Effect of Oral L-carnitine Supplementation on the Mortality Markers in Hemodialysis Patients

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ABSTRACT

Hemodialysis (HD) is a process of purifying the blood of a person whose kidneys are not working normally. HD patients have high mortality rate compared with general population. Serum albumin, alkaline phosphatase, white blood cell count and monocyte count were recognized as mortality markers in HD patients. L-carnitine is small endogenous molecule that its level tends to be low in HD patients. Reduced L-carnitine input in HD patients, due to low intake, impaired absorption, and reduced L-carnitine biosynthesis by kidney, combined by absence the homeostatic control of the kidney is probably behind low L-carnitine level in HD patients. This study aimed to evaluate the effect of oral L-carnitine supplementation on the mortality markers in HD patients. In this controlled clinical trial, 40 HD patients, maintained at least 6 months on HD, were randomly allocated into 2 groups: L-carnitine group in which the HD patients supplemented daily with 1000mg oral L-carnitine and control group in which the HD patients just observed (without L-carnitine supplementation), 8 weeks for both group. Blood was taken from all patients at start of study and after 8 weeks to measure the level of serum albumin, ALP, and both WBC and monocyte counts. This study showed a non-significant effect on all studied mortality markers by L-carnitine supplementation, so it can be concluded that oral L-carnitine supplementation has limited benefit to improve mortality markers in hemodialysis patients.

Keywords: Hemodialysis, L-carnitine, mortality markers.

INTRODUCTION

Chronic kidney disease (CKD) defined as progressive loss of kidney functions occurring over several months to years. Based on structural kidney damage and/or change in the glomerular filtration rate (GFR), National Kidney Foundation (NKF) staged the CKD into five stages: stage 1 to stage 5. In stage 5 CKD; there is a complete or almost a complete failure of kidneys so that patients cannot stay a live without the intervention with one of the three modalities of renal replacement therapy (RRT): hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation. Hemodialysis is process that facilitates removal of excess water and toxins from the body by removing the blood from the patient to a special machine (artificial kidney) and then returning it to the patient’s bloodstream.

In spite the large improvement over the past decades, it still mortality rate in HD patients is at least six to seven times than general population, even after adjustment of the age, gender, race, and primary cause of death, and only 50 % of dialysis patients are still alive three years after start of dialysis therapy. Cardiovascular diseases, collectively, are the major cause of death and contribute to about half of deaths in this population. The risk of death due to CVD in HD patients is about 10 to 30 times than general population. Infection is the second highest cause of death in HD patients.

Over past years, many molecules or laboratory findings were recognized to be as mortality markers in HD patients, for example; C-reactive protein, alkaline phosphatase, low albumin, white blood cell (WBC) count, and monocyte count. Actually, all the above mentioned mortality markers are also inflammatory markers which reflect the vital role of the inflammation in contributing to the mortality in this population. L-carnitine is endogenous, low molecular weight (161.2KDa), polar, and highly soluble compound that found in all animal species, in many microorganisms, and in many plants. L-carnitine plays a vital role in fatty acid oxidation, by facilitating transport of long chain fatty acids across the inner mitochondrial membrane to matrix of mitochondria, where fatty acid oxidation occurs. L-carnitine also involved in modulation of the acyl CoA / CoA ratio in cellular compartments, in shuttling of short and medium chain acyl groups from peroxisomes to mitochondria, and in removal of excess and unwanted acyl groups from the body. The Long term hemodialysis treatment is associated with significant reduction in plasma L-carnitine. Because of low molecular weight, high hydrophilicity, and lack of protein binding, L-carnitine is extensively removed by the HD process, and about 74% of plasma L-carnitine lost in each dialysis session. However, combination of reduced L-carnitine input in HD patients by one or more of impaired absorption, reduced intake of L-carnitine, and reduced L-carnitine biosynthesis by kidney with the absence the...
The homeostatic control of the kidneys is probably behind the reduced L-carnitine level in this population.

This study aimed to evaluate the effect of oral L-carnitine supplementation on the mortality markers in HD patients.

**METHODS**

This study was designed as multicenter randomized controlled clinical trial with 8 weeks follow up period at dialysis units in Al-Yarmouk teaching hospital, Al-Kindi general teaching hospital, and Al-Karama teaching hospital. The HD patients were randomly allocated to two groups: control group in which the HD patients just observed for 8 weeks (without L-carnitine supplementation), and L-carnitine group in which the HD patients receive L-carnitine tablet 1000 mg daily. Every 4 weeks, at maximum, patients in L-carnitine group were observed and asked for presence of any unusual side effects for L-carnitine.

