Saudi J Kidney Dis Transpl 2017;28(3):477-482

Saudi Journal of Kidney Diseases and Transplantation

Original Article

Carnitine Reduced Erythropoietin Dose Required and Improved Cardiac Function of Patients on Maintenance Hemodialysis

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ABSTRACT. Intravenous administration of 2 g carnitine in every hemodialysis (3 times/week), for 8–10 months, reduced doses of darbepoetin alfa required to maintain adequate hemoglobin levels (10–11 g/dL) into 10% of the initial doses. There was also a significant increase in plasma transferrin saturation, increase in left ventricular ejection fraction, and decrease in plasma brain natriuretic peptides.

Introduction

Patients on maintenance hemodialysis (HD) often develop anemia, cardiac dysfunction, muscle weakness, and muscle cramp. In almost all HD patients, carnitine is deficient because it is removed from the body by HD, atrophied kidneys of patients in renal failure cannot create sufficient amount of carnitine, and HD patients usually refrain from taking enough meat or fishes which contain a large amount of carnitine.

A quarter of carnitine, a quaternary ammonium with one carboxyl group, is produced in the body. The rest is taken from food. It plays an important role in lipid metabolism because it binds to acyl-coenzyme A (CoA) to produce acylcarnitine by carnitine palmitoyltransferase in the intermembrane space of mitochondria. Acylcarnitine is transported into matrix by carnitine-acylcarnitine translocalase in the internal membrane, where it is converted to acyl-CoA. Acyl-CoA is metabolized by β oxidation to produce adenosine triphosphate (ATP). Therefore, carnitine is considered to play an essential role in the metabolism of fatty acids (particularly long chain fatty acids) in the mitochondria producing ATP by transporting acyl-CoA to mitochondrial matrix.

In patients on maintenance HD, carnitine is removed through hemodiafilter causing carnitine deficiency.

Functions of carnitine have been reported to suppress thyroid function,[1] improve of cardiac function,[2,3] and male sterility.[4,5]

In this report, we investigate the role of carnitine in the improvement of renal anemia and cardiac function.

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Materials and Methods

Determination of plasma carnitine concentration

Plasma carnitine concentration was determined as follows: the incubation mixture contained 0.1M Tris-HCL (pH 8.0) 0.5 mL, acetyl-CoA (3 mg/mL) 0.04 mL, 5,5'-dithiobis (2-nitrobenzoic acid, 1 mg/mL) 0.04 mL, carnitine acetyltransferase (Sigma, 4 mg/mL) 0.02 mL, and 0.05 mL of plasma in a final volume of 0.65 mL. Tubes were incubated at 37°C for 15 min, and the absorbance at 412 nm of the supernatant was determined to calculate carnitine concentration in plasma.

Table 1 shows characteristics of 98 patients enrolled in this study. Ages of patients ranged from 40 to 92 years old (36 males and 18 females). Duration of HD ranged from nine months to 39 years. The cause of chronic kidney disease was diabetes mellitus in 46 patients, chronic glomerulonephritis in 24 patients, and renal arteriosclerosis in 28 patients. Patients with severe comorbidities such as active chronic hepatitis, serious heart failure, severe gastrointestinal hemorrhage, and those with antibodies against darbepoetin alfa were excluded from this study. Darbepoetin alfa was employed as erythropoietin in this study.

Twenty-three patients were injected with 2 g carnitine at the end of every HD for 8–10 months and thereafter 1 g carnitine was injected on every HD for 10 months. HD was performed on every patient for 3.5–4 h/day, three times a week with Kt/V between 1.2 and 1.6.

Table 1. Patients' characteristics.

Patients	54
Male/female	36/18
Age (years)	75.114.0
Duration of hemodialysis (years)	7.2±7.4
Primary causes	
Diabetes mellitus	24
Glomerulonephritis	14
Nephrosclerosis	16
Total cholesterol	161±30.5
HDL (mg/dL)	43.0±9.7
Triglyceride (mg/dL)	87.9±43.0

HDL: High-density lipoprotein

Brain natriuretic peptides (BNP), serum iron, and plasma transferrin levels were determined by Hokenkagaku Institute in Yokohama. Left ventricular ejection fraction (LVEF) was determined by echocardiogram. Cardiothoracic ratio (CTR) was calculated from breast X-ray films.

Data were expressed as the mean ±SD. Student's *t*-test for paired samples was applied for analysis of results.

Results

As shown in Figure 1, the plasma carnitine level of patients on maintenance HD before carnitine therapy was extremely low when compared with that of normal participants (P <0.01). After carnitine treatment for two to three months, it increased significantly to normal or above the normal levels (P <0001).

