CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Research Article

INVESTIGATION OF THE IMPROVEMENT EFFECT OF L-CARNITINE ON CYCLOPHOSPHAMIDE INDUCED-TESTICULAR DAMAGE IN ADULT MALE RATS

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Abstract:
Cyclophosphamide is an antineoplastic drug that has many useful effects in cancer treatment, but it has toxic effects due to induced free radicals. In this study the effects of L-carnitine as an antioxidant drug on testis tissue and its sexual hormones was investigated. 48 adult male wistar rats were selected randomly and divided to 6 groups including :control, sham (received normal saline) , cyclophosphamide received group (5 mg/kg), and experimental groups 1, 2, and 3 (receiving 250, 500, and 1000 mg/kg doses of L-carnitine, respectively). L-carnitine and normal salin were administered as gavage. After dissection, the rats' testes were removed and put in 10% formalin for fixation and slides preparation processes were carried out. Also their serum samples were separated in order to measure the LH,FSH and testosterone with eliza. The results revealed a significant decrease in number of spermatogonia, spermatocyte, spermatids, sertoli, leydig cells, LH, FSH and testosterone hormones in rats that received cyclophosphamide in compared to control and sham groups($P \leq 0.05$). So the results revealed an increase in the number of sexual cells, and sexual hormones in the under treatment with L-carnitine high dosage groupes compared to cyclophosphamide group ($P \leq 0.05$).
The concurrent use of cyclophosphamide and L-carnitine can decrease the cyclophosphamide toxic effects on testes tissue and its sexual hormones.
Key words: *L-carnitine, cyclophosphamide, Testis, Rat.*

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Please cite this article in press as Sara Rahimi and Mehrdad Shariati, ***Investigation of the Improvement Effect of L-Carnitine on Cyclophosphamide Induced- Testicular Damage in Adult Male Rats,****Indo Am. J. P. Sci, 2017; 4(87).*

INTRODUCTION:

Chemotherapy and radiation therapy are associated with many changes in the reproductive system, and among these agents alkylated drugs have the most adverse effects on gonads [1]. Today, especially in developed countries, successful treatment of malignancies And the life expectancy of these people has increased significantly, and most of these people, especially young people, tend to have fertility and childbirth after recovery[2]. Cyclophosphamide is an anti-neoplastic drug (an anticancer drug) that converts to an active metabolising metabolite with the same effects as mostin (an anti-cancer drug) in the body. The cyclophosphamide is well absorbed from the gastrointestinal tract and is widely distributed in body tissues and fluids and passes through the blood-brain barrier. This drug is converted into active metabolites in the liver and eventually excreted through the kidneys[3]. Studies have shown that cyclophosphamide is a teratogen in mice, rats, rabbits, and monkeys with much lower amounts than humans. Its use in humans has led to the production of natural and abnormal infants (including the absence of fingers and legs, heart abnormalities and hernias) [3]. Considering the above and considering the antico-plastic effects of cyclophosphamide, a study to find ways to reduce complications from chemotherapy is very important. Nowadays, methods used to prevent infertility after chemotherapy are freezing testicular and ovarian tissue, increasing the resistance of the stem cells of the stem cells, and helping to maintain or regenerate these cells, while retaining Cells are more commonly used in chemotherapy than other methods [4](2004, Fossa and Magelssen). Biological compounds with antioxidant properties are capable of Protect cells and tissues from disorders caused by active oxygen species and free radicals [5,6]. Therefore, administration of antioxidants during chemotherapy is necessary in order to reduce oxidative stress and to detoxify tissues. In other words, simultaneous administration of antioxidants and chemotherapy drugs reduces the toxicity of reproductive toxicity [7]. One of the materials found by researchers is the L-carnitine antioxidant with the chemical formula beta-hydroxy-gamma-nitro-aminobutric acid, which is found to be high in meat and dairy products. L-carnitine is made from lysine and methionine amino acids and plays an important role in the transmission of free fatty acid to the mitochondrial matrix in the beta-oxidation process [8] (Stephens et al., 2007). Research has shown that L-carnitine plays a positive role in sperm motility and metabolism [9] by supplying the energy needed for sperm. The concentration of L-carnitine in the epididymis and sperm is 2000 times greater than that in plasma. It also protects the cell membrane and DNA, from damage caused by free oxygen radicals. There are several studies Which shows a decrease in the level of L-carnitine in seminal fluid in infertile men [10] (Sigman et al., 2006). A study by Vitali et al. Found that administration of l-carnitine increased the number of sperm motility and movement [11]. Also, the results of Lenzi et al. Showed a positive effect of L-carnitine on increased fertility, number and motility of sperm in 86 infertile men [9].

