INFLUENCE OF L-CARNITINE SUPPLEMENTATION ON REGULATION OF ANEMIA AND INTRADIALYTIC HYPOTENSION OF PATIENTS ON HEMODIALYSIS - OUR EXPERIENCES

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ABSTRACT

Introduction: *One of the most convincing therapeutic effects of L-carnitine is an improvement of uremic anemia, and positive effect on intradialytic hypotension. The aim of this study was to determine the effect of L-carnitine therapy on anemia and hypotension in hemodialysis patients.*

Materials and Methods: *Study organized as a single-center, observational investigation, during the three month, in Clinic of Nephrology and Dialysis, University Clinical Center Kragujevac, Serbia. Study it's included eleven hemodialysis patients, received L-carnitine intravenously (20 mg/kg/body weight), bolus at the end of each dialysis.*

Results: *A statistically significant difference was found in creatinine concentration (932.9±192.6 μmol/L vs. 772.7±213.9 μmol/L; p=0.001), and average values of diastolic blood pressure (58.6±14.2 mmHg v.s. 69.1±9.4 mmHg; p=0.042) before and after L-carnitine supplementation therapy. It has been determined a significant positive correlation between L-carnitine dose and total iron binding capacity after therapy (rho 0.691; p=0.019). The age of the subjects was negatively correlated with the dose of L-carnitine (rho-0.768; p=0.006).*

Conclusions: *In the our patients we determined increase in the value of total iron binding capacity, with higher doses of L-carnitine, as well as significant increase of diastolic blood pressure and decrease in creatinine levels. Our elderly patients received lower doses of L-carnitine.*

Keywords: *L-carnitine, anemia, intradialytic hypotension, hemodialysis.*

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Introduction

Annually, the number of hemodialysis patients in the world increase by about 6%, accompanied by numerous complications of the treatment itself[1]. Renal anemia, as a common complication of chronic kidney disease, is associated with development of heart complications and failure, impairing the quality of life and leading to an increase in mortality[2, 3]. In addition to erythropoietin deficiency, factors and mechanisms that contribute to the development of renal anemia include iron deficiency, secondary hyperparathyroidism, inflammation, malignancy, aluminum intoxication and hemolysis[4-6]. The second most common complication of hemodialysis treatment is intradialytic hypotension caused by dialysis settings, such as shortening the treatment time, higher ultrafiltration speed, relatively high dialysate temperatures. The prevalence of intradialytic hypotension defined by European Best Practice Guideline (EBPG) ranges from 5.0% to 11.2% and is associated with increased

cardiovascular morbidity and mortality[7]. Several clinical trials showed that L-carnitine supplementation can improve erythrocyte survival[8], leading to a reduction in erythropoiesis-stimulating agent usage[9]. On the other hand, a meta-analysis published in 2008 does not confirm a beneficial effect of L-carnitine supplementation on dialysis-related hypotension[10]. However, recent clinical trial showed that the frequency of the hypotensive episodes during dialysis significantly decreased, from 4 to 1.3 per month, after 3 months of L-carnitine supplementation, implying the L-carnitine treatment potential[11]. In 2003, the National Kidney Foundation developed a practice recommendation of the use of L-carnitine in dialysis-related carnitine disorders, most notably erythropoietin-resistant anemia, intradialytic hypotension, cardiomyopathy, and fatigability[12].

Three years later in the updated of National Kidney Foundation practice recommendations was stated that "there was insufficient evidence to recommend the use of L-carnitine in the management of anemia in patients with hemodialysis and chronic kidney disease"[13]. In the United States, reimbursement for the use of intravenous and oral L-carnitine for patients with end-stage renal disease was approved in 2004 and 2012, respectively[14]. L-carnitine is an amino acid derivative synthesized mainly in the liver and kidneys, and more than 90% of L-carnitine is present within the skeletal and cardiac muscles[15]. Patients with chronic renal failure, especially those receiving hemodialysis, suffer from L-carnitine deficiency due to reduced dietary intake, intestinal malabsorption, decreased renal synthesis, accumulation of metabolic intermediates or rapid clearance during dialysis[1, 16, 17]. The aim of this study was to determine the association of L-carnitine therapy with anemia and hypotension in hemodialysis patients.

