Is there a Role for Oral L-Carnitine Therapy in Anemia and Cardiac Dysfunction Management in Egyptian Patients on Maintenance Hemodialysis?

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ABSTRACT

Aim: *L-carnitine is a short organic hydrosoluble molecule and is present in biological materials like free carnitine and acylcarnitines, which constitute the carnitine system. Long-term intermittent hemodialysis is associated with a reduction in plasma and tissue L-carnitine levels. Available studies on carnitine supplementation suggest the use of this molecule in dialysis, especially for those patients with cardiac complications, impaired exercise and functional capacities, and increased episodes of hypotension. Moreover, in some patients, the improved stability of erythrocyte membranes with L-carnitine supplementation may decrease erythropoietin requirements, thus leading to a reduction of dialytic costs. To study if there a possible advantageous effects for L-carnitine oral supplementation in anemia and cardiac dysfunction management in a cohort of Egyptian patients on maintenance hemodialysis.*

Methods: *Fifty-five patients with chronic renal failure on maintenance hemodialysis were classified into 2 groups:* ***L-carnitine group:*** *20 patients (12 male and 8 female, mean age 47.66±17.73 years, hemodialysis duration 51.36±18.14 months, subjected to three sessions/week reaching a Kt/V of 1.49±0.37) they received oral L-carnitine therapy 1.500 mg/day and* ***control group:*** *35 patients (24 male and 11 female, mean age 37.9±14.7 years, hemodialysis duration 53.83±15.17 months, subjected to three sessions/week reaching Kt/V of 1.33±0.23). Both groups were on Erythropoietin therapy and IV iron whenever indicated. Echogardiographic studies were performed before and at the end of the study.*

Results: *Serum hemoglobin were comparable in the L-carnitine group and control group at the start and six months after therapy (8.63±1.77 and 9.39±2.02 gm/dl, p= 0.18, 10.49±1.65 and 10.92±2.48 gm/dL p= 0.76 respectively). The weekly maintenance dose of Erythropoietin in spite of being lower in L-carnitine group (80.16±35.61 units/kg) compared to control group (91.9±38.21*

units/kg) it does not reach a statistical significance (p= 0.20). No significant improvement could be observed in echogardiographic findings in the L-carnitine group after therapy.

Conclusion: *The role of L-carnitine in hemodialysis patients is questionable. Our study revealed no observed significant improvement in echocardiographic findings 6 months after therapy. However, -a statistically non significant-reduction in Erythropoietin dose was achieved in the L-carnitine-treated compared to the control group while maintaining comparable target hemoglobin in both groups. Long-term studies including larger number of patients are required to clarify its role in hemodialysis patients.*

Key words: *L-carnitine, hemodialysis, anemia.*

INTRODUCTION

Carnitine (3-hydroxi-4-*N*-trimethylammoniobutanoate) is a short organic hydrosoluble molecule and is present in biological materials like free carnitine and acylcarnitines, which constitute the carnitine system.

In humans, carnitine plays a pivotal role in energy metabolism through the transportation of long-chain fatty acids across the inner mitochondrial membrane and controlling the rates of beta oxidations of long-chain fatty acids with subsequent energy production (1).

The endogenous plasma levels of L-carnitine in the healthy human (L-carnitine + acylcarnitines) are 40–50 mmol/L; acetyl-L-carnitine (the most abundant acylcarnitine) levels are usually 3–6 mmol/L. Nonetheless, plasma carnitine only account for approximately 1% of the total body carnitine pool, with over 98% of carnitines present in the skeletal and cardiac muscles. A small amount is also present in the kidney, liver and brain (2,3).

Hemodialysis (HD) may promote excessive losses because filters do not allow carnitine reabsorption. Serum carnitine is considered a problem when it is lower than 20 µmol/L. Plasma concentration of free carnitine is in dynamic balance with that of acylcarnitines, and the acyl to free carnitine ratio is considered normal when it is ≤0.4.HD involves carnitine as one of the solutes capable of crossing the dialyzer membrane through osmosis. Dialysis therapy in uremic patients determines a decrease in both free carnitine and plasmatic acylcarnitines after only 6 months of dialysis treatment (4).