Therefore, in light of the above, the aim of this study was to investigate the effects of l-carnitine on the prevention of cyclophosphamide complications on testicular tissue in adult male rats.

Introducing cyclophosphamide cyclophosphamide))

Cyclophosphamide is an anti-neoplastic drug (an anticancer drug) that converts to an active metabolising metabolite with the same effects as mostil (anticancer drug) in the body. The cyclophosphamide is well absorbed from the gastrointestinal tract and is widely distributed in body tissues and fluids, and from the cryopreservation of the brain goes on. This drug turns into active metabolites in the liver and ultimately excretes through the kidneys **[12-14].**

How to use and half-life of cyclophosphamide

Duration of work	Peak Effect	Start the effect	The way of consumption
21 days	10-14 days	7 days	Edible
21 days	10-14 days	7 days	Intravenous injection

El Carnitine, L-carnitine is an unnecessary amino acid. Deformed amino acids L-carnitine is produced in the form of androgens in almost all species of animals and even in some excellent herbaceous species[15]. This substance exists in two forms of di-L-carnitine, a form of di-carnitine that is synthetic and not produced at the biological level. Carnitine with the formula $C_7 H_{15} NO_3$ is a betaine compound which, on the one hand, dissolves as an internal salt in water, and on the other hand exhibits strong hydroscopic properties. Its molecule has a molecular weight of 161.2 [15]. Cyclophosphamide is an anticancer drug used in the treatment of diseases such as lymphoma, leukemia, neuroblastoma, ovarian carcinoma, breast cancer, and autoimmune diseases (Dollery, 1999). Kang et al. (2011)[16,17] showed that administration of L-carnitine induced a significant decrease in apoptotic cells in the wall of the seminal tubes of diabetic rats (Kang et al., 2011). Research has shown that L-carnitine plays an important role in protecting the sperm membrane from free radicals and oxidative stress due to its antioxidant properties (Kerner and hoppel, 1998). McDermott et al. (1996)[18,19] discovered that chemotherapy with cyclophosphamide, in patients with breast cancer that has not yet experienced menstruation, causes a chemical infertility, as well as in the treatment of women with systemic lupus erythematosus, the drug Create untimely menstruation in them
(McDermott et al., 1996). Parandak et al. (2014) [19,20] reported that daily intake of 2 grams of L-carnitine supplementation for 2 weeks during endurance exercise reduced the effects of lipid peroxidation and muscle damage
(Parandak et al., 2014). Premkumar et al. (2006)[20,21] also reported that saffron has prevented DNA damage from bone marrow cells in mice due to the use of anti-tumor drugs, synplatin, cyclophosphamide and mitomycin [21]. Bokser et al. (1990)[22] considered ovarian dysfunction in rats following cyclophosphamide due to degradation of granulose cells[22].
It has been shown that single-dose and intraperitoneal injection of cyclophosphamide causes the destruction and degradation of particles within the mitochondria and the smooth endoplasmic net of hepatocytes and also increases the level of hemoglobin malondialdehyde [23]. Kraemer et al. (2003)[24] stated that daily intake of 2 grams of L-carnitine supplementation during 3 weeks of resistance training reduces free radicals and also increases the synthesis of muscle structural proteins [24].

RESEARCH METHODOLOGY:

