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Carnitine for Body Composition in Hemodialysis Patients Hideki Kakutani¹, Yoshikane Kato¹, Tomomi Fujikawa¹, Takafumi Kawata¹, Masami Yamamoto¹, Koichi Wada¹, Kazuyo Ishikura¹, Yujiro Shirai¹, Miyuki Narutaki¹, Setsuko Kanazawa¹, Sayuri Matsuzaki¹, Shinnichi Waka¹ and Hiroshi Bando^{2*}

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Abstract

Background: Authors and colleagues have continued clinical research for hemodialysis patients. Currently, a pilot study presents intervention of carnitine for changes of the body composition.

Subjects and Methods: Subjects were six patients on hemodialysis with intervention of carnitine (group 1). Average data were 74.3 years, 65.4 kg, 22.6 in BMI. As levocarnitine, L-Carnitine FF injection 1000 mg was administered three times a week for six months. Group 2 has six control patients for age-, sex-, body weight, BMI-matched (group 2). Body composition of muscle and fat tissues were measured by InBody 770 on 0 and 6 months.

Results: In group 1, muscle volume and skeletal muscle showed increasing tendency without statistical significance. In contrast, there were significant decreases of body fat volume (22.3 kg vs 20.5 kg, 39.0% vs 35.8%) ($p < 0.05$). No significant differences were found in hemoglobin, total protein, albumin and Cardio-Thoracic Ratio (CTR) of chest X-ray. Group 2 showed no significant changes.

Discussion and Conclusion: Hemodialysis patients often have muscular reduction. Previous reports showed improved lean body mass by carnitine administration, which may support our result. These results from current pilot study would be expected to become useful reference data in the pathophysiological investigation in patients on hemodialysis.

Keywords: Chronic kidney disease, Endogenous erythropoietin, Erythropoiesis stimulating agent, Carnitine, Cardio renal anemia syndrome.

Abbreviations: CKD-Chronic Kidney Disease, EPO-Endogenous Erythropoietin, ESA-Erythropoiesis Stimulating Agent, CTR-Cardio-Thoracic Ratio, TCA-Tricarboxylic Acid, FC- Free-Carnitine, AC-Acyl-Carnitine, HD-Hemodialysis, BMI-Body Mass Index, ECW-Extracellular Water, TBW-Total Body Water, GCP-Good Clinical Practice, CRF-Chronic Renal Failure, HRQL-Health-Related Quality of Life, NCV-Nerve Conduction Velocity, DCD-Dialysis-Related Carnitine Disorder, LBM-Lean Body Mass, FTI-Fat Tissue Index, LTI-Lean Tissue Index, MIS-Malnutrition-Inflammation Score.

Introduction

In recent years, diabetes and Chronic Kidney Disease (CKD) have been increased worldwide and become crucial problems from medical, social and economic points of view. As clinical condition of these patients aggravates, their renal anemia status reveals exacerbation. These causes include decreased production of the Endogenous Erythropoietin (EPO), which is accompanied with decreasing renal function [1].

Furthermore, the life of the red blood cell shortens from impaired renal function or uremia. Then, this process may decrease the reactivity of EPO for hematopoietic cell. When renal anemia is left untreated, CKD will be aggravated. Then, it will lead to the end-stage renal failure and cardiovascular disease associated with CKD more frequently [2]. Therefore, treatment with Erythropoiesis Stimulating Agent (ESA) has been recommended for renal anemia. ESA has also been used for patients with end-stage renal failure in the actual clinical practice.

On the other hand, carnitine has been an important factor in hemodialysis treatment. L-carnitine is a water-soluble amine, which has been present in the mitochondria of the tissues of cardiac muscle, skeletal muscle, brain, liver and so on. It exists as Free-Carnitine (FC) or Acyl-Carnitine (AC). Carnitine shows high dialyzability and is often deficient in patients with hemodialysis. The reason is that those patients are undernourished due to inflammatory condition.

Energy may be produced by beta-oxidation or through the Tricarboxylic Acid (TCA) cycle. It is by conveying long-chain fatty acids through the inner mitochondrial membrane to carnitine [3]. Carnitine deficiency has been known in patients on Hemodialysis (HD). It has been reported that administration of carnitine may bring clinical effects, such as improving cardiac function, decreasing muscle symptoms with muscle spasm and increasing the response of EPO to anemia [4].