It has been observed that the palmitoiltransferase carnitine activity is reduced in the skeletal muscle and in the red cells of the dialysis patient (5).

Anemia is an independent risk factor for the development of heart failure and a predictor of mortality in dialysis patients (6). Furthermore, recombinant Human Erythropoietin (rHuEPO) resistance has been associated with congestive heart failure and dialysis-related hypotension. Therapies that could improve hyporesponsive rHuEPO-dependent anemia thus would be beneficial. L-carnitine therapy was reported to be an effective treatment for these problems associated with anemia (7).

Supplemental carnitine may protect cardiac muscles against oxidative stress, hypoxia, and ischemia (8).

A number of studies have shown improvements in cardiac function in patients with kidney failure associated with carnitine therapy (9,10), however, many of these studies were small or not well controlled.

Until now, the debate over carnitine use in dialysis patients has not been solved. With all these results in mind we conducted this study to investigate whether there is any possible role for oral L-carnitine supplementation in anemia and cardiac dysfunction management in a cohort of Egyptian patients on maintenance hemodialysis.

MATERIAL AND METHODS

We conducted this prospective controlled study to investigate the role of oral L-carnitine supplementation in chronic renal failure (CRF) patients on maintenance HD and possible effects on reversing uremic cardiomyopathy and reduction in rHuEPO dose.

Patients were recruited from the maintenance HD populations at Mansoura Urology and Nephrology Center units during the period from Janurary 2006 till June 2006, Fifty- five patients were included. Patient enrollment requirements included a diagnosis of ESRD, HD treatment three times weekly for a period of at least 6 months, age older than 18 years, secondary causes of erythropoietin resistance were excluded (malignancy, infection, inflammation, thyroid disorders,….). Patients with claudication were

excluded from participation. During the screening period, it was also confirmed that patients were effectively dialyzed and unlikely to require changes in dialysis prescription. This assessment was based on stability in urea clearance, assessed by Kt/V at a value greater than 1.2 with less than 20% variation during the previous 3 months, during which time postdialysis weight had to be stable within 3 kg.

Laboratory Investigations

Baseline blood samples were obtained to define baseline predialysis chemistry (Blood urea nitrogen, creatinine, calcium, phosphorus, sodium, potassium, complete blood count, iron studies- serum iron, ferritin, transferrin saturation-, and liver function test).

Echocardiographic Studies

Transthoracic Echocardiography was done for patients on L-carnitine therapy before starting therapy and repeated 6 months later by the same operator.

L-Carnitine Therapy

After baseline evaluations, patients were randomized to drug or placebo. L-carnitine group patients were administered 1500 mg L-carnitine orally at the termination of each dialysis session.

All treatment-emergent adverse events occurring during the course of the study were recorded.

Erythropoietin Therapy

Patients received erythropoietin therapy subcutaneously targeting hemoglobin levels between 11-12 gm/dL with supplemental iron saccharate therapy whenever indicated.

End of the Study

After 6 months all patients were re-assessed both clinically and laboratory by the same investigations done at the initiation of the study.

Statistical Analysis

It was performed using the statistical package for social studies (SPSS) for windows software package release 11. Results are presented as mean±SD for normally distributed data or median and confidence intervals for skewed data. Student *t*-test and Chi-squared test were applied as appropriate. A p value of ≤ .05 was considered significant. This study was approved by our local Institutional Research and Ethics board.

RESULTS

Demographic Criteria

Both groups were comparable regarding gender distribution (male/female 12/8 and 24/11 in L-carnitine and control groups respectively, (p= 0.36), HD durations (51.36±18.14 and 53.83±15.17 months, (p= 0.86). Patients in L-carnitine group were elder (47.66±17.73 years) compared to control group patients (37.9±14.7 years) however the difference was not statistically significant (p= 0.06).