Methods and procedures for conducting the test

How to select and maintain the animals tested
The animals tested in this study included 48 Wistar male rats, which were completely randomized from Shiraz University of Medical Sciences and were tested at the experimental animals' laboratory. To feed animals, we used compressed food (pellets) from the feed and livestock feed company. The water used by the rats was plumbing water provided to them in plastic containers for drinking water in rats. Animals used in transparent macrolon cages of 20 × 55 × 55 cm were covered with stainless steel mesh ceilings and the floor of the cages was covered with sawdust and wood chips. It should be noted that the wood chips in the cages were replaced every two days, and the cages were washed and disinfected with alcohol and soap. Ambient temperature 22±2° c and humidity was 55 ± 3 and the 12-hour light period and the 12-hour dark period were provided. The floor and the equipment in it were disinfected by Saulen.
Grouped animals tested
In this study, 48 adult male Wistar rats were grouped in 8 groups. Mice were weighed before and after the test.
Animals were categorized completely randomly in the following groups:
- Control group: There are no animal treatments in this group, and animals only use ordinary water and food.
- Sham group: In this group, the animals also receive the solvent volume given to the experimental groups as a gavage for the drug, i.e., the serum of physiology.
- Experimental group 1: Group treated with cyclophosphamide (mg / kg 5) (vasegh et al., 2014).
- Experimental group 2: The group treated with L-carnitine (mg / kg 500) (Yari et al., 2009).
- Experimental group 3: Group treated with cyclophosphamide (5 mg / kg) + lactartin (250 mg / kg).
- Experimental group 4: Cyclophosphamide treated group (5 mg / kg) + lactartin (500 mg / kg).
How to prepare and prescribe cyclophosphamide and carnitine
The cyclophosphamide pill used in this study was packed in 10 packs (50 mg) from the pharmacy of Namazi Hospital in Shiraz. On the other hand, L-carnitine powder was purchased from Sigma as a 100 g vial. In order to prescribe cyclophosphamide and L-carnitine, the drug dose ((cyclophosphamide 5 mg / kg body weight) and (L-carnitine 250, 500 and 1000 mg / kg body weight) were used first (required values, weight And dissolved in normal saline. Then, given the weight of the rats, administration was made for 30 days.
The method of measuring the concentration of LH, FSH and testosterone hormones

ELISA method was used to measure the concentration of LH, FSH and testosterone hormones. This method combines the specificity of antibodies and the sensitivity of simple enzyme measurements.

Method of study of tissue sections

Slides prepared from cross-sectional testicles of adult adult rats were separately studied by optical microscope with a magnification of 40 ×. In each slide, the average number of spermatogonium, spermatocyte, spermatid, sertoli and leydig cells in the spermatogonial tubes was performed in 20 tubules per lam by counting with optical microscope and solvent counterpart. After counting the cells, a Nikon microscope was used for photomicrographs.

Statistical analysis and statistical methods

The crude numbers obtained by measuring serum concentrations of LH, FSH and testosterone hormones, as well as body weight, testicles and sexually transmitted cells in SPSS software were analyzed by one way ANOVA and tukey test for each separate test. They were compared with each other and their charts were plotted by one-way ANOVA based on the data obtained from the analysis of numbers. The values used are mean ± SD and SEM ($p \leq 0.05$).

RESULTS:

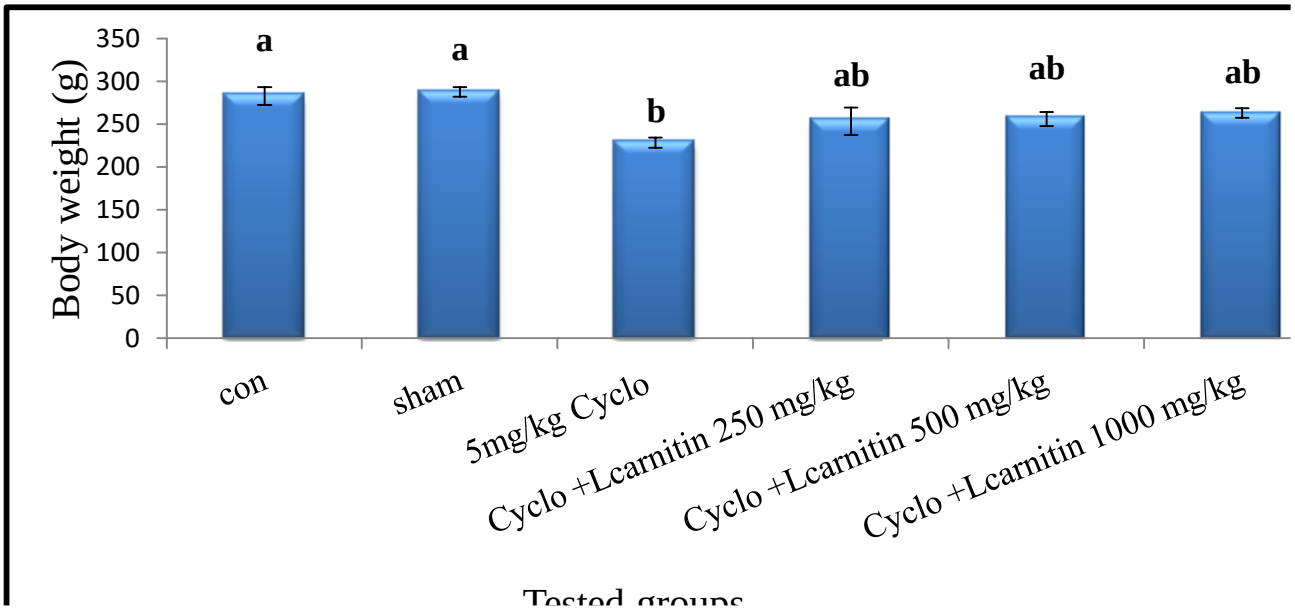

Fig1: Results of mean body weight in the studied groups

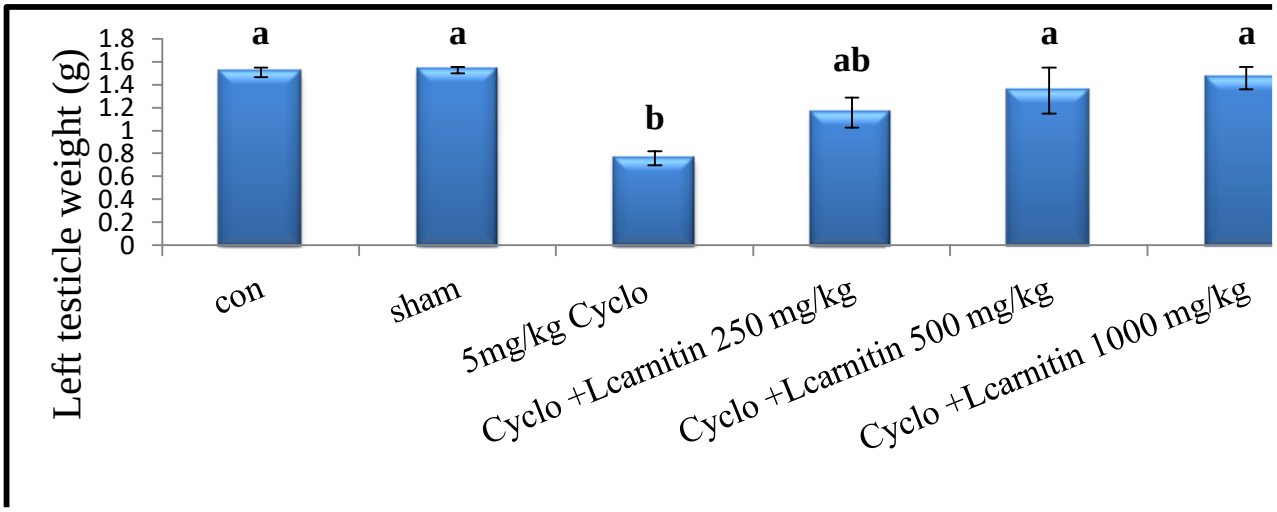

Fig 2: shows the results of mean left testicle weight in the studied groups

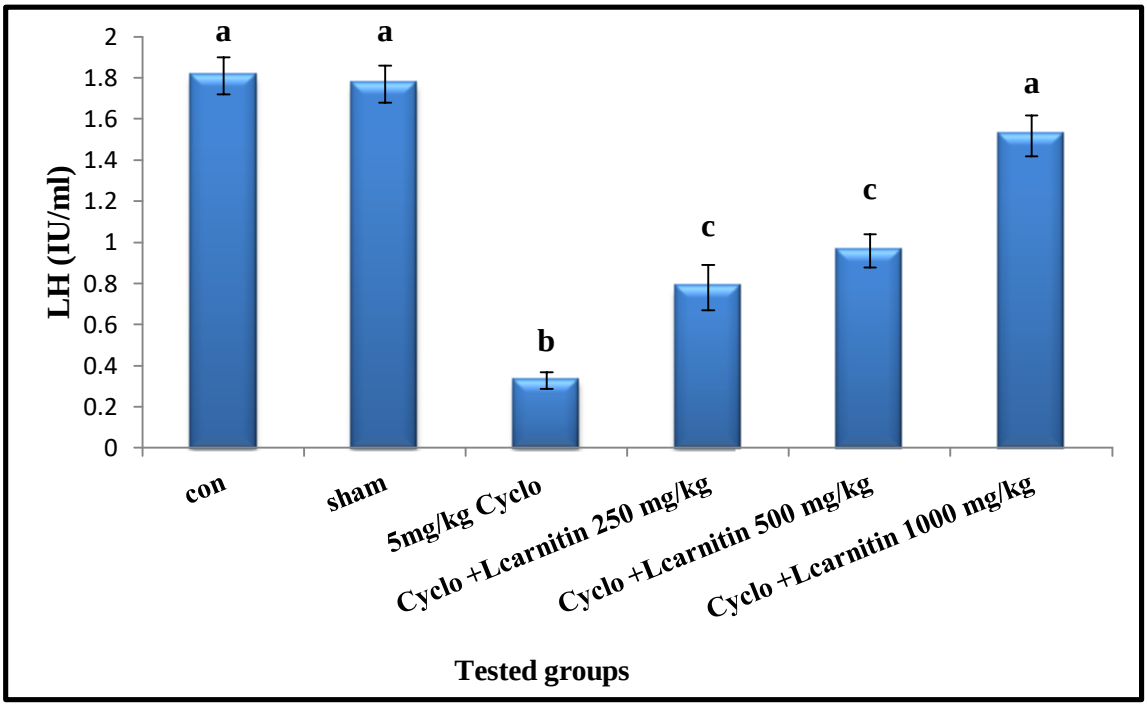

Fig 3: Shows the results of the mean concentration of LH in the studied groups

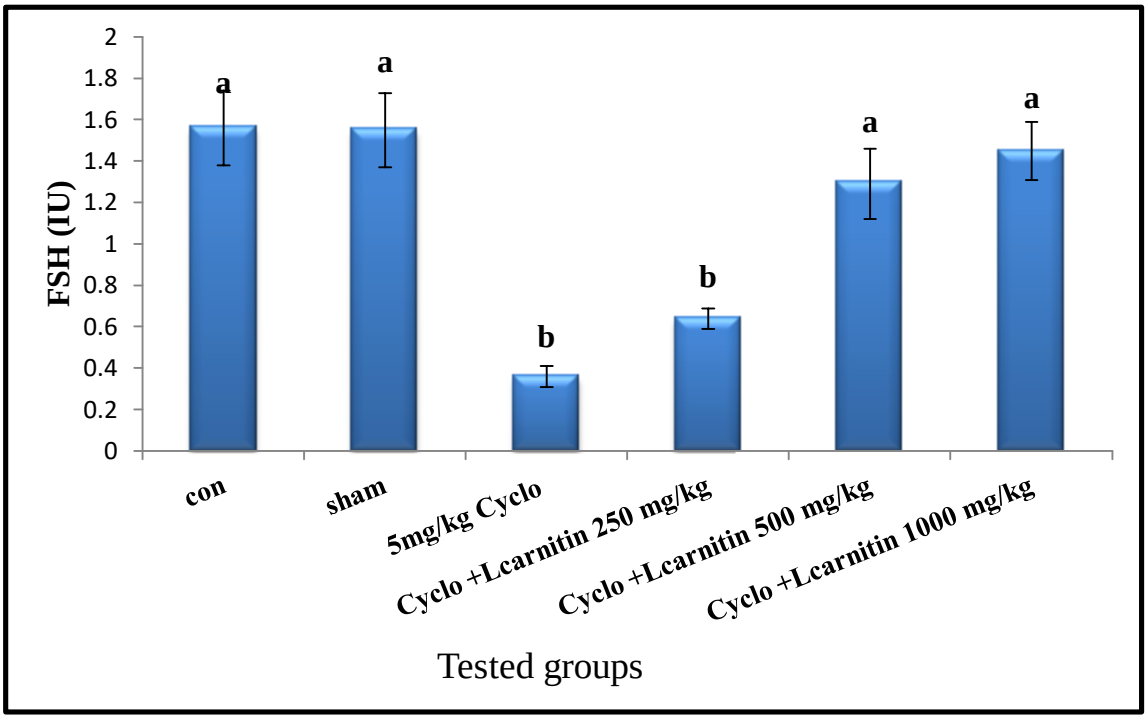

Fig 4: Results of the mean concentration of FSH in the studied groups

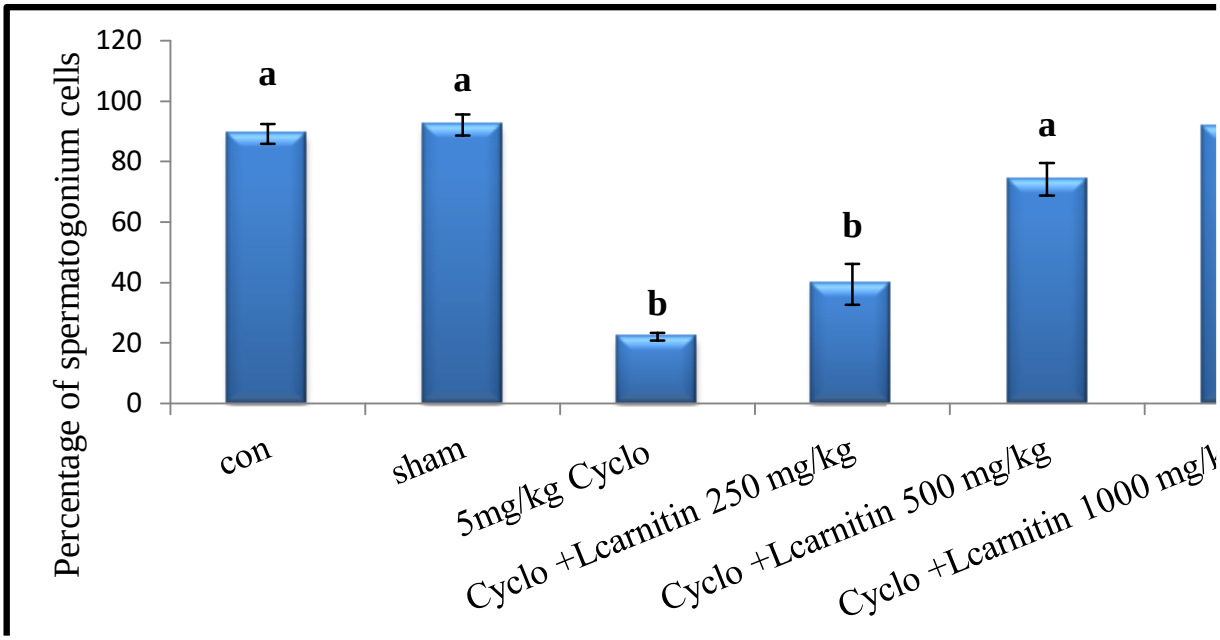

Fig 5: Results of spermatogonial cells count in the studied groups

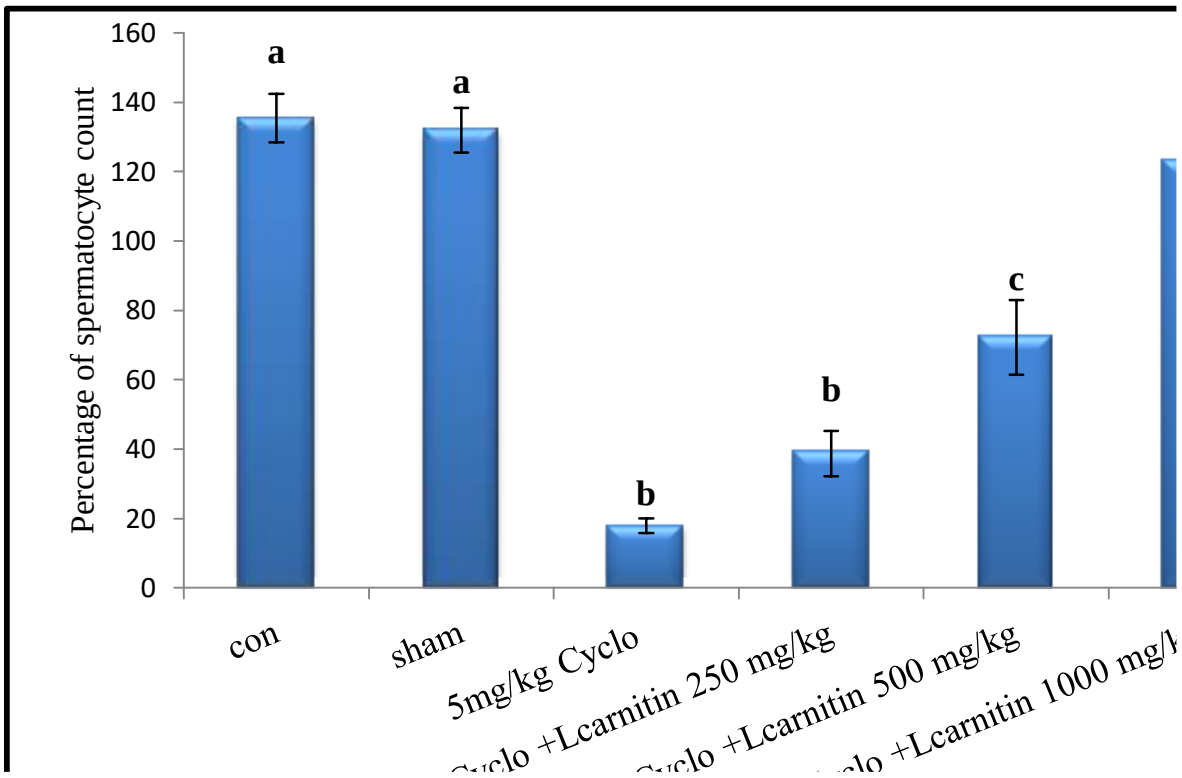

Fig 6: shows the results of spermatocyte count in the studied groups

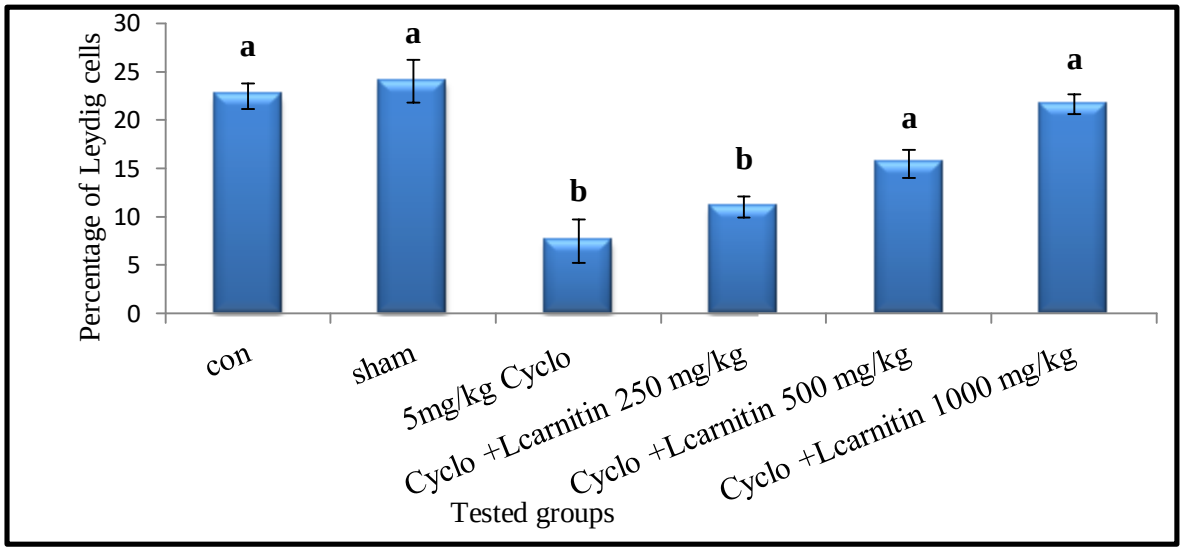

Fig 7:The results of the Leydig cell count in the studied groups