The dose of darbepoetin alfa required to maintain hemoglobin levels at the 10–11 g/dL range in patients receiving 2 g carnitine in every HD decreased markedly as compared with those required by patients without carnitine therapy (Figure 2). Figure 3 shows changes

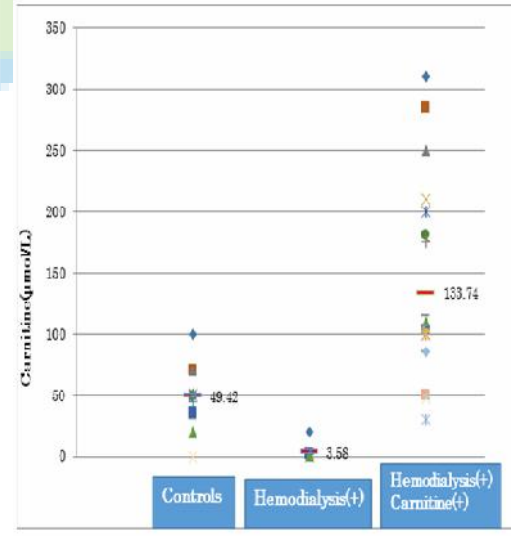

Figure 1. Plasma carnitine levels in patients on maintenance hemodialysis.
Left, normal participants: middle, patients on maintenance hemodialysis before carnitine treatment: right, patients on maintenance hemodialysis after carnitine administration for 2–3 months.

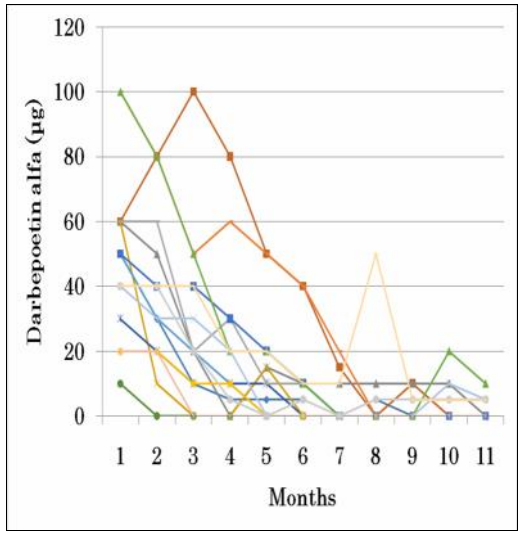

Figure 2. Changes of amounts of darbepoetin alfa required to maintain subnormal hemoglobin levels (10–11 g/dL) in the peripheral blood during carnitine therapy. Amounts of darbepoetin alfa required were monitored for 11 months.

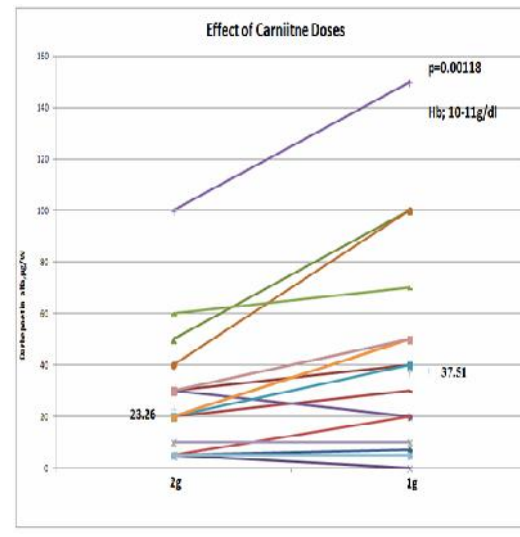

Figure 4. Comparison of doses of carnitine on the amount of darbepoetin alfa required to maintain subnormal (10–11 g/dL) hemoglobin levels in the peripheral blood.
Left, 2 g carnitine. Right, 1 g carnitine.

of the amount of darbepoetin alfa required between that before carnitine therapy and that after 8–10 months of carnitine administration. It can be seen carnitine therapy for 8–10 months resulted in a 90% reduction amount in the dose of darbepoetin alfa. On the other hand, patients without carnitine therapy required essentially the same dose of darbepoetin alfa.