No statistical difference was observed regarding neither the cause of ESRD in both groups nor the dose of dialysis (Data are given in Table 1).

Hematological Studies

At the start and six months after therapy serum hemoglobin were comparable in the L-carnitine group and control group (8.63±1.77 and 9.39±2.02 gm/dl, p= 0.18, 10.49±1.65 and 10.92±2.48 gm/dl p= 0.76 respectively).

The weekly maintenance dose of Erythropoietin despite being lower in L-carnitine group (80.16±35.61 units/kg) compared to control group (91.9±38.21 units/kg) it does not reach a statistical significance (p= 0.20). Both groups were comparable regarding number of patients (8 in L-carnitine and 11 in control group (p= 0.55) receiving IV iron and monthly dose of IV iron therapy (250±34.165 in L-carnitine and 187±22.65 mg in control group, P = 0.14). Also serum ferritin were comparable (543.81±49. 63 in L-carnitine and 538.75±83.31 ng/ml in control group, p= 0.97) in L-carnitine and control groups respectively (Data are given in Table 2).

Echocardiographic Studies

No significant improvement could be observed in echogardiographic findings in the L-carnitine group after therapy (Data are given in Table 3).

DISCUSSION

Our study showed that 6 months oral L-carnitine supplementation in Egyptian HD patients resulted in decrease in Erythropoietin requirement-nevertheless this is a nonsignificant finding-while maintaining comparable hemoglobin level compared to the control group, meanwhile no much improvement was observed regarding echocardiographic findings.

In healthy individuals, plasma and tissue levels of L-carnitine remain relatively constant because of ho-

Table 1. Demographic data for fifty- five patients included in the study.

Group/parameter (Mean±SD)	L-carnitine (20 patients)	Control (35 patients)	p value
Male/female	12/8	24/11	0.36
HD duration (Months)	51.36±18.14	53.83±15.17	0.86
Age (years)	47.66±17.73	37.9±14.7	0.06
Original kidney disease			
Unknown	4	5	
DM	4	5	
HTN	3	5	
PKD	2	2	
Hereditary nephritis	0	1	
Pregnancy related			0.61
Graft failure	2	2	
NS	2	7	
GN	0	2	
SLE	1	2	
PUV	1	2	
	1	2	
Kt/v	1.49±0.37	1.33±0.23	0.07

DM: Diabetes mellitus, HTN: Hypertension, PKD: Polycystic kidney disease, NS: Nephritic syndrome, GN: Glomerulonephritis, SLE: Systemic lupus erythematosis, PUV: Posterior uretheral valve.

Table 2. Hematological parameters in both groups before and at the end of the Study.

Parameter	L-carnitine Group	Control group	p Value
Hemoglobin (gm/dl)			
Before	8.63±1.77	9.39±2.02	0.18
After	10.94±1.65	10.92±2.48	0.76
Maintenance weekly Erythropoietin dose (units/kg).	80.16±35.61	91.9±38.21	0.20
Erythropoietin duration (months)	16.73±2.0	10.90±2.21	0.16
Serum ferritin (ng/ml)	543.81±49.63	538.75±83.31	0.97
IV iron (dose) mg/month	250±34.16	187±22.65	0.14

meostatic control mechanisms. The healthy human kidney has a vital role in this control, primarily through extensive and saturable tubular reabsorption, synthesis of L-carnitine, and selective excretion of short chain carnitine esters. HD lacks the homeostatic control mechanisms involved in the conservation of L-carnitine.

The principal biological role of L-carnitine is to facilitate the transport of fatty acids across the inner mitochondrial membrane (11).

Studies done to identify L-carnitine levels in HD patients revealed that before starting maintenance hemodialysis mean predialysis plasma levels were slightly greater than the normal range (> 50 mmol/L), indicating L-carnitine accumulation in uremia caused by impaired renal excretion of the molecule. However, during the first month of hemodialysis therapy, plasma L-carnitine concentrations declined by approximately 30%, and after 12 months they had decreased by approximately 40%, with a pattern suggesting an ongoing decline (12).

