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BRIEF REPORT

L-carnitine supplementation and EPO requirement in children on chronic hemodialysis

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Abstract L-carnitine supplementation has been the subject of heated discussion in the context of the treatment of pediatric hemodialysis patients. The aim of this study was to analyze the effect of intravenous L-carnitine supplementation on the erythropoetin (EPO) requirement in six pediatric hemodialysis patients. All patients were on intravenous L-carnitine (2.5 g per session for patients >30 kg and 1 g for those <30 kg) for 9 months. The EPO dose was adapted monthly to maintain a target hemoglobin (Hb) level of 11–13 g/dl. Prior to the initiation of L-carnitine supplementation, the EPO requirement was 1.15±0.22 (range 0.37–1.75) μg/kg darbepoetin alpha. Free carnitine (FC) levels were measured before (40.4±4.9 μmol/l), immediately after the 9-month L-carnitine supplementation period (378.5±77.3 μmol/l), and 4 months after withdrawal of L-carnitine (95.6±4.0 μmol/l). After 9 months, the EPO dose was 0.47±0.10 μg/kg ($p<0.002$). The Hb levels increased from 12.2±0.97 to 14.0±0.54 g/dl ($p<0.05$) within the first 2 months, and the EPO dose was then decreased in a stepwise manner. In conclusion, following intravenous carnitine supplementation, FC levels were higher and persisted longer than expected. This rise was associated with increased Hb levels and decreased EPO requirement. Since controls were missing for this study, prospective long-term multi-center studies on a large number of patients are required to provide solid answers to the controversial question of L-carnitine supplementation in hemodialyzed children.

Keywords Anemia · Erythrocyte · Erythropoetin · Hemodialysis · L-Carnitine · Uremia

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Introduction

Carnitine (MW 162 Da) is a water-soluble, unbound, quaternary amine. It plays an important role in fatty acid metabolism and energy production by transporting the long chain fatty acids across the internal membrane of the mitochondria [1]. In addition, the palmitic acid ester of carnitine may stimulate erythropoeisis, and L-carnitine deficiency destabilizes erythrocyte membrane and its metabolism, causing a reduction in survival time. It has been suggested that excess free fatty acids secondary to L-carnitine deficiency leads to altered function of the erythrocyte sodium–potassium pump in chronic renal failure and thereby reduces erythrocyte survival time [2, 3]. It is a common finding in chronic dialysis patients to have deficiency in carnitine such patients are on a low protein diet and this molecule is easily dialyzed. L-carnitine deficiency has been correlated to the duration of dialysis [4, 5].

The aim of this study was to evaluate the effects of L-carnitine supplementation on the use of erythropoietin (EPO) requirement in pediatric hemodialysis (HD) patients.

Patients and methods

This was a prospective study that included six children (three girls) without residual renal function who were on regular HD (three 4-h sessions per week) on high-flux membranes. All patients were started on intravenous L-carnitine supplementation at the same time. The whole observation period was 16 months: 3 months before L-carnitine (phase 1), 9 months on L-carnitine (phase 2), and 4 months after L-carnitine withdrawal (phase 3). The pathology of end stage renal disease (ESRD) was steroid-resistant nephrotic syndrome (two patients), atypical hemolytic uremic syndrome (one patient), IgA nephropathy (one patient), lupus erythymatous (one patient), and renal dysplasia (one patient).

All patients received L-carnitine intravenously (2.5 g per session for patients >30 kg and 1 g for those <30 kg, with an average dose of 50 mg/kg per session) for a total duration of 9 months.

Patients were analyzed monthly for hemoglobin, iron level, ferritin, transferrin saturation, and parathyroid hormone (PTH) levels. All patients received intravenous darbepoetin alpha once per week. Oral vitamin C, vitamin B6, and niacin were given during the whole observation period. The KT/V was measured monthly.

The EPO dosage was adjusted to maintain a hemoglobin (Hb) level between 11 and 13 g/dl. If Hb was >13 g/l on two consecutive analysis or >14 in one analysis, we decreased EPO by 20%, while if Hb was <11 g/dl on two consecutive analysis or <10 g/dl in one analysis, we increased EPO by 20%.

Carnitine levels (free and total) were measured by mass spectrometry. Normal values for free carnitine (FC) and total carnitine levels are 20–60 and 25–70 μmol/l, respectively.

Statistical analysis

Statistical analysis was performed with SigmaStat ver. 3.5 and 8.02 (Systat Software, San Jose, CA), and graphs were created with SigmaPlot (ver. 8; Systat Software). Continuous data were summarized as mean ± standard error of the mean (SEM) for normally distributed data and as median and range for data that were not normally distributed. p values <0.05 were considered to be statistically significant.

Results

Mean patient age was 13.5±6.03 years, and mean duration on HD was 11±4 (range 7–13) months. Free carnitine blood level values were 40.4±4.9 μmol/l before supplementation, 378.5±77.3 μmol/l immediately after the 9-month supplementation period, and 95.6±4.0 μmol/l 4 months after L-carnitine withdrawal (Fig. 1). Hemoglobin levels remained stable for most of the patients during the 4 months after L-carnitine withdrawal. Two patients required a re-increase of EPO doses during this period.

