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THE EFFECTS OF L – CARNITINE ON RESPIRATORY FUNCTION TESTS IN CHILDREN UNDERGOING CHRONIC HEMODIALYSIS*

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SUMMARY: Kavukçu S, Türkmen M, Salman Ş, Önvural B, Oktay G, Karaman Ö, Çevik NT. (Hemodialysis and Transplantation Institute, and Departments of Pediatrics and Biochemistry, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). The effects of L-carnitine on respiratory function tests in children undergoing chronic hemodialysis. Turk J Pediatr 1998; 40: 79-84.

Respiratory functions are affected during hemodialysis. Ultrafiltration rate, acid-base balance and the strength of respiratory muscles have been suggested as important factors in adults undergoing chronic hemodialysis. L-carnitine is crucial for energy producing utilization fatty acid and, possible amino acids. Carnitine treatment has been associated with hypertrophy of type I muscle fibers. Carnitine supplementation in non-dialysis patients increases exercise tolerance. Eventually, administration of L-carnitine to adult hemodialysis patients improves exercise capacity, energy metabolism and muscle mass. This study was performed to investigate the chronic effects of L-carnitine treatment on respiratory functions in children receiving chronic hemodialysis therapy. Predialytic and postdialytic respiratory function tests were performed in ten children with end-stage renal disease before and after a three-month L-carnitine treatment period. The mean age was 12 ± 4 years. L-carnitine was administered at a dose of 20 mg/kg intravenously at the end of each hemodialysis session. Mean predialytic serum carnitine values before and after the carnitine treatment period were 21.8 ± 3 and 132.0 ± 48.5 mmol/L, respectively, and the increase was significant ($p < 0.05$). Respiratory function tests performed just before the carnitine treatment period implied bronchospasm that was clinically vague and could only be detected by a significant decrease in FEV1/FVC, PEF and FEF25-75 values ($p < 0.05$). Nevertheless, at the end of the three-month carnitine therapy period these respiratory function parameters did not show any significant variation. Hence, it is implied that carnitine therapy might have prevented the subclinic bronchospasm that developed in children during hemodialysis. *Key words: L-carnitine, respiratory functions, hemodialysis.*

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In the maintenance hemodialysis patients, loss of renal mass, limited dietary intake of meat and dairy products, and dialytic loss of L-carnitine during hemodialysis are the factors believed to increase the propensity towards deficiency or depletion of carnitine in the body[1]. The alterations in respiratory functions during hemodialysis in adults have been shown previously[2-5]. Exercise capacity, muscle mass and energy metabolism may affect respiratory function tests[2,3,5]. L-carnitine is crucial for energy producing utilization fatty acid and, possibly, amino acids. Carnitine treatment has been associated with hypertrophy of type I muscle fibers. Carnitine supplementation in non-dialysis patients increases exercise tolerance. Eventually, administration of L-carnitine to adult hemodialysis patients improves exercise capacity, energy metabolism and muscle mass[6,7]. Casciani et al.[8] have reported that astenia, cramp and dyspnea after exertion showed a ratio inversely proportional to the blood concentrations of carnitine. Because no detailed study has been done on children documenting any relation between serum L-carnitine and respiratory function tests, this study investigates the effects of carnitine treatment on respiratory functions of chronic hemodialysis patients in the pediatric age group.

Material and Methods

Ten pediatric age group chronic hemodialysis patients (9 male, 1 female) were enrolled in this prospective study. Clinical characteristies of the patients are shown in Table I. All the patients received orally essential amino acids, calcitriol, calcium carbonate, B complex vitamins, folic acid and iron supplementation, while two also received nifedipine, captopril, and prazosin as antihypertensives. Five of the patients were on a thrice weekly program and the remainder a twice weekly program, each session lasting four hours. All the children were moderately malnourished as detected by body mass indices (BMI) and triceps skin fold thickness measurements; these parameters did not change throughout the study period. All the patients had normal cardiac functions echocardiographically. Toray-321 hemodialysis machines were employed. Hollow fiber cuprophane membranes with surface areas that approximate 75 percent of the calculated body surface were used. Acetate dialysates were utilized throughout the study. Routine heparin protocols were applied. Hemodialysis was effective for all patients, with urea reduction rates of 60 percent or higher. Before the initiation of the study all the patients underwent clinical and radiological evaluation for their respiratory functions and no evident pathology was detected. An automatic spirometer (Vitalograph PFT2 Spirometer, Vitalograph Ltd., Buckingham, England) was employed for all the patients. Tests were performed in a 45 ° semi-sitting position pre- and postdialytically. All pulmonary tests were repeated three times at room temperature, with the best performed test curve taken into consideration.

