Archive of SID

## Original Article

# Efficacy of L-carnitine on liver function in childrens under chemotherapy with acute lymphoblastic leukemia

**Hashemi1.A[1] MD, Souzani.A[2] MD, Meshkani.M[3] MD, Osia.S[4] MD, Shahvazian.N[5] MD, Keshavarzi.S[6] MD, Atefi.A[7] BSc**

**1-Pediatric Hematology oncology, Hematology, Oncology and Genetics Research Center, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran**
**2,3,5,6- MD, Hematology, Oncology and Genetics Research Center, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran**
**4- Pediatric Gastroenterologist, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran**
**7-bbHematology, Oncology and Genetics Research Center, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran**

**Received: 22 October 2010**
**Accepted: 17 March 2011**

## Abstract

### Background

Patients who are to receive chemotherapy require careful assessment of liver function prior to treatment to determine which drugs may not be appropriate, and which drug doses should be modified. Following therapy abnormalities of liver function tests may be due to the therapy rather than to progressive disease, and this distinction is of critical importance. Toxicity such as hepatotoxicity could be reduced by L-Carnitine (L.C) with out affecting its anti-cancer therapeutic efficacy. The objectives of the present study were to assess the role of L-Carnitine by evaluating the liver functions.

### Materials and Methods

We performed randomized, double-blind, placebo-controlled study, the number of 64 ALL patients were enrolled in our study. Patients was randomly divided into two groups (each group 32 patients), and using double-blind administration, group A was treated with L-Carnitine and group B with placebo for 90 days.

### Results

We observed differences in serum AST level 3,7,30 days after chemotherapy ($p=0.006$, $p<0.001$, $p= 0.001$), serum ALT level 7,30 days after chemotherapy ($p=0.009$, $p<0.001$), serum ALK-P level after 30,90 days after chemotherapy ($p<0.001$), Prothrombin time 3,7,30 days after chemotherapy ($p=0.017$, $p=0.010$, $p=0.012$).No significant differences were observed in Alb and GGT in either group of patients treated with L-Carnitin or placebo.

### Conclusion

The benefits of L-Carnitine in comparison with placebo are demonstrated in reduction serum AST, ALT, ALK-P and PT but not in Alb and GGT. These issues deserved to evaluate the value of L-Carnitine in ALL patients.

### Key words

ALL, L-Carnitine, LFT, Liver function

**Corresponding Author:**
Azamsadat Hashemi, Pediatric Hematologist & Oncologist, Assistant professor – Hematology, Oncology and Genetics Research Center, Shahid Sadoughi Hospital ,Yazd- Iran Email:dr_a_hashemi@yahoo.com


www.SID.ir

Archive of SID

## Introduction

L-Carnitin is synthezid in the human brain, and kidney by the enzyme Acetyl-L-Carnitine-Transferase facilitates the uptake of acetyl coA into the mitochondrial for fatty acid oxidation stimulates protein and membrane phospholipid synthesis(1,2). l-Carnitine and its short chain derivative, propionyl-l-carnitine, are naturally occurring compounds that are synthesized endogenously as well as obtained from dietary sources (3). Carnitines play an essential role in transporting long-chain fatty acids from cytoplasmic compartment into mitochondria, where they are oxidized to produce energy, and act also as scavengers of oxygen free radicals in mammalian tissue(4-7).

One of the mechanisms of liver toxicity is cell membranes that Human studies have shown L-Carnitine has the ability to stabilize cell membrane fluidity via regulation of sphingomyeline levels(8).

Administration of L-Carnitine could prevent the drug induced mitochondrial damage in drug exposed cells (9).

L-Carnitine and palmitoyl-l-carnitine were reported to increase the formation of colony-forming unit-erythroid (CFU-E) colonies in cultures of fetal mouse liver cells, an effect that depended on the concentration of palmitoyl-l-carnitine but not of l-carnitine (10).Toxicity such as hepatotoxicity could be reduced by L-Carnitine with out affecting its anti-cancer therapeutic efficacy (11).

Side effects and toxicity L-Carnitine is considered safe at theraputic dosages and without incidence of significant side effects, even with long term (one year) administration. The most common adverse reactions noted have been agitation, nausea, and vomiting (12,13).

The objectives of the present study were to assess liver response to L-Carnitine supplementation by evaluating the liver enzymes.

