - 52.73)	10.00 \pm 27.44 (-7.00 - 27.00)	33.33 (66.66)	0 (25)	0.22
MH	43.20 \pm 25.90	55.60 \pm 25.60	53.60 \pm 18.39	37.20 \pm 13.86	10.40 \pm 24.95 (-5.06 - 25.86)	-18.40 \pm 25.52 (-34.21 - -2.58)			0.02
PH	29.68 \pm 9.89	38.44 \pm 14.05	48.12 \pm 12.48	34.08 \pm 11.18	18.44 \pm 15.41 (8.88 - 27.99)	-4.36 \pm 16.37 (-14.51 - 5.79)	20.8 (10.1)	-2.5 (16.8)	0.005
MH	32.70 \pm 15.61	45.48 \pm 18.25	50.17 \pm 11.10	34.41 \pm 12.66	17.43 \pm 15.02 (8.11 - 26.74)	-11.07 \pm 21.12 (-24.16 - 2.02)			0.002
Total SF-36	32.38 \pm 11.47	42.58 \pm 13.97	50.68 \pm 9.83	36.15 \pm 10.22	18.29 \pm 12.71 (10.41 - 26.17)	-6.4 \pm 16.39 (-16.59 - 3.73)			0.001

All values are expressed as mean \pm SD

Abbreviations: PF- Physical functioning, RP-Role physical, BP-Bodily pain, GH-General health, SF-Social functioning, RE-Role emotional, MH-Mental health, PH-Physical health, CI-Confidence interval, IQR-Interquartile range.

*Figures in parentheses are 95% CI

†Figures in parentheses are interquartile range expressed as Q1-Q3 and is calculated only for data showing non-normal distribution.

‡P value is for difference (8wks-baseline) between the 2 groups

Degree of freedom = 20-2 = 18

responders in the L-carnitine group while only one patient (10%) responded in the placebo group ($P=0.001$). This was an absolute risk reduction of 80% and relative risk reduction (RRR) of 88.88%. The number needed to treat (NNT) to achieve this advantage of risk reduction was 1.2.

Amongst the laboratory parameters evaluated, L-carnitine resulted in significant increase in hemoglobin and serum albumin and significant reduction in serum creatinine as compared to placebo. Hemoglobin in L-carnitine group increased from baseline of 7.22 ± 0.91 g/dL to 8.11 ± 1.48 while in the placebo group, there was a reduction in hemoglobin from 7.28 ± 0.77 to 6.81 ± 0.00 .

All the other parameters showed no significant difference between L-carnitine and placebo groups.

At baseline, all the patients from both the groups complained of muscle cramping, muscle weakness and fatigability and two patients each from both the groups suffered from intradialytic hypotension. After eight weeks treatment with L-carnitine, only two patients complained of muscle cramping, six patients each complained of muscle weakness and fatigability and one patient still suffered from intradialytic hypotension whereas in the placebo group, eight patients each complained of muscle cramping, muscle weakness and fatigability and one patient still

Table 3: Effect of L-carnitine versus placebo on laboratory parameters in MHD patients