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Furthermore, there are other beneficial effects, including facilitation of decrease in hypotension during dialysis, cardiomegaly, increasing the red blood cell lifespan, improvement of erythrocyte membrane fat metabolism and improving the nutritional status. Our medical group has been involved in dialysis treatment for many patients with chronic renal failure for years. We have continued some research studies concerning patients on hemodialysis [5-7]. We have conducted a study that combined the above-mentioned situations. As a pilot study, carnitine was administered under the conventional treatment associated with fundamental ESA treatment. For the protocol, we examined the changes in muscle mass/proportion and fat mass/proportion. In this article, these data are shown and discussed in comparison with similar previous reports concerning carnitine and hemodialysis [8,9].

Methods

Subjects

Subjects in this study were six patients with CRF undergoing hemodialysis three times a week. They included one male and five females, aged 68-86 with an average of 74.3 years old. The average body weight was 65.4 kg and the average BMI was 22.6 kg/m². There were two groups in this study. Group 1 is an intervention group, in which 6 subjects were administered carnitine for 6 months. Group 2 is a control group, in which 6 subjects were not given carnitine. As to the control group, 6 subjects were selected as age-, sex-, body weight-, Body Mass Index (BMI)-matched in comparison with those of 6 subjects of an intervention group.

Methods

The main research purpose was the measurement the body composition. It included the data of muscle mass and proportion and fat mass and proportion. These data were analyzed by InBody 770 (CryoUSA) [10]. The measurements were done 0 and 6 months along the schedule of the intervention of carnitine.

Body Composition

Analysis of the body composition was conducted by using InBody 770 [10]. It can measure not only fat tissue, but also the amount of muscle tissue and distribution of body water [11]. It can be checked by using compliment Cryoskin, red light therapy and other tools. As a useful apparatus in the clinical practice, the InBody 77 can store and track the data including total body composition analysis, muscle-fat analysis, obesity analysis, segmental lean analysis, Extracellular Water/Total Body Water (ECW/TBW) analysis and body composition history of the case.

General Protocol

These patients have been on regular hemodialysis for years. In detail, they have i) regular HD treatment three times a week, ii) regular ESA treatment twice a month. In this study, there are two groups, which are intervention group and control group. In the former group, regular carnitine was administered three times a week just after each hemodialysis. The study protocol includes the administration for 6 months. Several data of biomarkers were measured and compared at two points, which were before and after the intervention. The data are shown in 0 and 6 months in **Table 1** and **Table 2**. This report included six HD patients with the intervention of carnitine administration. The ordinary protocol has two groups with and without the intervention, but this report would be the pilot study of carnitine administration. Consequently, there is one group of HD patients that are investigated for the measurement of muscle and fat at 0 and 6 months along the schedule of the intervention of carnitine.

Medical agents

The administered medical agents involved in this study are ESA and carnitine. As the treatment of ESA, Darbepoetin Alfa (Genetical

Recombination) was provided to the patients with Chronic Renal Failure (CRF).

Patients were provided Darbepoetin Alfa injection syringe (40 or 60 microgram). It is recognized as anti-anemic, erythropoietin receptor agonist, and for anemia due to CKD with B03 X A02 for ATC code and pharmaceutical classification No. 3999 [12]. Darbepoetin alfa was proved to be beneficial for adult and also pediatric patients [12]. The reasons are from similar pharmacokinetics, greater maximum dose and less injection frequency in comparison with that of recombinant human erythropoietin. Carnitine was administered by L-Cartin FF injection 1000mg to patients three times a week in an average with Levocarnitine, which is (R)-3-Hydroxy-4-trimethylammonio-butanoate [13]. It was registered as 22400AMX01482, which has been provided for the treatment for carnitine deficiency [4].

	Group 1 (carnitine)			Group 2 (control)		
	0 month	6 month	dif	0 month	6 month	dif
Subjects						
Age (years old)	74.3 ± 2.7	75.3 ± 2.7		73.8 ± 2.4	74.8 ± 2.4	
Body Weight (kg)	56.4 ± 4.9	56.1 ± 5.5	np	56.2 ± 4.9	56.0 ± 5.0	np
BMI (kg/m ²)	22.6 ± 1.5	22.4 ± 1.7	np	23.1 ± 1.7	23.0 ± 1.8	np
Muscle						
Muscle volume (kg)	32.1 ± 2.7	33.6 ± 3.0	np	32.9 ± 3.2	32.5 ± 2.9	np
Skeletal muscle (kg)	17.7 ± 1.7	18.3 ± 1.9	np	18.7 ± 2.0	18.3 ± 1.9	np
Skeletal muscle (%)	31.4 ± 1.9	32.8 ± 1.9	np	32.6 ± 2.2	32.3 ± 2.0	np
Fat tissue						
Body Fat (kg)	22.3 ± 3.0	20.5 ± 3.3	*	20.9 ± 3.2	21.3 ± 3.4	np
Body Fat (%)	39.0 ± 3.3	35.8 ± 3.6	*	36.9 ± 4.4	37.7 ± 4.6	np

Note: Data represent the mean value and standard error of the mean (SEM), Intervention is the administration of Carnitine injection for six months, dif: difference between 0 month and 6 month, *: significant difference between 0 month and 6 month (p<0.05), np: not significant between 0 month and 6 month.