Table 3. Echocardiographic findings before and after L-carnitine therapy.

Measurement (Mean±SD)	Before	After	p Value
Left ventricular end systolic dimension (cm).	7.64±1.05	7.54±1.07	0.77
Left atrial dimension (cm).	4.23±.28	4.07±.53	0.31
Right ventricular dimension (cm).	1.88	1.79	0.97
Interventricular Septum (cm).	1.24±.46	1.31±.93	0.51
Posterior wall (cm).	1.11±.38	1.36±.b5	0.18
Ejection fraction (%).	72.4±1.9	60.09±5.4	0.67
Fractional shortening (%).	43.7±7.7	38.9±6.5	0.95

L-carnitine is not bound to plasma proteins and therefore is freely filtered at the

Glomerulus (13). However, at plasma concentrations greater than approximately 60 mmol/L, fractional reabsorption begins to decrease because of partial saturation of the tubular transporter (14).

L-carnitine is efficiently removed from blood during HD. Within a single HD session, plasma L-carnitine levels decrease by approximately 70% to 75%. Plasma clearance of L -carnitine during HD is approximately 7.8 L/h, or 130 mL/min. This is at least 30 times greater than the expected renal clearance of L-carnitine in a healthy individual (1 to 3 mL/min). However, HD is an intermittent process (typically 12 h/wk), whereas renal clearance is continuous; thus, direct comparisons are not meaningful. Compared with the roles of the normal human kidney, the HD procedure is more effective in removing L-carnitine from the body and lacks the ability to conserve L-carnitine when plasma levels decline. Moreover, hemodialysis tends to promote a greater acyl-L-carnitine to L-carnitine ratio than the healthy kidney (3).

In conclusion, patients on chronic HD therapy are likely to have a dialysis-associated carnitine disorder (DCD) in which a secondary carnitine deficiency arises because of a combination of factors: inadequate intake, impaired renal synthesis of carnitine and its efficient removal by HD. In addition to the absolute deficiency of L-carnitine encountered with a DCD, there is disruption of the normal ratio of free to acylcarnitines (15).

A large number of studies have been conducted over the past 20 years to assess the efficacy of supplemental L-carnitine in treating certain dialysis-related clinical disorders. However, many of these studies have been small, retrospective trials, and few blinded, placebo-controlled, large-scale trials have been conducted. In addition, the prescription of L-carnitine (e.g. dose, route, duration of treatment) and patient population (e.g. dialysis age) differ greatly from one study to the next, making between-study comparisons difficult.

Anemia is a well-recognized complication of chronic kidney disease and ESRD (15).

Anemia is an independent risk factor for the development of heart failure and a predictor of mortality in dialysis patients. Furthermore, EPO resistance has been associated with congestive heart failure and dialysis-related hypotension. L-carnitine therapy was reported to be an effective treatment for these problems associated with anemia (6).

There is also a convincing evidence for Studies conducted before the availability of rHuEPO focused on the efficacy of L-carnitine in correcting anemia in HD patients (10,17).

Results of studies investigated the rule of L-carnitine as adjuvant for the treatment of rHuEPO hyporesponsivness in HD patients show inconsistencies while several studies have reported the therapeutic effects of L-carnitine in hemodialysis patients others failed to confirm this.

Matsumoto et al (18) evaluated the effects of 3 months of treatment with L-carnitine (500 mg/day oral) on anemia in a hemodialysis patient resistant to erythropoietin treatment. The results showed an increase in hematocrit levels and total ability of iron binding together with a significant reduction of ferritin serum levels. Our data are not in agreement with Matsumoto et al inspite we used a higher doses of L –carnitine (500 mg/TID) with the same route of administration (oral) and longer duration (6 months). A difference in the study population, serum carnitine

levels – not measured in our study - may explain this controversy.