DISCUSSION AND CONCLUSION:

Interpretation of results related to body weight in rats

In the present study, the mean weight of rats only decreases significantly in the cyclophosphamide group than in the control group. In other groups, there was no significant change in relation to each other. Studies have shown that cyclophosphamide interferes with appetite and nausea and vomiting[13,25], which can be due to stimulation of the chemical receptor located on the fourth ventricle in the inferior alveolar region [26]. It also causes toxic effects on the sexual organs, liver and proteinuria[25]. Lopez et al. (2004) [27]report the weight loss of mice in the group prescribed only cyclophosphamide [27]. Deleve 2003[28] also observed a decrease in weight loss in the group that used the cyclophosphamide alone in a study on toxic effects of cyclophosphamide on the liver, due to the effects of cyclophosphamide toxicity on the liver, kidneys and other organs [28]. study by Das in 2002 found that cyclophosphamide-receptor rats significantly decreased weight (Das, 2002), which is consistent with the findings of the study. Therefore, it can be said that probably cyclophosphamide has been able to reduce body weight by inhibiting proteinuria and affecting the amount of fat due to low appetite, and decreased protein and fat mass. But if we want to express the role of L-carnitine, it should transfer the active fat from fat storage masses into mitochondria and act as a cofactor in the production of energy, and develop the process of production of middle-chain fatty acids and pyruvate as well as ketone bodies It also controls the internal environment of the cell and detoxifies it [29]. In the study, L-carnitine reduced abdominal fat resulting from a high-fat diet in mice [30]. In a study conducted on diabetic obese subjects, the findings showed that supplementation of two grams of L-carnitine With Orlistat, it has found better results in improving lipid and lipid profiles than Orlistat alone [31]. A number of studies have shown that supplementation of L-carnitine can stimulate the increase of l-carnitine in different tissues and, consequently, increase the oxidation of fatty acids, and increase the oxidation of fatty acids in reducing fat mass [32-34].