## Materials and Methods

We performed a randomized, double-blind, placebo-controlled study, the number of 64 ALL patients with an age range of 1 to 14 years old (Average 8 years old) from 2009 until the end of 2010 in the Shahid Sadoughi hospital Yazd were enrolled in our study. Exclude criteria were relapse of ALL and hepatitis. Patients were randomly divided into two groups (each group 34 patients), and using double-blind administration, group A was treated with L-Carnitine and group B with placebo for 90 days.

Based on current knowledge of carnitine use, its metabolism, and treatment of deficiency, daily oral dose 1 gr fractionated in two single doses of LC for 90 days was selected for present study. Chemotherapy consisted of vincristin 1.5 $mg/m^2$ ,max 2mg ,6-MP75$mg/m^2$ ,MTX 20$mg/m^2$ and prednisol 45 $mg/m^2$.

Laboratory finding in enrolled patients were evaluated at base line before chemotherapy, after 3 days, 7days, 30days and 90 days after chemotherapy.

After baseline evaluated patients started treatment with 2gr of an oral L.C solution (from.alborz daru.).

Venous blood samples were collected in plain evacuated tubes from a forearm vein with minimal stasis after approximately 10 min of rest in a sitting position.

In this study laboratory findings in patients before chemotherapy and 3, 7, 30, 90 days after chemotherapy was assessed as a measure ALT (SGPT), AST (SGOT), ALK-P(Alkaline phosphatase), PT(prothrombin time) ,GGT(Gama glutamyl tranferase),Alb(Albumin).

Stsatistical methods included T-test, Chi square, ANOVA, and Fisher exact.

## Results

We observed significant differences in serum AST level 3,7,30 days after chemotherapy ($p=0.006$, $p<0.001$, $p= 0.001$), serum ALT level 7,30 days after chemotherapy ($p=0.009$,


www.SID.ir

Archive of SID

p<0.001), serum ALK-P level 30,90 days after chemotherapy (p<0.001), Prothrombin time 3,7,30 days after chemotherapy (p=0.017, p=0.010, p=0.012)
No significant differences were observed in Alb and GGT in either group of patients treated with L-Carnitin or placebo.

## Discussion

Chemotherapy with ifosfamide and cisplatin-based agents may result in increased urinary excretion and serum carnitine deficiency because they compete with carnitine reabsorption at the proximal convoluted tubule (14).
Dodson et al. observed a significant decrease in LC level in 23 patients with cancer compared with 13 healthy aged-matched controls15. Cruciani et al. observed that 67% of adult patients who had cancer and fatigue and resided in a hospice had carnitine deficiency (14).
A decrease in fatigue with LC supplementation in patients with cancer has been demonstrated in recent studies (14,16).
Concerning the possibility that LC supplementation accelerates cancer progression or interferes with the chemotherapeutic effect of certain agents, the current evidence suggests that LC does not have either effect (11,16).
Further studies should investigate in more depth the effect of LC supplementation on more detailed metabolic indexes, laboratory parameters, and significant clinical outcomes.
In review of research studies of cancer treatments that influenced the carnitine system, Peluso and colleagues noted that animal models suggest that there is interference by anti-cancer drugs on the carnitine network. Doxorubicin is an anthracycline antibiotic chemotherapy drug that is an important agent in the treatment of many pediatric malignancies including leukemia, lymphoma, and solid tumors but has the potential for cardiotoxic side effects.11
In animal models, carnitine supplementation improved these metabolic changes. Yoon, and et al found that rats treated with doxorubicin had a significant decrease in carnitine palmitoyl transferase (CPT) activity when compared to a control group (17).
In an adult cancer study of 10 patients receiving cisplatin chemotherapy, subjects had normal plasma carnitine levels pre-chemotherapy when compared to healthy controls. Carnitine plasma levels increased by 39% during the 3 days of chemotherapy and then normalized 7 days after a course of chemotherapy was completed (18).
In a pediatric study, total plasma carnitine levels of 51 children, ages 3 to 16 years with a variety of oncologic diagnoses and treatments, were similar in sex and age to 20 healthy controls at diagnosis (10). At month 3 of treatment, the children with cancer had a significant decrease in total carnitine levels ($p = 0.004$) and the levels were significantly different than the healthy controls ($p = 0.02$). The carnitine levels were not related to age, sex, type of cancer, or stage of disease (10).
In animal models, carnitine has been shown to be a modulator of the glucocorticoid receptor glucorticoids are used in the treatment of leukemia and lymphoma. Further research is needed to understand how carnitine plasma levels change in children and adolescents over the course of cancer treatment, what chemotherapy drugs may decrease carnitine levels, and how these levels influence other symptoms (19).
Results from one study indicate that d-carnitine alone did not alter the level of total carnitine in liver tissues. theire results are in good agreement with earlier and recent studies that have demonstrated that d-carnitine depletes l-carnitine in specific tissues including skeletal muscles, heart and kidney and not in the liver (20-22). The fact that l-carnitine is mainly synthesized in the liver and then largely exported towards muscles (23). Leads one to presume that depletion of carnitine from the liver would be partly compensated by carnitine released from muscles and partly through endogenous synthesis.