The EPO requirement before L-carnitine was 1.15±0.22 (0.37–1.75) μg/kg darbepoetin alpha. During the intravenous L-carnitine supplementation period of 9 months, the EPO dose was decreased stepwise and reached 50% of the initial dose after 9 months (0.47±0.10 μg/kg; $p<0.001$; Fig. 2a). All patients experienced an important reduction in EPO requirement during L-carnitine supplementation (Fig. 2b). The mean Hb level before L-carnitine supplementation was 12.9±0.50 g/dl, and after the 9-month supplementation period the Hb level was unchanged. However, there was a significant increase during the first 2 months (12.2±0.97 to 14.0±0.54 g/dl; $p<0.05$; Fig. 3). The EPO dose during the first 2 months was unchanged.

The KT/V did not change significantly during the study and remained within adequate levels: KT/V was 1.35 (range 1.22–1.60) during phase 1, 1.39 (1.25–1.50) during phase 2, and 1.34 (1.25–1.55) during phase 3. Nutritional status was normal in all patients. Iron supplementation was adapted during the study according to serum iron level (24.2±2.4 vs. 28.8±3.2 μmol/l; $p=0.22$). The transferrin saturation coefficient was in the normal range (20–27%) for all patients during the whole observation period. The PTH level was 247±76 versus 177±40 ($p=0.27$).

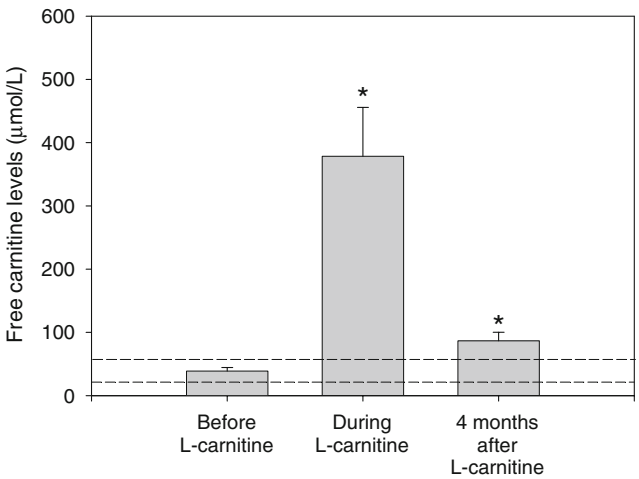

Fig. 1 Free carnitine plasma levels in six hemodialyzed children immediately before, after 9 months of intravenous L-carnitine supplementation, and 4 months after L-carnitine withdrawal. *Broken horizontal lines* Upper and lower normal values. *$p<0.05$ vs. free carnitine levels before L-carnitine supplementation

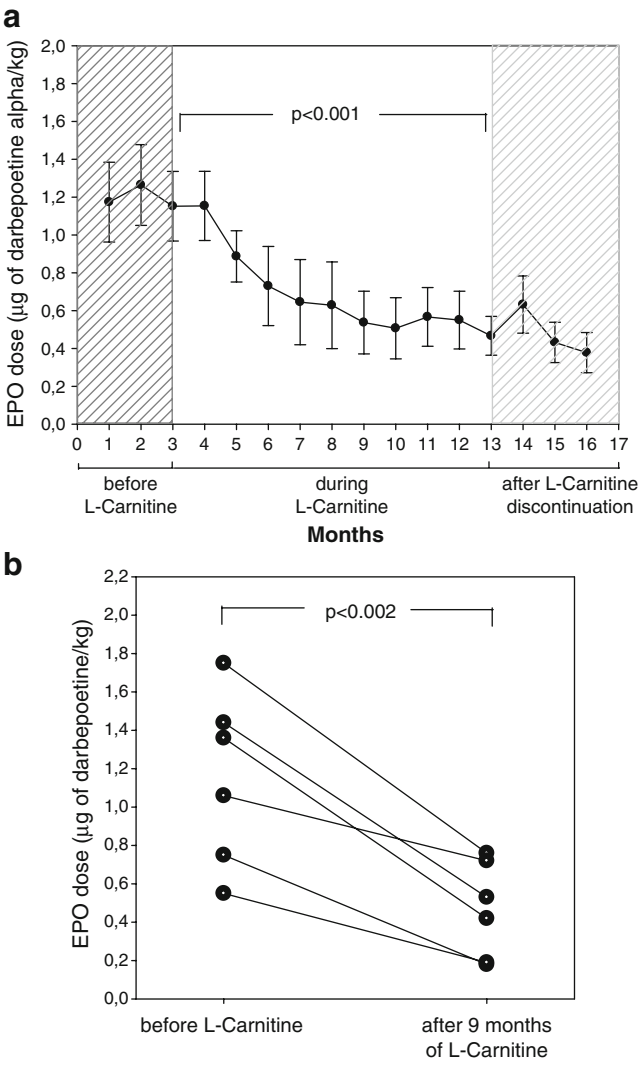

Fig. 2 **a** Erythropoietin (*EPO*) requirement before, during, and after intravenous L-carnitine supplementation in six hemodialyzed children. **b** Erythropoetin requirement before and at the end of the L-carnitine supplementation. Patients with a higher EPO dose had a relatively higher benefit in terms of EPO dose reduction