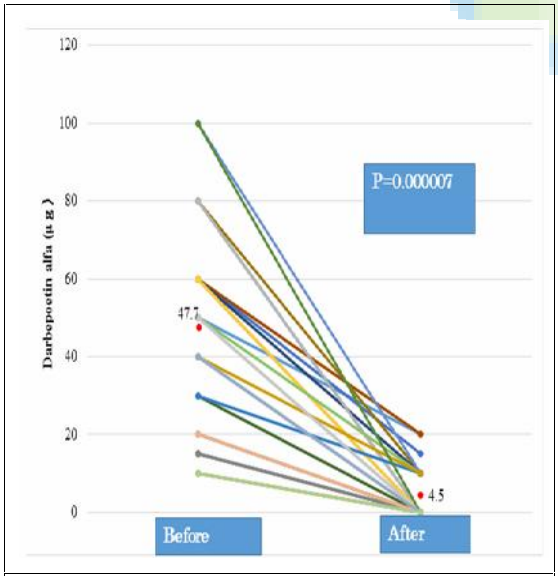

Figure 3. Amounts of erythropoietin (darbepoetin alfa) required to maintain hemoglobin levels in the peripheral blood between 10 and 11 g/dL.
Left, amounts of darbepoetin alfa required before carnitine therapy, and right, those after 8–10 months of carnitine therapy.

Effect of different doses of carnitine on the dose of darbepoetin alfa required to maintain adequate hemoglobin levels is shown in Figure 4. A dose of 2 g carnitine at the end of every HD session was significantly more effective in reducing the dose of darbepoetin alfa than that of 1 g carnitine as shown in Figure 4.

Although plasma ferritin levels remained essentially unchanged after carnitine therapy for 8–10 months, the level of transferrin saturation significantly increased after carnitine therapy (Figure 5).

LVEF which shows systolic capacity of left ventricle increased significantly (P <0.001) after carnitine therapy for 8–10 months as shown in Figure 6 also. The level of plasma BNP, on the other hand, decreased significantly (P <0.002) (Figure 7). CTR which indicates relative volume of heart decreased slightly but not significantly (Figure 8).

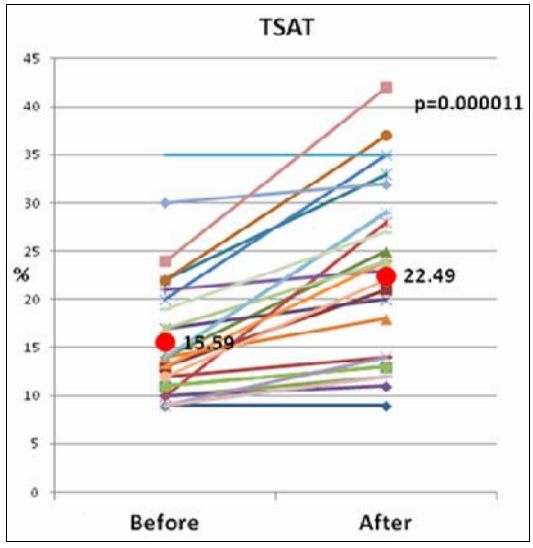

Figure 5. Effect of carnitine administration on TSAT.
Left, TSAT of patients before canitine therapy, and that after 8–10 months of carnitine administration.

TSAT: Ttransferrin saturation.

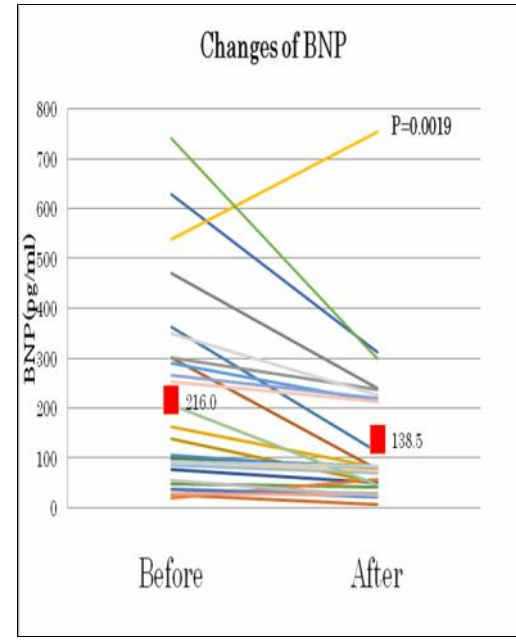

Figure 7. Changes of BNP by carnitine administration for 8–10 months.

NBP: Brain natriuretic peptides

Discussion

Carnitine deficiency causes dysfunction of heart and muscle.[2,3] Administration of carnitine improved renal anemia.[6,7] Carnitine also reduced the amount of erythropoietin required to treat anemia in patients on maintenance HD.[18-11] Carnitine deficiency of patients on maintenance HD may result from its loss during HD. decrease synthesis by failing kidneys