www.SID.ir

Archive of SID

In early experiments investigated the protective effects of carnitine against acute (high-dose) and chronic (intermittent, low dose) DOX toxicity in rat and mice. They found that carnitine was able to decrease both acute and chronic DOX-linked lethality in normal rats without decreasing its antineoplastic activity or raising its bone marrow toxicity (24).
In carnitine-depleted rat model, investigated whether or not carnitine deficiency is a risk factor and could contribute to CDDP-induced liver toxicity, and if so, whether carnitine supplementation using PLC could offer protection against this toxicity. The author concluded that oxidative stress is not the main cause of CDDP-related hepatotoxicity but rather carnitine deficiency provokes CDDP-induced hepatotoxicity and that carnitine supplementation prevents the development of CDDP-induced liver injury (20).
Abd-Allah et al. have initiated an in vitro study utilizing bone marrow cell cultures and reported that L-carnitine is effective not only in protecting against carboplatin-induced kidney damage but it is also effective in protecting against carboplatin-induced myelosuppression (25).
Shaker ME et al described the potent effect of L-Carnitine in reducing hepatic oxidative stress (4) (26).
Our results show the benefits of L-Carnitine in comparison with placebo in reduction serum AST, ALT, ALK-P and PT but not in Alb and GGT.
In conclusion, a more complex approach to mechanisms that underlie tumor growth, which takes into account the altered metabolic pathway in cancer disease, could represent a challenge for the future of cancer research. From this point of view, the study of the L-Carnitine system represents a tool to understand the molecular basis underlying the metabolism normal and cancer cells.
All metabolic changes and chemotherapy-induced toxicity are more sever in chidren with malignant disease in comparison with adults, because of the growth process in children is not yet complete. Every effort in decreasing the side effects of the anticancer drugs, without affecting their antineoplastic efficacy, would be of major importance, as a better quality of life could be provided.

## Conclusion

L-Carnitine therapy appears to be safe and effective when administrated in ALL patients in this study. How ever, these issues deserved further investigation in controlled, randomized and probably multicenter trials to evaluate the value of L-Carnitine in ALL patients.

## References

1- Parnetti L, Gaiti A, Mecocci P, Cadini D, Senin U. Pharmacokinetics of IV and oral acetyl-L-carnitine in a multiple dose regimen in patients with senile dementia of Alzheimer type. Eur J Clin Pharmacol. 1992; 42:89-93.
2- Marcus R, Coulston AM . Water-soluble vitamins . In: Hardman JG, Limbird LE, Eds. The Pharmacological Basis of Therapeutics, 9th Ed. New York: McGraw-Hill; 1996.
3- Goa KL, Brogden RN. l-Carnitine. A preliminary review of its pharmacokinetics, and its therapeutic use in ischaemic cardiac disease and primary and secondary carnitine deficiencies in relationship to its role in fatty acid metabolism. Drugs. 1987;34:1–24.
4- Arafa HM, Sayed-Ahmed MM. Protective role of carnitine esters against alcohol-induced gastric lesions in rats. Pharmacol Res 2003;48:285–90.
5- Arockia Rani PJ, Panneerselvam C. Carnitine as a free radical scavenger in aging. Exp Gerontol. 2001;36:1713–26.
6- Vanella A, Russo A, Acquaviva R, Campisi A, Di Giacomo C, Sorrenti V, et al. l-propionyl-carnitine as superoxide scavenger, antioxidant, and DNA cleavage protector. Cell Biol Toxicol. 2000;16:99–104.
7- Yasui F, Matsugo S, Ishibashi M, Kajita T, Ezashi Y, Oomura Y, et al. Effects of chronic acetyl-l-carnitine treatment on brain lipid hydroperoxide level and passive avoidance learning in senescence-accelerated mice. Neurosci Lett. 2002;334:177–80.