Materials and methods

This observational single-center study was conducted at the Clinic of Nephrology and Dialysis, University Clinical Center Kragujevac, Serbia. The study design was approved by the appropriate ethics review boards of the institution where the study was conducted, in accordance with the Declaration of Helsinki. The criteria for including patients in the study were as follows: at least 6 months of hemodialysis treatment, intradialytic hypotension, or anemia that did not respond to erythropoiesis stimulators. Eleven hemodialysis patients who were included in the study had been subjected to regular hemodialysis using polysulfone dialyzer membranes with bicarbonate buffers for 4 h three times per week. Clinical and demographic data about the patients as well as the type of vascular access were obtained from the medical records.

All patients included in the study received L-carnitine at the end of each hemodialysis intravenously (20 mg/kg/body weight), in a slow bolus over 2-3 minutes and were then followed for three months. None of our patients had the side effects (nausea, vomiting, diarrhea, abdominal pain).

Intradialytic hypotension was defined as a decrease of systolic blood pressure by ≥20 mmHg. Systolic and diastolic blood pressure were measured immediately before, during and after hemodialysis. Laboratory parameters were measured before and three months after L-carnitine supplementation. Blood samples were drawn from the arterial site of the arteriovenous fistula, and controlled biochemical parameters were measured using standard laboratory techniques.

Statistical analysis

The statistical package SPSS Windows, version 19, was used for data analysis. The level of statistical significance was set at $p < 0.05$. Measures of central tendency, measures of variability and relative numbers were used in the descriptive analysis. The t test for dependent and independent samples and ANOVA were used to analyze the differences between the examined variables. The correlation between the results was analyzed by Spearman 's correlation coefficient test.

Results

The study included eleven patients, seven (63.6%) male and four (36.4%) female patients. The largest number of patients reported diabetes as the etiology of renal insufficiency (45.5%), 18.2% reported polycystic kidney disease, 9.1% had hypertensive nephropathy, while 27.3% of patients cited other causes. As a vascular access 90.9% of patients had an arteriovenous fistula and 9.1% a Hickman catheter (Table 1). The average age of our patients was 67.1±8.8 years.The average number of ampoules of L-carnitine received by our patients was 24.8±13.4. The blood creatinine concentration in our subjects before L-carnitine therapy was 932.9 ± 192.6 μmol/L, while after three months of

L-carnitine therapy, the mean of blood creatinine concentration was 772.7±213.9 μmol/L. There was a statistically significant difference in blood creatinine concentration before and after L-carnitine therapy (p=0.001). Likewise, statistically significant difference was found (p = 0.042) between the mean value of diastolic blood pressure before therapy (58.6±14.2 mmHg) and after three months of therapy (69.1±9.4 mmHg). Statistically significant differences in the values of other examined clinical and laboratory parameters, before and after application of L-carnitine therapy were not observed in patients of our study (Table 2).

By examining the correlation of clinical and laboratory parameters with L-carnitine supplementation dose, a significant positive correlation was observed between L-carnitine dose and total iron binding capacity (TIBC) after therapy (rho 0.691; p=0.019). The age of the patients was negatively correlated with the dose of L-carnitine (rho -0.768; p=0.006). No correlation between other examined parameters and L-carnitine dose was observed (Table 3).

Variable		Total dose of L-carnitine in ampoules (mean ± SD)	p value
Gender	Mele	26.1±16.6	0.614
	Female	22.5±5.9	
Etiology kidney disease	Diabetic kidney disease	15.4±7.5	0.120
	Other causes	35.3±16.3	
	Polycystic kidney disease	34.5±7.8	
	Hypertensive nephropathy	21.0±0.0	
Vascular access	Arteriovenous fistula	23.2±13.0	/
	Hickman catheter	41.0±0.0	

Table 1: Demographic and clinical characteristics of patients included in the study.
SD: standard deviation.