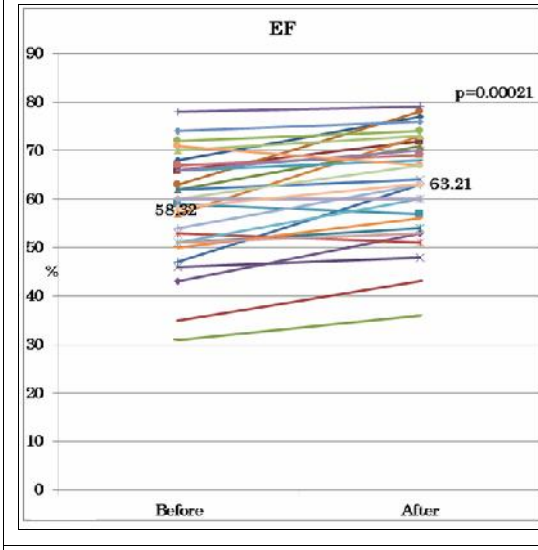

Figure 6. Changes of LVEF by the treatment with carnitine for 8–10 months.

LVEF: Left ventricular ejection fraction.

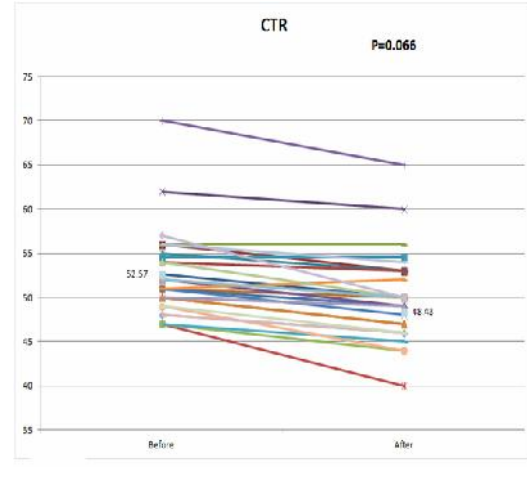

Figure 8. Effect of carnitine on CTR. Changes of CTR by carnitine therapy were monitored before and after carnitine therapy for 8–10 months.

CTR: Cardiothoracic ratio.

and poor intake of foods rich in carnitine.

The mechanism of improvement of renal anemia by carnitine treatment is not so clear until now. Although carnitine is said to reduce apoptosis of erythrocytes, because it alters lipid components in plasma membrane of erythrocytes,[6] erythrocyte survival of uremic patients is not so short as to explain every reason of renal anemia.[12] Long-chain acyl-carnitine is speculated to enhance erythropoiesis based on the finding that palmitoyl-carnitine enhanced erythroid colony formation in the fetal mouse liver cell culture.[13] However, the effect of carnitine on the development of erythroblasts from precursor cells in the bone marrow remains to be clarified.

Carnitine plays an essential role in acyl-CoA metabolism by transporting it into the mitochondrial matrix from the cytosol, where it is oxidized by β oxidation to produce ATP and acetyl-CoA which is metabolized in TCA cycle to succinyl-CoA. Succinyl-CoA is the substrate of delta-aminolevulinic acid (ALA) synthetase, the rate-limiting enzyme in heme synthesis pathway.[14,15] ALA formed in the mitochondrial matrix is transported into the cytosol and metabolized to protoporphyrin IX.

Administration of carnitine to patients on maintenance HD was reported to reduce the dose of the requited erythropoietin by 20–65%.[8-11] In contrast to previous reports[8-11] which saved 20%–65% of erythropoietin by carnitine treatment, the present study saved 90% of that as shown in results. The reason is speculated that the amount of carnitine administered intravenously (2 g/HD, 6 g/week) is larger than that of other studies reported until now.[8-11] Larger amounts of carnitine are considered to be more effective in improving renal anemia than small amounts. In fact, administration of 2 g carnitine in every HD was more effective than that of 1 g carnitine as shown in our study. Furthermore, longer duration of carnitine treatment in the present study may be another reason for the excellent effect of carnitine.[8-11]

The improvement of cardiac functions such as the decrease of BNP in the plasma and the increase of LVEF are considered to be caused by enhanced metabolism of fatty acids in the mitochondria of heart muscles producing ATP.

From carnitine, trimethylamine is produced in the intestine by intestinal bacteria.[16] Trimethylamine is metabolized to trimethylamine N-oxide by flavin-containing oxidase in the liver. Trimethylamine N-oxide is known to worsen arteriosclerosis.[16] However, trimethylamine cannot be produced from carnitine in other organs, other than the intestine because intestinal bacteria are not present in them. Because carnitine injected intravenously cannot be converted to trimethylamine in the body, even a large amount of carnitine injection is not expected to worsen arteriosclerosis.

In conclusion, this report showed that intravenous administration of a large amount of carnitine to patients on maintenance HD for long periods improves renal anemia markedly and also cardiac function.

Acknowledgments

Technical assistance of Miss Yuko Ishimori and Miss Yu Okubo is greatly appreciated.

Conflict of interest: None declared.

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