The parameters investigated were Vital Capacity (VC), Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV1), FEV1/VC, FEV1/FVC, Peak Expiratory Flow (PEF) and Forced Expiratory Flow between 25 and 75 percent of expired vital capacity (FEF25-75). All participants were older than six years of age and cooperative. Results were reliable and no patient needed to be excluded from the study.

Table I: Clinical Characteristics of the Participants

Case No.	Sex	Age	Primary Renal Disease	Treatments Per Week	Time on Dialysis (Months)
1	M	16	Chronic pyelonephritis	3	5
2	M	14	Chronic pyelonephritis	2	3
3	M	16	Unknown	3	14
4	M	7	Obstructive nephropathy	2	3
5	M	10	Chronic glomerulonephritis	3	5
6	F	15	Amyloidosis	3	21
7	M	11	Unknown	3	14
8	M	10	Amyloidosis	2	3
9	M	12	MPGN	2	3
10	M	7	Chronic pyelonephritis	2	8

MPGN: Membranoproliferative glomerulonephritis, M: male, F: female.

Acceptable values for FVC, FEV1 and PEF lie within 100 ± 20 percent of the predicted values. For FEF, the range is 100 ± 35 percent of the predicted value. Among the pediatric age group, FEV1/FVC should be greater than 75 percent of the predicted value. VC, FVC, FEV1 and PEF values decrease in obstructive disorders[9]. Obstructive disorders are also associated with FEV1/FVC below 75 percent of the predicted value[9]. Body weights, the arterial line blood gases, hematocrit, blood urea nitrogen (BUN), plasma creatinine and electrolytes were also measured. Wieland et al.'s[10] enzymatic colorimetric method was used for the measurement of total serum carnitine level. During the treatment period L-carnitine was administered at the dose of 20 mg/kg intravenously at the end of each dialysis session for three months. Same pulmonary function tests and other measurements were repeated after this treatment period.

VC, FVC, FEV1, FEF25-75 and PEF data are expressed as a percentage of predicted values for age, sex, weight and height for each case (Table II). FEV1/VC and FEV1/FVC data are shown as percentage of deviation from predicted values. A negative sign indicates a decrease from predicted value. Data are shown as mean ± standard deviations. Information obtained by described pulmonary functions tests before and after the L-carnitine treatment period was compared. Each child served as his or her own control. In the statistical evaluation of the obtained data, nonparametric Wilcoxon test and correlation analysis were used.

Table II: The Predialytic and Postdialytic Findings Before and After L-Carnitine Treatment Period

	Before L-Carnitine Treatment			After L-Carnitine Treatment		
	Predialytic	Postdialytic	P	Predialytic	Postdialytic	P
Serum carnitine (mmol/L)	21.8 ± 4.4	8.7 ± 1.9	< 0.01	132.9 ± 48.5	39.1 ± 18.1	< 0.01
VC	131.6 ± 43.8	87.4 ± 24.0	NS	75.1 ± 5.0	68.9 ± 5.4	< 0.05
FVC	68.4 ± 4.7	67.4 ± 6.9	NS	74.4 ± 6.1	74.0 ± 4.9	NS
FEV1	66.0 ± 4.0	61.3 ± 6.6	NS	71.4 ± 6.6	73.0 ± 4.7	NS
FEV1/VC	-26.2 ± 11.2	-14.1 ± 9.5	NS	-8.0 ± 4.9	-0.6 ± 2.2	NS
FEV1-FVC	-2.2 ± 2.5	-8.1 ± 3.2	< 0.05	-3.3 ± 3.2	-1.0 ± 2.0	NS
FEF 25-75	61.1 ± 6.4	51.1 ± 8.1	< 0.05	67.7 ± 7.8	68.9 ± 6.6	NS
PEF	55.0 ± 5.1	46.0 ± 6.9	< 0.05	62.1 ± 6.4	65.5 ± 5.3	NS

VC: Vital capacity, FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 second, FEF25-75: Forced expiratory flow between 25 and 75 percent of expired vital capacity, PEF: Peak expiratory flow. VC, FVC, FEV1, FEF25-75 and PEF data are shown as a percentage of the predicted values. Data shown as mean ± standard deviation. FEV1/VC and FEV1/FVC data are shown as a percentage of deviation from predicted values. Negative sign indicates a decrease from predicted value.