Parameter	Baseline		After 8 weeks		Difference (8 weeks -baseline) with 95% CI*		Median & IQR for difference*		P value
	L-carnitine	Placebo	L-carnitine	Placebo	L-carnitine	Placebo	L-carnitine	Placebo	
Hb (g/dL)	7.22 ± 0.91	7.28 ± 0.77	8.11 ± 1.48	6.81 ± 0.00	0.89 ± 0.56 (0.53 - 1.24)	-0.47 ± 0.77 (-0.95 - 0.01)			0.001
Sr. Alb (g/dL)	2.72 ± 1.13	2.98 ± 0.14	2.85 ± 1.13	2.50 ± 0.49	0.13 ± 0.00 (0)	-0.48 ± 0.35 (-0.69 - -0.26)	0.15 (0.1)	-0.4 (0.5)	0.001
Sr. Cr (mg/dL)	10.21 ± 7.21	6.93 ± 0.84	8.37 ± 2.19	9.1 ± 1.13	1.84 ± 5.02 (-4.95 - 1.27)	2.17 ± 0.28 (1.99 - 2.34)	-1.15 (1.22)	1.4 (1.6)	<0.001
BUN (mmol/L)	155.53 ± 84	138.04 ± 5.51	132.19 ± 52.89	138.89 ± 16.75	-23.34 ± 31.11 (-42.62 - -4.05)	0.85 ± 11.24 (-6.11 - 7.81)			0.18
RBS (mg/dL)	112.59 ± 9.4	98.22 ± 8.27	104.89 ± 7.35	94.50 ± 7.63	-7.70 ± 16.75 (-18.08 - 2.68)	-3.72 ± 15.90 (-13.58 - 6.14)			0.51
TC (mg/dL)	168.63 ± 54.23	154.00 ± 22.98	149.41 ± 33.58	155.00 ± 7.7	-19.22 ± 20.64 (-32.01 - -6.42)	1.00 ± 30.68 (-18.02 - 20.02)			0.12
LDLC (mg/dL)	103.86 ± 28	97.61 ± 31.96	88.86 ± 21.14	94.32 ± 5.72	-15.00 ± 6.85 (-19.25 - -0.74)	-3.29 ± 15.90 (-19.54 - 12.96)			0.22
HDLC (mg/dL)	40.05 ± 14.14	33.58 ± 4.38	38.13 ± 5.58	33.46 ± 0.42	-1.92 ± 8.55 (-7.22 - 3.38)	-0.12 ± 3.95 (-2.57 - 2.33)			0.66
TG (mg/dL)	127.89 ± 60.66	152.97 ± 5.44	114.18 ± 37.19	135.76 ± 68.02	-13.71 ± 23.47 (-28.26 - 0.84)	-17.21 ± 62.57 (-55.99 - 21.57)	-3.8 (30.3)	8.1 (56.07)	0.43

All values are expressed as mean SD

Abbreviations: Hb-Hemoglobin, Sr. Alb-Serum albumin, Sr.Cr- Serum creatinine, BUN-Blood Urea Nitrogen, RBS-Random blood sugar, TC-Total cholesterol, LDLC- Low density lipoprotein cholesterol, HDLC- high density lipoprotein cholesterol, TG-Triglycerides, CI-Confidence interval, IQR-Interquartile range.

Figures in parentheses are 95% CI

* Figures in parentheses are interquartile range expressed as Q1-Q3 and is calculated only for data showing non-normal distribution.

@ P value is for difference (8wks-baseline) between the 2 groups

Degree of freedom = 20-2 = 18

suffered from intradialytic hypotension. Taken together, dialysis related symptoms were relieved in four out of ten patients in L-carnitine group and two out of ten patients in the placebo group. Thus more number of patients from L-carnitine group were relieved of dialysis related symptoms although the difference was not statistically significant.

L-carnitine and placebo were well tolerated by all the patients.

DISCUSSION

L-carnitine showed significantly greater increase than placebo in the primary efficacy end-point of total SF-36 score. The 95% confidence interval (CI) for placebo included zero whereas the lower limit of 95% CI for L-

carnitine was higher than ten. Increase in SF-36 score by 10 has a strong clinical significance. Each 10 unit decrease in SF-36 score has a relative risk of death of 2.07 ($P=0.02$) and relative risk of hospitalization of 1.27 ($P=0.041$). Each 10 unit decrease in overall mental health score has even stronger association with mortality, the relative risk of death for each 10 unit decrease in this score is 2.46 ($P<0.01$).^[4]

Among the secondary efficacy end-points, L-carnitine showed significantly greater increase in hemoglobin as compared to placebo while there was no significant difference between the two groups in other secondary efficacy endpoints. L-carnitine also resulted in greater increase in serum albumin and a greater reduction in serum creatinine

as compared to placebo. Increase in hemoglobin and albumin had been found to have significant correlation with the SF36 QoL score.^[4] No significant effect of L-carnitine on lipid parameters was observed in this study. Beneficial effect of L-carnitine on renal anemia has been demonstrated even in the pre-erythropoietin era; later, L-carnitine has been shown to reduce erythropoietin dose requirements.^[10] The proposed mechanism of beneficial effect of L-carnitine is modification of lipid composition and intensification of Na-K pump function in RBC membranes eventually resulting in increased half-life of the RBCs.^[11-13] A beneficial effect on erythroid precursors has also been postulated.^[14] Changes in creatinine observed in this study are rather intriguing. A closer look at 95% CI of change in serum creatinine indicates that, it includes zero for the L-carnitine group and the lower CI is 1.99 for the placebo group. This indicates that L-carnitine has not resulted in improved renal function; it may have prevented deterioration seen in placebo group. However change in creatinine was not paralleled by change in BUN in the L-carnitine group. Though increase in serum creatinine can be regarded as a marker of improvement in nutritional status, it was not paralleled with increase in serum albumin in the placebo group. This raises the suspicion that change seen in serum creatinine is just an effect "Regression to mean".