Table 1: Results of intervention of Carnitine.

	Group 1 (carnitine)			Group 2 (control)		
	0 month	6 month	dif	0 month	6 month	dif
Blood test						
Hb (g/dL)	9.7 ± 0.5	10.7 ± 0.6	np	10.2 ± 0.5	9.8 ± 0.4	np
Total Albumin (g/dL)	6.7 ± 0.1	6.8 ± 0.1	np	6.9 ± 0.2	6.6 ± 0.1	np
Albumin (g/dL)	3.4 ± 0.1	3.3 ± 0.1	np	3.5 ± 0.2	3.3 ± 0.1	np
Chest X-ray						
CTR (%)	52.9 ± 3.7	53.1 ± 3.4	np	53.3 ± 4.2	52.8 ± 3.6	np

Note: Data represent the mean value and standard error of the mean (SEM), Intervention is the administration of Carnitine injection for twelve months, dif: difference of data between 0 month and 6 month, np: not significant difference between 0 month and 6 month.

Table 2: Results of changes of biomarkers.

Ethical Considerations

This research study has been fundamentally conducted in compliance with the adequate ethical principles that were based on the Declaration of Helsinki. Furthermore, there was some commentary for the Ethical Guidelines for Research in the medical field for Human beings and in the conduction of the Good Clinical Practice (GCP). As to the protection of human rights, there were some ongoing considerations. Moreover, "Ethical Guidelines for Epidemiology Research" was adequately applied according to the related guideline. These principles were originated from Japan by the Ministry of Education, Culture, Sports, Science and Technology and also by the Ministry of Health, Labor and Welfare.



Regarding the current investigation about carnitine administration for hemodialysis patients, we have obtained the written informed consents from all of the subjects of carnitine group and control group. In addition, the ethical committee for the clinical research in Kanaiso Hospital was established. The committee included the president, the vice-president, and the director of the Pharmaceutical department, the head nurse of the nursing department, director of the administration department and experts in the medical and legal specialties. We have fully discussed the research content and made confirmation that this study would be adequate and agreed with all members with no problems.

Results

The main data of this study are shown in Table 1. In group 1 (intervention group), average value in age, weight and BMI before intervention was 74.3 years old, 56.4 kg and 22.6, respectively. As for the changes of muscle between before and after the intervention of providing carnitine, muscle volume (kg), skeletal muscle (kg) and skeletal muscle (%) showed the increasing tendency. However, these were not statistically significant ($p > 0.05$). There was significant decrease of body fat volume (22.3 kg vs 20.5 kg) and percentage (39.0% vs 35.8%) between before and after intervention ($p < 0.05$). In group 2 (control group), the values of the age, weight and BMI were almost similar to those of group 1. There were not significant changes in those biomarkers, including muscle and fat tissues. The adventitious data of both groups between before and after intervention were shown in Table 2. There were not significant differences in hemoglobin, total protein, albumin and CTR of chest X-ray in both of the groups (carnitine and control).

Discussion

Authors and colleagues have continued pathophysiological research among hemodialysis, diabetes, Nerve Conduction Velocity (NCV) and so on. [6,7,14,15]. During our continuous clinical research, we have tried a pilot study this time, in which carnitine was administered to HD patients with the investigation of the changes in muscle mass/proportion and fat mass/proportion. There are several important matters to be discussed in this article. They include hemodialysis, chronic renal failure, ESA, carnitine and current research data, which are described in this order as follows.

Firstly, the administration of ESA has become widespread for renal anemia in recent years. ESA is a peptide preparation with a structure similar to EPO produced in the kidney. It can act on erythroid progenitor cells in the bone marrow, promote differentiation and proliferation into red blood cells, and improve renal anemia. According to the ESA administration guideline; it is recommended that the Hb level of approximately 10-12 g/dL for dialysis patients and approximately 11-13 g/dL for CKD patients as a treatment target for ESA administration [16]. The guideline has been practically useful with high quality in 46 pages and 282 references.