Variables		Mean values of SD	The difference between the mean values of ±SD	p-value
Er (10^{12}/L) mean ± SD	Before therapy	3.6±0.4	0.2±0.5	0.31
	After therapy	3.4±0.6		
Hgb (g/L) mean ± SD	Before therapy	111.7±10.1	2.7±15.4	0.584
	After therapy	109.1±15.9		
Platelets (10^9) mean ± SD	Before therapy	192.7±69.9	4.5±27.4	0.601
	After therapy	188.3±55.8		
Urea (mmol/L) mean ± SD	Before therapy	20.6±5.0	2.5±5.6	0.176
	After therapy	18.1±5.0		
Creat. (μmol/L) mean ± SD	Before therapy	932.9±192.6	160.2±85.2	0.001*
	After therapy	772.7±213.9		
K (mmol/L) mean ± SD	Before therapy	5.0±0.6	-0.3±0.7	0.229
	After therapy	5.3±0.7		
Na (mmol/L) mean ± SD	Before therapy	139.1±2.7	-0.5±2.1	0.402
	After therapy	139.6±2.8		
Ca (mmol/L) mean ± SD	Before therapy	2.2±0.1	-0.1±0.1	0.065
	After therapy	2.3±0.1		
P (mmol/L) mean ± SD	Before therapy	1.5±0.3	0.2±0.5	0.342
	After therapy	1.4±0.5		
Fe (μmol/L) mean ± SD	Before therapy	11.4±4.4	-2.6±4.9	0.113
	After therapy	13.9±5.5		
TIBC (μmol/L) mean ± SD	Before therapy	36.8±4.1	-3.3±6.8	0.141
	After therapy	40.1±7.2		
UIBC (μmol/L) mean ± SD	Before therapy	23.6±4.6	-2.0±9.7	0.668
	After therapy	25.6±7.7		
Ferritin (ng/ml) mean ± SD	Before therapy	749.6±243.0	17.4±202.7	0.782
	After therapy	732.3±221.1		
TSAT (%) mean ± SD	Before therapy	33.2±9.0	-1.9±6.5	0.356
	After therapy	35.1±11.6		
SBP (mmHg) mean ± SD	Before therapy	93.6±12.1	-8.6±18.2	0.146
	After therapy	102.3±19.7		
DBP (mmHg), mean ± SD	Before therapy	58.6±14.2	-10.5±14.9	0.042*
	After therapy	69.1±9.4		

Table 2: Difference in clinical and laboratory parameters of patients before and after L-carnitine therapy.
*Er: erythrocytes; Hgb: hemoglobin; Creat: Creatinine; K: Potassium; Na: Sodium; Ca: Calcium; P: Phosphorus; Fe: Serum iron; TIBC: total iron binding capacity; UIBC: free iron binding capacity; TSAT: transferrin saturation; SBP: Systolic blood pressure; DBP: diastolic blood pressure; *statistical significance.*

Discussion

In humans, carnitine is mainly obtained from the diet, and mainly sources of carnitine are red meat, fish, and dairy products. L-carnitine from foods is absorbed in the intestine via both active and passive transport across enterocyte membranes[6]. Unabsorbed L-carnitine is degraded in the colon, and excreted in the urine[18]. Carnitine is easily removed by dialysis with subsequent depletion of tissue carnitine stores, inadequate dietary ingestion, and reduced renal synthesis. It has been demonstrated that about 95% of dialysis patients have carnitine deficiency[19]. One of the most convincing therapeutic effects of carnitine is an improvement of uremic anemia[6], especially in patients unresponsive to erythropoietin. The meta-analysis Zhu et al.[2] has shown that L-carnitine therapy significantly increased plasma hemoglobin and hematocrit levels in hemodialysis patients. Real therapeutic effect of L-carnitine on anemic syndrome is full of doubts and contradictions, probably as a consequence of differently conceived and stratified study protocols.

