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Original Investigation

Levocarnitine Improves Cardiac Function in Hemodialysis Patients With Left Ventricular Hypertrophy: A Randomized Controlled Trial

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Background: Levocarnitine deficiency in hemodialysis patients is common. Although the effect of levocarnitine therapy on uremic anemia has been studied in small trials, its effects on cardiac function remain unclear.

Study Design: Multicenter, prospective, open-label, parallel, randomized, controlled trial.

Setting & Participants: Patients undergoing maintenance hemodialysis with carnitine deficiency (free carnitine plasma concentration < 40 μmol/L) enrolled in 3 hemodialysis centers.

Intervention: Random assignment to treatment for 12 months with oral levocarnitine therapy at a dose of 20 mg/kg/d or control group (no levocarnitine therapy).

Outcomes & Measurements: Cardiac function was assessed by echocardiography. The primary end point was change in ejection fraction from baseline at the end of the study. Secondary end points included changes in left ventricular mass index and clinical parameters from baseline at the end of the study.

Results: 222 patients were randomly assigned, of whom 148 patients (levocarnitine group, n = 75; control group, n = 73) were analyzed. Ejection fraction increased from baseline to the end of the study in the levocarnitine group by 5.43% (95% CI, 4.53%-6.32%), but not in the control group (change, −0.14%; between-group difference, 5.57% [95% CI, 4.48%-6.66%]; $P < 0.001$). Left ventricular mass index decreased from baseline to the end of the study in the levocarnitine group (change of −8.89 [95% CI, −11.7 to −6.09] g/m^2), but not in the control group (change of 1.62 g/m^2; between-group difference, 10.50 [95% CI, 7.51 to 13.60] g/m^2; $P < 0.001$). Levocarnitine therapy reduced N-terminal pro–brain natriuretic peptide (NT-proBNP) levels and improved the erythropoietin responsiveness index, whereas no such effects were observed in the control group.

Limitations: Not a double-blinded study.

Conclusions: Levocarnitine therapy is useful for hemodialysis patients with carnitine deficiency; these patients may benefit from such therapy, with amelioration of cardiac function and reduction of left ventricular mass index.

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INDEX WORDS: Carnitine; cardiac function; cardiac morphology; ejection fraction (EF); levocarnitine; hemodialysis (HD); left ventricular hypertrophy (LVH); left ventricular mass index (LVMI); N-terminal pro–brain natriuretic peptide (NT-proBNP); end-stage renal disease (ESRD); randomized controlled trial (RCT).

Patients on hemodialysis (HD) therapy are known to have carnitine deficiency,[1,2] which might contribute to clinical disorders (eg, cachexia, dyslipidemia, erythropoiesis-stimulating agent [ESA]-resistant anemia, insulin resistance and glucose intolerance, muscle weakness, and myopathy), as well as to intradialytic symptoms (eg, muscle cramps, hypotension, and cardiac arrhythmia).[3,4] There have also been reports of improvement in cardiac dysfunction following levocarnitine therapy, particularly in patients with lowered cardiac systolic function or symptoms of heart failure.[5,6] However, in individuals with normal myocardial function, one study found carnitine therapy to be beneficial, whereas another observed no benefits.[7,8] However, these previous studies were small or not well controlled; therefore, their results are controversial. Hence, in the

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present study, we investigated the effects of 12 months of levocarnitine therapy on cardiac morphology and function among patients undergoing HD.

METHODS

Patients and Study Protocol

This prospective, open-label, randomized, parallel, controlled, multicenter trial screened 346 patients, of whom 222 HD patients were randomly assigned to a levocarnitine therapy group or a control group. Patients in the levocarnitine group received oral levocarnitine (Otsuka Pharmaceutical Co, Ltd) at a dose of 20 mg/kg/d, and those in the control group received usual care (no levocarnitine therapy). Patients were monitored for 12 months. An independent investigator with no knowledge of the participants before commencement of the trial monitored the randomization of participant entry order. Dynamic balancing randomization was carried out based on age, sex, HD vintage, hemoglobin level, and presence or absence of diabetes mellitus. Thus, we ensured that there were no significant differences in baseline characteristics between groups. Details of the assignment were then given to 6 independent investigators. The study protocol was designed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Keiai Hospital, and all patients provided written informed consent. All patients were treated with HD or hemodiafiltration therapy 3 times per week in 4-hour sessions at 3 Japanese blood purification centers. This prospective study was conducted from June 2012 through December 2014.

Enrollment criteria for the study were as follows: (1) aged 20 years or older and 85 years or younger, (2) HD duration therapy longer than 6 months at enrollment, and (3) free carnitine plasma concentration < 40 μmol/L. Exclusion criteria were as follows: (1) aged younger than 20 years or older than 85 years; (2) history of severe heart failure, angina, myocardial infarction, or stroke within the past 6 months; (3) presence of infectious disease, thyroid disease, malignant tumors, or treatment with steroids or immunosuppressants; (4) current hospitalization; (5) atrial fibrillation; and (6) levocarnitine therapy or supplementation within the past 6 months. During the study period, patients continued their regular medications, such as antihypertensive agents, ESAs, phosphate binders, and lipid-lowering agents. Patients were regularly given dietary guidance by a dietician, especially those under dietary restrictions such as salt and protein intake.