Fourty patients of both sexes, which were on hemodialysis for at least 6 months, were included in this study. Patients younger than 40 years old, smokers, those with acute or chronic liver disease, signs of infection, cancer, and those using steroids or statins were excluded from participation in this study.

Serum ALP and albumin were measured using chemistry analyzer, cobas c311, made by Roche Diagnostic. Hematological investigation of WBC count, and monocyte number were measured by automated hematology analyzer, CELL-DYN Ruby, manufactured by Abbott Diagnostics.

**Results**

This study clearly showed that there was no significant difference in demographic data between the control group and L-carnitine treated group as shown in (Table 1).

In addition to that there was no significant difference within the studied parameters at the baseline levels of albumin; Alkaline Phosphatase; WBC count; and monocytes count as comparing between the control group and L-carnitine treated group (Table 2)

Regarding the effects of supplementation of 1000 mg/day L-carnitine for 8 weeks showed no significant difference on all mortality markers (albumin; Alkaline Phosphatase; WBC count; and monocytes count) as compared with pre-treatment values within the same group (Table 3).

The same results were obtained in control group after 8 weeks of observation, except there was a significant increment in Alkaline Phosphatase levels as compared with baseline levels (Table 4).

While the results of supplementation of 1000 mg/day L-carnitine for 8 weeks showed no significant difference on all mortality markers, as compared with control group for the same duration of treatment (Table 5).

<table>
<thead>
<tr>
<th>Table 1: Demographic data &amp; baseline characteristic of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age( year)</td>
</tr>
<tr>
<td>F/M Ratio</td>
</tr>
<tr>
<td>Diabetes(N) %</td>
</tr>
<tr>
<td>Hypertension(N) %</td>
</tr>
<tr>
<td>Months on dialysis</td>
</tr>
<tr>
<td>Patients with symptomatic atherosclerosis disease (N) %</td>
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</table>

Values are presented as mean ± SD

<table>
<thead>
<tr>
<th>Table 2: Baseline difference between control and L-carnitine group</th>
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</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Albumin (gm/dL)</td>
</tr>
<tr>
<td>ALP (U/L)</td>
</tr>
<tr>
<td>WBC (103 cell/μL)</td>
</tr>
<tr>
<td>Monocyte (103 cell/μL)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD

<table>
<thead>
<tr>
<th>Table 3: Effect of 8 week of supplementation with L-carnitine on the mortality markers in L-carnitine group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
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<tr>
<td>----------------</td>
</tr>
<tr>
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</tr>
<tr>
<td>Monocyte (103 cell/μL)</td>
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</tbody>
</table>

Values are presented as mean ± SD
DISCUSSION

Many studies confirmed that the low serum albumin is prevalent and associated with higher mortality in HD patients. Malnutrition and inflammation are the main incriminated causes behind low serum albumin in HD patients. Theoretically, L-carnitine could improve inflammation & malnutrition due to its anti-inflammatory, anabolic, and protein balance improving effects. However, in reality, the results of studying L-carnitine supplementation on the serum albumin in HD patients are inconsistent. While Savica et al., Duranay et al., and Vesela et al. found that the intravenous L-carnitine administration had improved serum albumin in HD patients, Suchitra et al. and Ahmad et al. reported that there is no effect of intravenous L-carnitine on serum albumin. The most reasonable explanation of this inconsistency is that the inflammation & malnutrition are not well adjusted or even not adjusted at all, at least in some of these studies. In this presented study, the oral route was used for L-carnitine administration; therefore, whatever the results of this study were, they should not be compared with results from studies in which intravenous L-carnitine is used because the large metabolic and pharmacokinetic differences between the two routes. Before this study, two studies had evaluated serum albumin after oral L-carnitine administration in HD patients which are Orasan et al. and Mortazavi et al., and their results regarding serum albumin are compatible with the result of this study.

Regardless of the cause, the elevated ALP in HD patients had found to be associated with many bad outcomes including secondary hyperparathyroidism, reduced left ventricular ejection fraction, left ventricular hypertrophy, and the more importantly, increased mortality & hospitalization rate. Based on the claiming that L-carnitine has ability to reduce ALP levels in many animal studies, this study has tried to evaluate the effect of oral L-carnitine on the ALP levels in HD patients. After 8 weeks, the result of this study showed a significant increase (p=0.035) in ALP levels in the control group and only minor insignificant (p=0.490) increase at L-carnitine group, compared with their baseline. Although this study had showed that there is no significant (p=0.091) difference in ALP levels between L-carnitine group & control group after 8 weeks, it is not impossible to assume L-carnitine supplementation had prevented the significant increase in ALP level that occur in the control group. No identical studies are available to compare the result of this study on serum ALP with them. However there is a one, although not identical but it is relatively similar study in which the effect of L-carnitine on secondary hyperparathyroidism and bone metabolism in HD Patients has been evaluated. Over six months in this close study, the L-carnitine had been given intravenously for 44 HD patients while placebo for another 39 HD patients. One of the assessed parameters between the two groups was bone alkaline phosphatase (b-ALP), which represents a significant portion of the total ALP that measured in the presented study. As with presented study, there is insignificant difference in b-ALP between L-carnitine group & control group after six months, but in contrast to presented study, there was significantly decrease in b-ALP in both L-carnitine group & control group. The limitation of the presented study on ALP result is that although all the patients at the start of enrollment in this study had reported, by data sheet, that they are taking vitamin D analogous (alfacalcidol) which reduce plasma ALP by reduction of plasma b-ALP but the dose and compliance with alfalcacidol are not checked throughout or at the end of the this study.