Interpretation of the results of the mean left and right testicles in rats.

In the present study, there was a significant decrease in the mean of left and right testicles in the cyclophosphamide receiving group compared to control and sham groups. On the other hand, in the groups receiving l-carnitine 500 mg / kg and 1000 mg, the weight loss of the left and right testicles was significantly prevented. One of the reasons for the loss of testicular weight and atrophy of testicles is a disorder that disrupts spermatogenesis, such as cyclophosphamide. By creating free radicals and breaking DNA cells, this drug can cause apoptosis and necrosis. In other words, cyclophosphamide, by affecting the DNA molecule, inhibits the replication of the cells, resulting in a decrease in the number of spermatogonium, sperm, spermatid, spermatocyte cells and the testicular tissue is affected by oligospermia or azoospermia [35].

Due to the fact that the LH hormone secretes testosterone from the interstitial cells, and testosterone with FSH causes spermatogenesis, decreasing testosterone release (Guyton and Hall., 1996) decreases with decreasing LH as a result of spermatogenesis. By reducing the process Spermatogenesis The weight of the testicle also decreases.

Interpretation of the results of mean concentrations of LH, FSH and testosterone hormones in the studied groups. In this study, there was a significant decrease in the mean concentration of LH, FSH and testosterone in the cyclophosphamide receptor group compared to control and sham groups. Also, the mean concentration of these hormones in the groups receiving l-carnitine showed a significant increase compared to the cyclophosphamide recipient group. However, although the concentration of LH in the two groups of 250 mg / kg (250 mg / kg) and 500 (500 mg / kg) and testosterone concentrations in the larvalent group (500 mg / kg) received a significant increase compared to the recipient group Cyclophosphamide showed but not within the control and control groups, and they also show significant differences.

Interpretation of the results of spermatogonium, spermatocyte, spermatid, sertoli and leydig cells in the studied groups

In the present study, there was a significant reduction in the number of spermatogonial, spermatocyte, spermatoid and leydig cells in the cyclophosphamide receiving group compared to the control group. However, the reduction in the number of these cells was prevented in the groups receiving l-carnitine at a dose of 1000 mg / kg (and sometimes at a dose of 500 mg / kg). Which indicates the positive effects of l-carnitine against the effects of cyclophosphamide active metabolites (such as acrolein)? In fact, El Carnitine has been able to protect cells from apoptosis and necrosis due to its potent antioxidant properties. Kang et al. (2011)[17] also found that administration of carnitine induced a significant reduction in apoptotic cells in the wall of the spermatozoon tubes. The results of Lenzi et al. Showed positive effects of l-carnitine on increased fertility, Showed the number and motility of sperm in 86 infertile men [36]. Another study by Shrilatha et al. 2007, [37]revealed increased lipid peroxidation and the production of free radicals as a cause of destructive effects on Testicular tissue and spermatogenesis process [37]. Therefore, considering the above studies and the positive effects of l-carnitine on testicular tissue cells, it can be argued that l-carnitine has been able to protect testicular tissue cells from cyclophosphamide damage due to its potent antioxidant properties.

CONCLUSION:

The results of this study showed that L-carnitine was dose-dependent in doses of 500 and 1000 mg / kg body weight, and somewhat reduced the testicular weight, spermatogonia, spermatocyte, spermatid, sertoli, leydig and serum concentrations Testosterone, LH and FSH inhibit hormones. So it can be used in therapeutic cases.

ACKNOWLEDGEMENT:

This article is extracted from my thesis under the title of “Investigation of the Improvement Effect of L-carnitine on Cyclophosphamide Induced- Testicular Damage in Adult Male Rats”. Hereby, I extend my sincere appreciation to Islamic Azad university of Shiraz for the efforts and supports they provided to me.

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