Discussion

The role of L-carnitine in maintaining erythrocyte membrane stability and increasing erythrocyte life span has been investigated [2]. Carnitine homeostasis is profoundly perturbed in patients with chronic renal failure (CRF). A low protein diet and reduced appetite related to CRF result in low carnitine intake. Further, considerable losses of carnitine occur during HD as it is filtered due to its low molecular weight, resulting in carnitine depletion directly related to the duration of chronic dialysis.

Placebo controlled data and studies with longer evaluation periods after L-carnitine withdrawal are still missing on the pediatric population. In our prospective study, we were unable to create an adequate control group as the number of adequate patients in a single center is restricted. A longer observation after carnitine withdrawal ('wash-out' period) is also warranted, but half of our patients were transplanted during the observation period. However, our observation period on carnitine supplementation was longer than that reported in previous studies. We chose intravenous supplementation in order to avoid difficulties due to heterogeneous intestinal carnitine absorption.

The results of our study suggest that there is need for a long-term controlled multi-center study with a large number of patients. As the waiting time for a renal graft is much lower in pediatric patients, such a future study should take into account a probable high drop-out rate. In uremic patients undergoing HD, plasma and tissue L-carnitine levels initially (during the first month) remain within the normal range, following which (during the first year) they may progressively fall to plasma levels 30–60% lower than normal [4, 6].

We measured free and total carnitine levels, but only reported FC levels because FC is more closely correlated to tissue level [7]. Free carnitine <20 µmol/l can be considered as evidence of carnitine deficiency. However, normal carnitine plasma levels may persist even while muscle stores are already reduced. Another more accurate approach to evaluate L-carnitine storage is to perform muscle biopsy, which we felt was not ethical in children.

Our results showed a significant decrease of about 50% in EPO dose over the L-carnitine supplementation period, while Hb levels remained unchanged during the study period. However, our study design does not definitively exclude the possibility that other parameters may have played a role in this result, as a control group was missing. This result stands in contrast to a study carried out by Verrina et al. [8] that

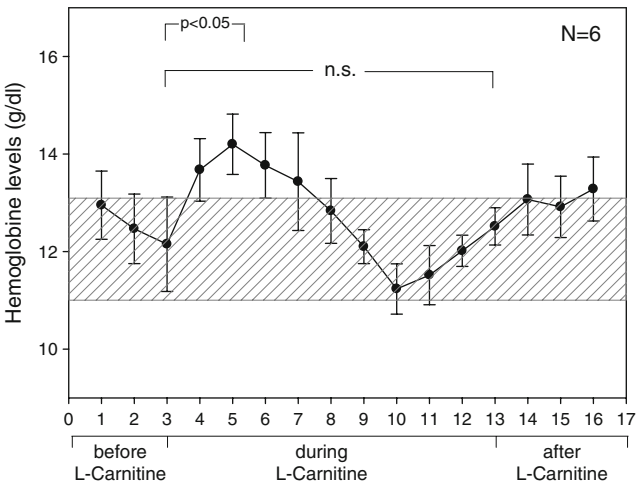

Fig. 3 Hemoglobin levels before, during, and after intravenous L-carnitine supplementation in six hemodialyzed children. *n.s.* Not significant

showed no effect of L-carnitine on hematological parameters. However, the L-carnitine supplementation period in their study was only 3 months, which may have been too short and may explain the negative result.

The plasma FC levels of our patients were in the normal range before the onset of L-carnitine supplementation. After nine months of L-carnitine supplementation (phase 2), plasma FC levels had increased dramatically to supra-physiological levels (about fivefold higher than the upper normal value). During the supplementation period we were able to reduce the EPO requirement by 50%, while all other factors involved in hematopoesis remained stable. This result may give rise to the hypothesis that higher carnitine levels may be necessary to decrease EPO needs [9]. In fact, the aim of carnitine supplementation might not be normalization of plasma levels or increased muscle storage, but rather an increase of anti-oxidant activity [10, 11] in order to counterbalance the effect of ESRD on erythrocyte membrane stability. Four months after L-carnitine withdrawal, the plasma FC levels had returned to values twice the pre-supplementation level.

In summary, as our patients were supplemented with higher L-carnitine doses, the plasma carnitine levels increased more than expected and the time necessary to return to pre-supplementation levels was relatively long. This high supplementation dose may have been responsible for the longer persistence of normal plasma FC levels, which probably helped to reduced the need for EPO for a longer period. However, there is no evidence that high dose intravenous L-carnitine supplementation with supra-physiological carnitine plasma levels plays a role in the reduction of EPO requirements in children on chronic HD. Therefore, a prospective long-term multi-center study is required to find solid answers to the controversial subject of whether L-carnitine should be a supplement for hemodialyzed children.

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