Results

The data obtained before and after the L-carnitine treatment period are shown in Table II. There was a significant decrease in serum carnitine levels during dialysis both before and after the L-carnitine treatment period ($p < 0.05$). Predialysis serum carnitine levels after the L-carnitine treatment period were significantly higher than those obtained before the L-carnitine treatment period ($p < 0.05$). End-dialytic serum carnitine levels, and other parameters observed before and after the L-carnitine treatment period, did not show significant difference. Body weights, potassium and other biochemical and hematologic variables were not significantly different before and after the L-carnitine treatment period. Postdialytic body mass indices (BMI), expressed as a percentage of the expected values, prior to and after the L-carnitine treatment period were 81.1 ± 3.7 and 82.1 ± 3.8, respectively. While a statistically significant difference between predialytic serum carnitine values before and after the treatment period was found ($p < 0.05$), the increase of body mass indices during the same time period was not significant. Before the L-carnitine treatment period, significant decreases in FEV1/FVC, FEF25-75 and PEF values were noted between the pre- and post-dialytic measurements ($p < 0.05$). After the L-carnitine treatment period, only the vital capacity (VC) measurements showed a significant decrease ($p < 0.05$). The decrease in the vital capacity in the period prior to L-carnitine treatment was not significant. When the relation between the rate of changes in the parameters and the rate of changes in the carnitine levels before and after the L-carnitine treatment period were analyzed, a significant positive correlation was found between the rate of changes in the carnitine levels and those in FEV1/VC at the beginning of hemodialysis ($r: 0.84$, $p < 0.05$).

Discussion

During the periods both before and after commencing L-carnitine treatment significant decreases in carnitine levels were detected by the end of dialysis ($p < 0.05$), demonstrating that carnitine was lost during hemodialysis, as is consistent with the literature[6, 11, 12]. Subsequent to L-carnitine administration significant increases in predialytic serum carnitine levels were observed.

Volume overload, metabolic acidosis and uremic toxins are known as the main factors affecting the respiratory function tests in end-stage renal disease patients[13]. While alleviating these factors, hemodialysis may also cause undesirable changes in respiratory functions[2]. Some studies suggested no change in respiratory functions[3], while others detected restrictive changes due to volume overload[2] in the adult hemodialysis population. There is no detailed study reported for the pediatric age group on this issue. In this study, prior to carnitine treatment, postdialytic FEV1/FVC, PEF, FEF25-75 values declined significantly which most likely indicates bronchospasm. The cause of this bronchospasm was beyond the scope of this study. After commencing carnitine treatment, predialytic serum carnitine levels increased significantly, hence it may be suggested that the carnitine therapy is responsible for the prevention of this subclinic broncospasm that developed during hemodialysis. Some studies implied that during hemodialysis, carnitine may cause blockage of the lipooxygenase route so that arachidonic acid can be metabolized via the cyclooxygenase route; therefore, formation of mediators that are responsible for bronchospasm may have been prevented by carnitine administration[14].

Before and after the carnitine therapy, when the relation between the rate of changes in hemodialysis parameters and the rate of changes in serum carnitine levels were investigated, a significant positive correlation was observed between the changes of carnitine levels and the FEV1/VC at the beginning of hemodialysis ($r: 0.864$, $p < 0.05$). This may also support the theory that carnitine has an effect in preventing bronchospasm during hemodialysis. All cases were reevaluated after the L-carnitine treatment and the postdialytic workup revealed a decrease in vital capacity while the rest of the tested respiratory function parameters did not show any significant change. Carnitine has a positive effect on striated muscle strength and exercise capacity. In this study, in the period following carnitine treatment, only postdialytic vital capacity showed a significant decrease, which depicts that carnitine does not affect the respiratory function tests by the proposed mechanism. A decline in the vital capacity both prior to and following the carnitine treatment could be explained as loss of strength during hemodialysis, which cannot be prevented by the carnitine treatment. The possible effect of respiratory muscles on respiratory function tests has been ruled out due to the negligible increase of body mass index in our cases. On the other

hand, results of respiratory function tests after carnitine treatment have not implied an improvement of respiratory muscle insufficiency by carnitine replacement.

In conclusion, it was felt that hemodialysis displayed subclinic bronchospasm in children who did not receive carnitine treatment whereas this subclinic bronchospasm did not appear following carnitine treatment. Here we consider carnitine as a factor that could prevent the bronchospasm which may occur during hemodialysis.

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