Results of this study are partly in accordance with a report by Sloan RS *et al.*^[15] In the study by Sloan RS *et al*, oral L-carnitine had early positive effect on QoL while prolonged supplementation beyond 3 to 4.5 months was not associated with improvement in QoL. The

poor association observed in this study may be attributed to the oral route of administration. Studies have shown that only 15% of an oral dose of L-carnitine is absorbed and the NKF guidelines specifically recommend IV L-carnitine supplementation.^[16] Moreover about 12 months may be required for replenishment of tissue carnitine stores. This may be the reason why in this study also all the patients from L-carnitine group were not relieved of dialysis related symptoms within eight weeks.

Findings of this study are again only partly in accordance with a previous study by Brass *et al.*^[7] In the later, L-Carnitine significantly improved the fatigue domain of the Kidney Disease Questionnaire compared with placebo but did not significantly affect the total score or other domains of the instrument.

Results of this study are substantiated by a very recent double-blind, randomized, controlled study, in 50 hemodialysis patients.^[17] In this study, the role-physical and SF-36 physical component summary scores improved significantly from baseline in the L-carnitine group compared to changes in the control group.

Responder rate analysis shows that L-carnitine provided RRR of 88.88% and the NNT was also small (1.2). This implies that almost every additional patient treated with L-carnitine may get the benefit of improvement in SF-36 by at least 10 which is expected to significantly lower the risk of death and hospitalization in that patient had he/she been not receiving L-carnitine. It would

therefore be advisable to follow L-carnitine supplementation to almost all of the MHD patients having poor QoL. In fact IV L-carnitine supplementation has been approved by the US-FDA in hemodialysis patients experiencing malaise, muscle weakness, cardiomyopathy and arrhythmias. The Dialysis Outcomes Quality Initiative (DOQI) clinical practice guidelines also recommend L-carnitine in individuals who manifest symptoms such as malaise, muscle weakness, intradialytic cramps and hypotension, EPO-resistant anemia and poor QoL and who have not responded adequately to standard therapies.^[16]

Smaller sample size and single blind design are two major limitations of this study. As a result, the study population appears to be a selected subset of ESRD patients. This reflects in much higher proportion of males in the study. This should not pose any threat to statistical validity of the study as the trend is there in both the groups. Extrapolation of results to female patients may however pose the question of external validity. Smaller sample size has not permitted multivariate analysis to detect association between laboratory parameters and change in QoL. Normal baseline lipid profile of both the groups might have obscured the effect of L-carnitine on lipid profile. This could have been prevented by keeping hyperlipidemia also as an inclusion criterion. Baseline serum creatinine was significantly higher in L-carnitine group which may have an impact on QoL. Infrequent schedule of administration of erythropoietin in both the groups is not expected to influence results of the primary and secondary efficacy end-points. Apparently it appears that the SF-

36 scores were lower in L-carnitine group than in placebo at baseline. Statistical analysis however confirms that there was no significant difference in baseline scores of the two groups. Even if these lower scores in L-carnitine group are considered clinically significant, it only indicates that L-carnitine improves QoL in those MHD patients who have poor QoL. The strength of this study is that, this is one amongst the few studies to assess the impact of L-carnitine on QoL in MHD patients and possibly the first in Indian ESRD patients. The dialysis set-up with infrequent use of erythropoietin and IV iron reflects more realistic subset of Indian MHD patients with limited resources. Given the limitations and strengths of this study, more elaborate and larger scale studies are required to confirm the effect of L-carnitine on QoL in MHD patients.

CONCLUSION

Compared to placebo, L-carnitine improved quality of life in MHD patients with an increase of 18.29 ± 12.71 in the total SF36 score within 8 weeks of treatment. L-carnitine also significantly improved hemoglobin, serum albumin and serum creatinine levels as compared to placebo.

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Appendix I: Flow diagram of the progress through the phases of a randomized trial (enrollment, intervention allocation, follow-up and data analysis)