Variable		Age	Dose L-carnitine	Er. after therapy	Hgb after therapy	Platelets after therapy	Urea after therapy	Creat. after therapy	K after therapy	Na after therapy	Ca after therapy	P after therapy	Fe after therapy	TIBC after therapy	UIBC after therapy	Ferritin after therapy	TSAT after therapy	SBP after therapy	DBP after therapy
Age	Rho	1.000																	
	P	.																	
Josef L-carnitine	Rho	-0.768*	1.000																
	P	0.006	.																
Er.es after therapy	Rho	-0.101	-0.023	1.000															
	P	0.768	0.947	.															
Hgb after therapy	Rho	-0.201	0.128	0.982*	1.000														
	P	0.553	0.709	0.000	.														
Platelets after therapy	Rho	-0.096	-0.228	-0.373	-0.436	1.000													
	P	0.779	0.501	0.259	0.180	.													
Urea after therapy	Rho	0.105	-0.515	-0.500	-0.591	0.655*	1.000												
	P	0.758	0.105	0.117	0.056	0.029	.												
Creat. after therapy	Rho	-0.297	0.041	-0.236	-0.218	0.255	0.527	1.000											
	P	0.374	0.905	0.484	0.519	0.450	0.096	.											
K after therapy	Rho	-0.323	0.436	-0.055	-0.023	0.228	-0.032	0.351	1.000										
	P	0.332	0.180	0.873	0.947	0.501	0.926	0.290	.										
Na after therapy	Rho	-0.270	0.338	0.083	0.102	0.088	-0.069	-0.134	0.401	1.000									
	P	0.422	0.309	0.808	0.766	0.797	0.840	0.695	0.222	.									
Ca after therapy	Rho	0.190	-0.253	-0.319	-0.355	0.050	0.159	0.141	-0.050	-0.160	1.000								
	P	0.575	0.452	0.339	0.284	0.884	0.640	0.679	0.883	0.639	.								
P after therapy	Rho	-0.603*	0.130	0.123	0.118	0.251	0.323	0.747**	0.130	-0.079	0.114	1.000							
	P	0.049	0.703	0.719	0.729	0.457	0.332	0.008	0.703	0.818	0.738	.							
Fe after therapy	Rho	-0.218	0.073	0.278	0.296	-0.292	-0.032	0.032	-0.068	-0.488	-0.479	0.080	1.000						
	P	0.520	0.831	0.408	0.377	0.384	0.926	0.926	0.841	0.127	0.136	0.815	.						
TIBC after therapy	Rho	-0.315	0.691*	-0.384	-0.306	-0.164	-0.411	-0.160	0.414	0.118	-0.046	-0.156	0.005	1.000					
	P	0.346	0.019	0.244	0.360	0.629	0.209	0.639	0.205	0.729	0.894	0.648	0.989	.					
UIBC after therapy	Rho	0.126	0.360	-0.714	-0.821*	0.286	-0.214	-0.071	0.071	0.164	0.357	-0.250	-0.750	0.487	1.000				
	P	0.788	0.427	0.071	0.023	0.535	0.645	0.879	0.879	0.726	0.432	0.589	0.052	0.268	.				
Ferritin after therapy	Rho	0.178	-0.155	-0.127	-0.136	-0.145	-0.018	-0.418	-0.743*	-0.333	-0.410	-0.237	0.310	0.068	-0.071	1.000			
	P	0.600	0.649	0.709	0.689	0.670	0.958	0.201	0.009	0.318	0.210	0.483	0.354	0.841	0.879	.			
TSAT after therapy	Rho	0.288	-0.196	0.364	0.327	-0.409	-0.300	-0.509	-0.433	-0.494	-0.068	-0.401	0.497	-0.178	0.000	0.282	1.000		
	P	0.390	0.564	0.272	0.326	0.212	0.370	0.110	0.184	0.122	0.842	0.222	0.120	0.600	1.000	0.401	.		
SBP after therapy	Rho	0.054	-0.240	0.265	0.167	0.060	0.009	-0.436	-0.249	-0.175	0.247	-0.100	0.167	-0.193	0.128	0.009	0.719*	1.000	
	P	0.875	0.478	0.432	0.623	0.860	0.978	0.180	0.461	0.608	0.465	0.770	0.623	0.569	0.784	0.978	0.013	.	
DBP after therapy	Rho	-0.235	0.042	0.118	0.083	0.034	-0.049	-0.255	-0.251	-0.085	0.487	0.116	-0.057	-0.094	0.289	-0.123	0.495	0.856*	1.000
	P	0.488	0.903	0.730	0.807	0.920	0.886	0.449	0.457	0.804	0.129	0.735	0.869	0.784	0.530	0.720	0.121	0.001	.