In 2003, Hsu et al. had found that WBC count could predict one year mortality in hemodialysis patients. Although it is only one study, but its result is compatible with the fact that WBC count is inflammatory marker and the inflammation contribute to the all-cause and cardiovascular mortality in HD patients. The result of Hsu et al study also consistent with the results of studies that correlate WBC count with mortality & CVD in the

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Table 4: Effect of 8 of no supplementation with L-carnitine on the mortality markers in control group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>baseline</th>
<th>After 8 weeks</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (gm/dL)</td>
<td>3.35 ± 0.34</td>
<td>3.40± 0.38</td>
<td>0.602</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>106.2 ± 79.1</td>
<td>125.5 ± 72.4</td>
<td>0.035</td>
</tr>
<tr>
<td>WBC (103 cell/µL)</td>
<td>6.65 ± 2.47</td>
<td>7.03 ± 2.051</td>
<td>0.402</td>
</tr>
<tr>
<td>Monocyte (103 cell/µL)</td>
<td>0.588 ± 0.349</td>
<td>0.586 ± 0.211</td>
<td>0.490</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD

Table 5: Difference in the effect on mortality markers between treated and control group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>L-carnitine group</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in albumin</td>
<td>0.0015 ± (0.347)</td>
<td>0.047± (0.396)</td>
<td>0.705</td>
</tr>
<tr>
<td>Change in ALP</td>
<td>8.3 ± (37.54)</td>
<td>19.4 ± (46.13)</td>
<td>0.091</td>
</tr>
<tr>
<td>Change in WBC</td>
<td>0.208 ± (1.776)</td>
<td>0.384 ± (1.999)</td>
<td>0.329</td>
</tr>
<tr>
<td>Change in Monocyte</td>
<td>0.011 ± (0.132)</td>
<td>0.0012 ± (0.302)</td>
<td>0.194</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD
general population, and in populations close to HD patients (patients on peritoneal dialysis and patients with CKD not on dialysis). Based on papers that claimed the ability of L-carnitine supplementation to decrease the inflammatory markers levels in HD patients, the presented study had investigated the effect of 1000mg oral L-carnitine/day for 8 weeks on WBC count in HD patients. After 8 weeks, the presented study had revealed that WBC count decreased (3.43%) in L-carnitine group, while it increased (5.78%) in the control group, compared with their baselines. However, WBC count in L-carnitine group had no statistically significant difference (P=0.329) from the WBC count in control group (P=0.329). The result of this study on WBC count is consistent with the two studies that had evaluated the WBC count after L-carnitine administration in HD patients and their results were insignificant change in WBC count after L-carnitine administration, although in these two studies the L-carnitine given intravenously and for six month. Monocyte count is associated with atherosclerosis, CVD, and increased mortality in the general population. Recently, 3 studies evaluated the correlation of mortality and CVD with monocyte count in CKD and HD patients. While Kato et al found that monocyte count is independent predictor of long term mortality in chronic HD patients, Heine et al reported that a higher number of CD14+CD16+ monocyte subset rather than total monocyte count is associated with cardiovascular events and death in HD patients. However, the presented study had evaluated the effect of oral L-carnitine on total monocyte count in HD patients and its result revealed that although the percent of reduction of monocyte count was 11.3 times higher in L-carnitine group than control group, but difference in the monocyte count between the two groups was statistically insignificant (P=0.194). Although no identical study is available to compare with its result, but this result is consistent with effect of L-carnitine on the other assessed inflammatory markers (CRP, WBC count, and low albumin) in this presented study i.e. insignificant change after 8 weeks of oral 1000mg of L-carnitine.

CONCLUSION

Daily 1000 mg oral L-carnitine supplementation has limited benefit to improve mortality markers (Albumin, ALP, WBC and monocyte count) in hemodialysis patients.

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