www.SID.ir

Archive of SID

8- Capecchi PL, Laghi Pasini F, Quartarolo E, Di Perri T. Carnitines increase plasma levels of adenosine and ATP in humans. Vasc Med. 1997;2:77-81.
9- Nikula P, Ruohola H, Alhonen-Hongisto L, Jänne J.. Carnitine prevents the early mitochondrial damage induced by methyloglyoxal bis(guanylhydrazone) in L1210 leukemia cells. Biochem J. 1985; 228:513–516.
10-Yaris N, Akyüz C, Coşkun T, Büyükpamukçu M. Serum carnitine levels of Pediatric cancer patients. Pediatr Hematol Oncol. 2002;19:1–8.
11- Peluso G, Nicolai R, Reda E, Benatti P, Barbarisi A, Calvani M.. Cancer and anticancer therapyinduced modifications on metabolism mediated by carnitine system.J Cell Physiol. 2000; 182:339–350.
12- Rai G, Wright G, Scott L, Beston B, Rest J, Exton-Smith AN. Double-blind, placebo controlled study of acetyl-L-carnitine in patients with Alzheimer's dementia. Curr Med Res Opin 1990; 11:638-647.with Alzheimer's disease. Arch Neurol. 1992; 49:1137-1141.
13- Spagnoli A, Lucca U, Menasce G, Bandera L, Cizza G, Forloni G. Long-term acetyl-L-carnitine treatment in Alzheimer's disease.Neurology. 1991; 41:1726-1732.
14- Cruciani RA, Dvorkin E, Homel P, Culliney B, Malamud S, ShaiovaL, et al. L-carnitine supplementation for the treatment of fatigue and depressed mood in cancer patients with carnitine deficiency. Ann NY Acad Sci. 2004;1033:168 –76.
15- Dodson WL, Sachan DS, Krauss S, Hanna W. Alterations of serum and urinary carnitine profiles in cancer patients: hypothesis of possible significance. J Am Coll Nutr 1989;8:133– 42.
16- Graziano F, Bisonni R, Catalano V, Silva R, Rovidati S, Mencarini E, et al. Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anaemic patients. Br J Cancer. 2002; 86:1854 –7..
17- Yoon H, Hong Y M, Boriack R, Bennett M. Effect of L-carnitine supplementation on cardiac carnitine palmitoyltransferase activities and plasma carnitine concentrations in adriamycin-treated rats. Pediatric Research. 2003;53(5):788-792.
18- Heuberger W, Beradi S, Jacky E, Pey P, Krahenbuhl S. Increased urinary excretion of carnitine in patients treated with cisplatin. European Journal of Clinical Pharmacology. 1998; 54: 503-508
19- Alesci S., De Martino M.U., Kino T., Ilias, I. L-Carnitine is a modulator of the glucocorticoid receptor alpha Annals of the New York Academy of Sciences. 2004; 1024: 147-52.
20- Al-Majed AA, Sayed-Ahmed MM, Al-Yahya AA, Aleisa AM, Al-Rejaie SS, Al-Shabanah OA. Propionyl-l-carnitine prevents the progression of cisplatin-induced cardiomyopathy in a carnitine-depleted rat model. Pharmacol Res. 2006; 53:278–86.
21- Paulson DJ, Shug AL. Tissue specific depletion of l-carnitine in rat heart and skeletal muscle by d-carnitine. Life Sci. 1981; 28:2931–8.
22- Sayed-Ahmed MM, Eissa MA, Kenawy SA, Mostafa N, Calvani M, Osman AM. Progression of cisplatin-induced nephrotoxicity in a carnitine-depleted rat model. Chemotherapy. 2004;50:162–70.
23- Tanphaichitr V, Broquist HP. Site of carnitine biosynthesis in the rat. J Nutr. 1974;104:1669–73.
24- Alberts DS, Peng YM, Moon TE, Bressler R.Carnitine prevention of adriamycin toxicity in mice, Biomedicine 1978;29(8):265-8.
25- Abd-Allah AR, Al-Majed AA, Al-Yahya AA, Fouda SI, Al-Shabana OA. L-Carnitine halts apoptosis and myelosuppression induced by carboplatin in rat bone marrow cell cultures (BMC), Arch. Toxicol. 2005 Jul;79(7):406-13.
26- Shaker ME, Houssen ME, Abo-Hashem EM, Ibrahim TM.Comparison of vitamin E, L-carnitine and melatonin in ameliorating carbon tetrachloride and diabetes induced hepatic oxidative stress. J Physiol Biochem. 2009 Sep;65(3):225-33.


www.SID.ir