In our clinic of the authors, ESA has been administered to the hemodialysis patients according to this guideline. Furthermore, BUN, Cre, UA, Hb, TP and Alb were stable for half a year in six subjects and also in more than 90 other dialysis patients. However, current study showed no comparison between the six subjects and control subjects with the same age, sex, and renal failure severity. Conventionally, it has been said that end-stage renal failure has shown a vicious cycle interacting cardiac function, renal function, and anemia each other. These factors may be independent risk factors for ESA efficacy on dialysis [17]. Consequently, these three factors have been proposed to present the concept of Cardio-Renal-Anemia Syndrome [18,19]. Treatment of renal anemia with ESA has revealed to improve memory, motivation and quality of life, reduce hospitalization risk, and contribute to improving the prognosis of dialysis patients [19,20]. On

the other hand, there was an opposite report. As for the treatment of anemia from CRF, there was a study of effect of ESAs for Health-Related Quality Of Life (HRQOL). They were analyzed from 17 systematic review and meta-analyses. They have used Short Form-36 Health Survey (SF-36), Kidney Dialysis Questionnaire (KDQ) and others. The results showed that ESA therapy for higher hemoglobin targets did not have important differences of HRQOL in patients with CRF [21].

Secondly, L-carnitine has been one of the water-soluble amines, which molecular weight is 162 [3]. It is present in the mitochondria of several tissues, such as skeletal muscle, cardiac muscle, brain, liver and so on, as the molecular states of Acyl-Carnitine (AC) or Free-Carnitine (FC) [3]. Carnitine shows higher dialyzability and has been said to be often in deficiency in hemodialysis patients. It may be due to the malnourished condition of these patients from persistent inflammation. Hemodialysis patients have various clinical symptoms depending on the specific condition. They may include multiple factors, such as muscular symptoms (swelling, weakness, extreme malaise), cardiac symptoms (cardiac hypertrophy, cardiomyopathy, cardiac dysfunction, arrhythmia, hypotension during dialysis, sudden death, etc.), erythropoietin-resistant anemia. In such cases, pathophysiological involvement of carnitine deficiency has been strongly suspected [22]. These symptoms are called dialysis-related carnitine deficiency or Dialysis-Related Carnitine Disorder (DCD). There have already been reports of carnitine homeostasis and replacement therapy in dialysis patients [23].

Thirdly, we have conducted a pilot study of carnitine administration for patients with hemodialysis. As a result, the body composition showed that the muscle mass and proportion tended to increase slightly, and the fat mass and proportion significantly decreased. These changes may be involved in carnitine administration. However, from statistic point of view, the control group would be necessary to evaluate the possible effect of carnitine. In the current protocol, we applied several patients to give the intervention. In the next research schedule, we would plan to set several groups in order to compare the detail data.

There are some previous reports which can become reference research. The Lean Body Mass (LBM) by carnitine administration for 12 months was investigated by Maruyama, et al. [22]. They studied two groups ($n=42$, each), which were L-carnitine group and control group. LBM in the former did not change significantly, but decreased significantly in the latter. The difference in mean LBM between the groups was 2.92% (95% CI 1.28-4.61; $P=0.0007$). Furthermore, Arm Muscle Area (AMA) did not change significantly in the former, but decreased significantly in the latter. The difference in mean ABA between them was 6.22% ($p=0.037$) [8]. Consequently, L-carnitine supplementation seemed to be useful for preservation of muscle mass. There has been another report of L-carnitine supplementation for 6 months in 50 hemodialysis patients for 6 months [9].

As a result, some biomarkers increased such as prealbumin, Fat Tissue Index (FTI), total cholesterol and LDL-C, while some biomarkers decreased such as Lean Tissue Index (LTI), LTI/FTI ratio and HDL-C. Thus, L-carnitine supplementation has brought an improvement of Malnutrition-Inflammation Score (MIS) to some extent [9]. From these previous reports, there would be various possibilities of the effects by the administration of L-carnitine. Further accumulation of investigation will be necessary. Regarding the influence for cardiac and pulmonary function, our current study has showed that there was no significant change in the CTR value by chest X-ray. The improvement of cardiac function was reported in the previous report by L-carnitine supplementation [24].

There are several limitations in current study as follows:

- There are few cases,
- Control group would be necessary to compare,



- Various differences are observed as to the hemodialysis situation, administration amount of medical agents and control of anemia,
- Serum concentration of some biomarkers would be desirable to judge clinical efficacy.

In summary, current article has showed the intervention of carnitine for hemodialysis patients associated with the possible effects on muscle and fat tissues. Authors expect that this pilot report would be useful reference data for hemodialysis research in the future [25].

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