Also, Nikolaos et al (19) showed that 3 months of treatment with L-carnitine (30 m/kg for dialysis session) significantly reduces the deformability of red blood cells and significantly increases hematocrit.

In 1995 Labonia (20) showed a 38.1% reduction in rHuEPO dose after 6 months of therapy with L-carnitine, 1 g IV postdialysis, whereas there was no change in rHuEPO dose requirement in the placebo group. Our data are not in agreement with this study – as we only obtained 14% reduction in EPO dose, the difference in the administration route of L-carnitine between our study (oral) and labonia study (IV) may explain this inconsistency in results.

Meanwhile not all patients assigned to L-carnitine therapy in this study responded to therapy as only 7 patients – out of 13 patients - responded with a reduction in rHuEPO dosing requirement, whereas the others had no change. Responders had a tendency toward a greater mean rHuEPO requirement and greater endogenous erythropoietin levels at baseline. There was no correlation between serum carnitine level and response.

Our data are in agreement with what was reported by Kletzmayr et al (21) who obtained a 36.9% rHuEPO dose reduction in 8 of 19 patients treated with IV L-carnitine. However, when all L-carnitine treated patients were considered together, there was no significant change in rHuEPO dose. Patients responding to L-carnitine therapy had greater total serum carnitine levels at baseline than no responders; we did not measure L-carnitine serum level as no correlation between individual rHuEPO requirement and carnitine level was documented in that study.

In spite we used a high oral dose of L-carnitine we did not observe a sound response regarding rHuEPO saving effect, in concordance with our observation Kletzmayr J et al (21) was not able to show a clear advantage of low- or high-dose L-carnitine supplementation (25 mg/kg).

Indeed, Caruso et al (22) showed no overall effect of L-carnitine on hemoglobin level after 6 months of treatment in their entire population, but patients older than 65 years receiving L-carnitine needed a lower rHuEPO dose to maintain their hematocrit level 3 months after the end of trial, compared with elderly patients not receiving L-carnitine (22).

Two other studies showed no benefit of L-carnitine on anemia- related parameters (23,24) one of which involved iron-deficient pediatric patients (24).

We did not measure L-carnitine serum level because in 1994 the American Association of Kidney disease Consensus Group noted that plasma carnitine levels have not been shown to be good predictors of the clinically effective carnitine dose (25).

In our study we used L-carnitine without discrimination between those responsive and hyporesponsive patients aiming for EPO dose reduction even in responsive patients.

A number of studies have shown that the patient population appears to be separated into 'responders' and 'non-responders' (21,22). Although in all of these studies, the division of patients into these subgroups was retrospective, responders had higher baseline levels of all carnitines compared with non-responders, therefore it was suggested that 'severely carnitine-depleted patients might need a higher dosage or longer supplementation of carnitine in order to reduce the rHuEPO requirement'. However the apparent subgrouping of patients as responders and non-responders needs to be investigated further.

The salutary effects of L-carnitine on anemia center on improvement of erythrocyte survival, specifically through enhanced erythrocyte membrane stability (19,26,27).

Conversely, Kletzmayr et al (21) were unable to confirm an increase in erythrocyte survival time in a small number of L-carnitine–treated patients.

There are several additional cellular-based mechanisms that might explain the effect of L-carnitine on the erythropoietic process. rHuEPO resistance has been correlated with elevation of levels of inflammatory mediators, interleukin-6, tumor necrosis factor-α, and interferon (28). Ceramide is an intracellular mediator of apoptosis and thus would be involved in the life spans of erythroid precursors or mature erythrocytes. Therefore, inflammatory cytokines and other humoral factors seem to be associated with rHuEPO resistance and decreased erythroid colony formation.

The impact of L-carnitine on tumor necrosis factor-α, ceramide, and lipid peroxidation may help explain its positive effects on rHuEPO requirements and anemia correction. IV L-carnitine treatment led to a significant reduction in plasma malondialdehyde levels in a set of HD patients (29).