Table 2: Correlation of clinical and laboratory parameters of L-carnitine supplementation dose.
*Er: erythrocytes; Hgb: hemoglobin; Creat: Creatinine; K: Potassium; Na: Sodium; Ca: Calcium; P: Phosphorus; Fe: Serum iron; TIBC: total iron binding capacity; UIBC: free iron binding capacity; TSAT: transferrin saturation; SBP: Systolic blood pressure; DBP: diastolic blood pressure; *statistical significance.*

Actually, there are research results[20-25] that have not confirmed that L-carnitine affects the improvment of hemoglobin concentration, so it is recommended only as an adjuvant therapy to improve the effectiveness of erythropoietin in the treatment of renal anemia. The results of our study did not prove a positive correlation between L-carnitine supplementation and hemoglobin concentration. However, a significant positive correlation was observed between the dose of L-carnitine and TIBC after three months of L-carnitine supplementation. Bellinghieri et al.[26] had similar findings. In their study, 3-months of L carnitine therapy increased hematocrit and TIBC level, which was somewhat confirmed by the updated guidelines[27]. These authors stated that: „Although there is evidence that the use of L-carnitine may have a beneficial effect on the treatment of anemia, but it is necessary to

address other potential problems before continuing with L-carnitine therapy". The results of our study indicated a significant difference in serum creatinine values before and after three months of L-carnitine supplementation. Namely, after L-carnitine therapy, there was a significant decrease in creatinine levels, without any logical explanation. A possible explanation for this result is more speculative, related to the improvement in residual kidney function or dialysis efficiency, i.e. reduction of muscle mass and/or protein intake[28]. However, in our study, it is unlikely that the decrease in creatinine was due to increased dialysis efficiency, since we did not change the dialysis conditions during the study. Likewise, it is impossible to assess changes in dry weight in these patients, because it remained unchanged in every subject.

L-carnitine levels in tissues have been found to decline with age[29]. In a clinical trial of Levocarnitine-treated elderly patients, data suggest that administration of levocarnitine to elderly subjects may result in an increase of total muscle mass, and maybe reduce fatigue[30]. The American Association of Kidney Patients Consensus Group on the Role of Levocarnitine in Treating Renal Dialysis Patients[31], noted that plasma carnitine levels have not been shown to be good predictors of the clinically effective carnitine dose. Although the optimal dose has not been established, the group recommended a dose of L-carnitine of 20 mg/kg i.v. at the end of hemodialysis, which we followed in our research. In our study was found a negative correlation between the dose of L-carnitine supplementation and the age of the patients. Actually, elderly patients received lower doses of L-carnitine. This result again leads us to speculative explanations, which have not been confirmed in scientific studies and may be related to the administered doses of L-carnitine and the demographic structure of the patients.

Intradialytic hypotension is a serious complication of hemodialysis associated with vascular access thrombosis, inadequate dialysis dose, and mortality[32-34]. The prevalence of intradialytic hypotension ranges between 15% to 50%. There is no consensus regarding the definition of intradialytic hypotension, but the Disease Outcomes Quality Initiative (KDOQI) defines this condition as a decrease of 20 mm Hg or more in systolic blood pressure or a decrease of 10 mmHg or more in mean arterial pressure requiring therapeutic interventions. Intradialytic hypotension is usually associated with different symptoms such as dizziness, muscle cramps, abdominal discomfort, nausea, vomiting, yawning and sighing. It may reduce the effects of dialysis and require modification of treatment and discontinuation of dialysis, and its treatment is difficult and complicated. A small number of studies have been conducted in this area and their results are contradictory. Nevertheless, L-carnitine as an important cofactor required for smooth muscle and heart muscle function has been used in dialysis patients since some studies have shown its positive effect on intradialytic hypotension. However, some studies have failed to prove its effect. Thus, the routine use of this drug for the prevention of intradialytic hypotension has not been recommended[10, 35, 36].

In our study, after L-carnitine therapy, there was a significant jump in diastolic blood pressure of 10.5±14.9 mmHg, which could support the affirmation use of L-carnitine in nephrological practice of intradialytic hypotension treatment.

This study had important limitations. This was an observational study with a small sample size, and it was conducted at a single centre. Also, we did not determine the serum carnitine concentration before and after L-carnitine administration. The results may have been affected by differences in carnitine supplementation dose.

Conclusions

At the end of a three-month study, it was observed that higher doses of L carnitine were associated with an increase in the value of total iron binding capacity, there was a significant increase in the values of diastolic blood pressure and a significant decrease in creatinine levels.

Elderly patients received statistically lower doses of L-carnitine.

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