Patient withdrawal from the study was considered if intolerance to levocarnitine appeared during the study and in case of medical events that resulted in death, hospitalization, or significant disability or incapacity; transfer to other hospitals; or inability to measure ejection fraction (EF) and left ventricular mass index (LVMI) by echocardiography due to poor visualization, local left ventricular wall thinning, local ventricular asynergy, or EF $\geq 70\%$ at baseline.

Study Evaluations

The primary efficacy end point was the comparison of cardiac function between the 2 groups, as measured by the magnitude of change from baseline in EF evaluated by echocardiography. Secondary end points were the magnitude of changes from baseline in LVMI and clinical parameters in the levocarnitine group and a comparison to those in the control group at the end of the study. For exploratory end points, we compared levocarnitine subgroups of patients with left ventricular hypertrophy (LVH) with those without LVH.

Serum carnitine levels were determined by enzyme cycling methods as described previously.[9] Blood samples were obtained before the start of an HD session. All patients received the same ESA, namely, recombinant human erythropoietin (epoetin alfa). The erythropoietin responsiveness index (ERI) was defined as average weekly units of ESA divided by clinical dry weight (in kg) and average blood hemoglobin (in g/dL) as described previously,[10] to normalize the amount of required ESA to the severity of anemia. These variables were evaluated at baseline and 12 months (at the end of the study). N-terminal pro−brain natriuretic peptide (NT-proBNP) was measured by the electrochemiluminescence immunoassay method.

The safety and tolerability of levocarnitine treatment were assessed by monitoring and recording all adverse events, as well as monitoring clinical laboratory test results and physical assessment findings. Adherence to oral levocarnitine treatment was evaluated based on a pill count once every 2 weeks.

Assessment of Cardiac Function

Echocardiography was conducted immediately after the midweek HD session to minimize any influence of the patient's hydration state both at the beginning and end of the study. Echocardiography was performed using Vivid T7 (GE Healthcare). The echotracings were collected by 2-dimensional guided M-mode echocardiography, according to a widely accepted method.[11] All patients were examined by a single trained cardiologist, who was blinded to the documentation of participants' clinical characteristics; examinations were conducted at baseline and after 6 and 12 months of oral levocarnitine treatment (or equivalent times for the control group). For each participant, left ventricular end-diastolic dimension (LVDd), interventricular septal end-diastolic thickness (IVS), left ventricular posterior wall end-diastolic thickness (PW), left atrial dilation, and EF were measured. The normal range of LVDd was defined as 42 to 59 mm for men and 39 to 53 mm for women.[10] The ratio of early (E) to late (A) mitral valve flow velocity (E/A ratio) and the ratio of E to early tissue Doppler lengthening velocity (e′) (E/e′ ratio) were measured as the indexes of diastolic left ventricular dysfunction.[12,13] Left ventricular mass (LVM) was calculated using Devereux's method[11]: $\text{LVM (g)} = 0.8 \times \{1.04 \times [(\text{LVDd} + \text{IVS} + \text{PW})^3 - (\text{LVDd})^3]\} + 0.6$. At echocardiographic examination, each patient's body height and weight were measured to calculate body surface area; LVM was indexed per square area; and LVMI was calculated. LVH was defined as LVMI > 102 g/m^2 for men and > 88 g/m^2 for women.[11]

Statistical Analysis

Data were expressed as mean ± standard deviation or median and interquartile range as appropriate. Continuous variables were compared using *t* test or Mann-Whitney *U* test, and categorical variables were compared by χ^2 or Fisher exact test as appropriate to the data distribution. Changes in cardiac parameters by echocardiography, such as in EF (ΔEF) and LVMI (ΔLVMI), were defined as the differences between values at baseline and those at months 6 and 12. Those values were expressed as mean (95% confidence interval [CI]). Differences in echocardiographic parameters between the 2 groups from baseline to 6 and 12 months were analyzed by logistic regression. In order to identify which patients within the levocarnitine group showed a favorable response to the therapy, patients with LVH were compared with those without LVH in a levocarnitine subgroup analysis. Sample size was determined based on 80% power, assuming an effect size of a 5.2% difference in change in EF from baseline between groups with a standard deviation of 11.1%, based on a previous similar levocarnitine trial.[14-16] This yielded a 2-sided significance level of 0.05 and an estimated number of evaluable patients of 146 (73 per group). We allowed for a dropout rate of 35% after randomization. Thus, a sample size of 220 randomly assigned individuals (110 per group) was necessary for this study. Statistical significance was set at $P < 0.05$. All analyses were performed using JMP, version 12, software (SAS Institute Inc).