Cardiac disease is the leading cause of death among patients with ESRD accounting for almost half of all deaths in patients with and without diabetes (30).

Results of studies done to investigate the role of L-carnitine therapy in improvement of myocardial function in HD patients also are not consistent. Although mounting evidence exists in favour of the role of L-carnitine in the treatment of left ventricular dysfunction, other studies have been performed with negative results (31,32).

In our study no significant improvement observed regarding myocardial function assed by echocardiographic studies.

In agreement with our results, in a long-term controlled study, effects on LV function were examined (33). L-carnitine, 1 g, was administered IV at the end of each dialysis session for at least 3 years. There were no significant changes in LVEDV or cardiac output compared with controls. Meanwhile, Ahmad et al (6) showed no difference in electrocardiograms in patients treated with L-carnitine.

The influence of L-carnitine administration on fatty acid metabolism was studied using iodine 123-labeled -methyl-*p*-iodophenylpentadecanoic acid (BMIPP) myocardial scintigraphy (34). Echocardiography showed no changes in LVEDV. The investigators concluded that the aberrations in myocardial fatty acid metabolism were improved by carnitine administration and the period for carnitine administration may have been too short for translation of the cardiovascular biochemical benefit to an increase in Ejection Fraction (EF).

We also could assume that this improvement in myocardial fatty acid may precede the improvement in myocardial function detected by echocardiography in our series.

A number of studies have shown improvements in cardiac function in patients with kidney failure associated with carnitine therapy. However, many of these studies were small or not well controlled.

Our data are not in agreement with what reported Wanic-Kossowska M et al (35) who showed a statistically significant improvement of systolic and diastolic function of left ventricle.

Daniel F et al (36), also described in L-carnitine-treated patients, LVEDVs and LVESVs were significantly less than for placebo treated patients at 3, 6, and 12 months. EFs were significantly greater for carnitine treated versus placebo-treated patients at 3 months, but statistical significance disappeared at 6 and 12 months.

In another study the effects of 500 mg/d of oral carnitine for 6 months on symptoms of cardiac disease were studied in nine hemodialysis patients (18). Carnitine resulted in improvements of 11 out of 13 symptoms, including dyspnea on exertion, palpitations, and chest pain. EF increased from 44.9%±12.2% to 53.8%±13.8%. LV mass, measured in five randomly selected patients by magnetic resonance imaging, also significantly decreased by 18.3%. Thus, carnitine therapy was associated with partial correction of aberrant carnitine metabolism, improvement in patient symptoms, and improved measures of cardiac size and function.

Romagnoli et al (7) examined the addition of L-carnitine to conventional therapy in 11 hemodialysis patients with impaired LV function. A progressive improvement in mean LVEF was observed throughout the study, increasing from 31% to 41% overall. The clinical status of the patients' heart failure also was reported to improve, leading the investigators to conclude that L-carnitine was useful as an adjuvant therapy for dialysis patients with LV dysfunction. However these figures should be taken with caution as in this study all patients had been administered digitalis, and 10 patients had been administered ACE-inhibitor therapy, which is not the case in our study.

In Conclusion, the role of L-carnitine in Egyptian hemodialysis patients is still questionable. Our study revealed no observed significant improvement in echocardiographic findings 6 months after therapy. However, -a statistically non significant- reduction in Erythropoietin dose was achieved in the L-carnitine-treated compared to the control group while maintaining comparable target hemoglobin in both groups. Although numerous studies have demonstrated that L-carnitine is beneficial for the treatment of dialysis-related disorders, little is known about the specific patient groups for which L-carnitine supplementation provides the most benefit.

However, additional randomized controlled trials of sufficient power to clarify the mechanism of action and correlation of carnitine level with clinical efficacy may lead to an enhanced understanding of the beneficial effect of L carnitine on anemia in maintenance dialysis patients in the future.

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