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The Effect of L-carnitine on Improving Seminal Fluid Parameters in Male Infertility

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Abstract

Background L-carnitine is an important antioxidant present in a high concentration in epididymal fluid. It supplies energy for sperms to acquire their motility in the epididymis.

Objective To evaluate the effect of L-carnitine on improving some of the seminal fluid parameters in infertile males.

Methods Ninety-six infertile males were divided into two groups, a group received L-carnitine and the other group received multivitamin. Seminal fluid analysis performed before and after treatment in both groups. Analysis and comparison of the results were carried out between both groups for all patients then for patients with primary and secondary infertility in each group.

Results The patients received L-carnitine showed no improvement in semen volume but a significant raise in sperm concentration observed in all patients. A highly significant raise of sperm motility was observed especially in patients with primary infertility.

Conclusion L-carnitine significantly improves sperm concentration and sperm motility especially in patients with primary infertility. It is recommended for oligoasthenozoopermic infertile men.

Key words Male infertility, antioxidants, L-carnitine, azoospermia.

Introduction

Infertility is defined as the failure to achieve pregnancy within one year of regular unprotected intercourse. It affects approximately 15% of sexually active couples; however, male factor contributes to about 40% of the cases [(1)]. It is characterized by low sperm concentration and/or sperm motility and/or increased abnormal sperm morphology. These changes are collectively named oligoasthenoteratozoospermia (OAT) and they are considered significant only if observed in two semen analyses collected between one to four weeks apart. This complies with the WHO guidelines (2010) [(2)]. About 30% of these cases are idiopathic (iOAT) [(3-5)]. iOAT may be related to increasing age or to non inflammatory functional alterations in epididymis or to some viral and chlamydial infections [(6-8)].

The treatment of male infertility especially iOAT can be problematic. Different drugs, dietary supplements and antioxidants are used but still

lack evidence supporting their efficacy [9]. L-carnitine is one of the important antioxidants in male fertility. It is a water-soluble amino acid that was first isolated from bovine muscle in 1905. Its structure was definitively established in 1927 [10]. In human, 75% of carnitine derives from diet while 25% is synthesized from lysine and methionine [11]. Its concentration in the epididymal fluid is 2000 folds higher than in plasma [12]. It has a role in mitochondrial β-oxidation of long chain fatty acids to provide energy for sperms and it acts also to protect the cell membrane and DNA against damage induced by free oxygen radicles [13], therefore, it has been used in the recent years to treat iOAT [14].

The aim of this study is to evaluate the effect of L-carnitine on improving seminal fluid parameters of infertile males in Mosul province and to assess its effect in patients with primary and secondary infertility.

Methods

This is a prospective randomized controlled clinical study. The study was approved by the scientific and ethical committee of the Department of Surgery at Mosul College of Medicine. Written agreements were obtained from all participants. The study, initially, included 104 infertile male patients but during the study period, 8 patients were excluded because of using herbals and medicines other than the standard drugs of our study, therefore, 96 infertile patients completed the study. The period of the study started from January 2012 to February 2013. Patient assessment and data collection were conducted in Al-Salam Teaching Hospital in Mosul. All patients underwent complete history, physical examination and investigations, including seminal analysis (SA), semen culture, hormonal studies (Follicular stimulating hormone (FSH), luteinizing hormone (LH), prolactin and testosterone) and transrectal ultrasound (TRUS) for suspected obstructive azospermia. Patients were selected according to inclusion and exclusion criteria. The inclusion criteria, according to WHO guidelines [2], include one or more of the following:

a. Sperm count < 15 million/ml.
b. Sperm total motility (A+B) < 40%.
c. Sperm of rapid progressive motility (A) < 32%.

(The grades of sperm motility are: Grade A: rapidly progressive. Grade B: slowly progressive)

The exclusion criteria are:

1. Recent febrile illnesses, taking herbals or medications that might affect seminal parameters in the last 3 months prior to the study.
2. Presence of obvious causes of male infertility (varicocele, cryptorchidism, orchitis and epididymitis with pyospermia, radiation or chemotherapy, any scrotal, inguinal or pelvic surgery, clinical hormonal abnormalities in FSH, LH, testosterone or prolactin and patients with obstructive azoospermia (diagnosed by acidic, low volume semen with low seminal fructose level and confirmed by TRUS).

The patients were categorized into two groups, the control group (48 patients) kept on multivitamin treatment containing group B vitamins (1 tablet/day) and the carnitine group (48 patients) received L-carnitine (1 g tablet twice daily). The treatment period in both groups was 2.5 months. This dose was selected because it is the most commonly used dosage in past trials on this subject [15]. SA was done prior to the onset of the study and 2 weeks after the end of the treatment course. Semen samples were collected after 3-5 days of sexual abstinence and the standard manual semen analysis was performed according to the WHO guidelines [2]. During the study period, the patients were interviewed monthly to assess their compliance with treatment and if they took other medicines.

In each group, the patients were further subcategorized, according to the type of infertility, into primary infertility group (the couples who never had history of conception) and secondary infertility group (couples with previous history of conception but now are infertile).

The aim of this subgrouping was to assess the effect of L-carnitine in primary and secondary infertility by comparing each with their control group.

Statistical analysis was performed using SPSS software 2009. The differences between carnitine group and control group were assessed using the unpaired student's t-test. The results are given as mean ± standard deviation and *P* value ≤ 0.05 was considered statistically significant.

Results

The seminal fluid parameters to be assessed in the carnitine group and the control group are shown in table 1. The age in both groups shows no statistical difference. The mean age of patients in the carnitine group is 32±7.5 years. The seminal fluid parameters in both groups are comparable and show no statistical difference. The mean durations of infertility in patients with primary and secondary infertility are comparable (3.5±1.5 vs 4±2 years). These results are important prior to the onset of treatment to avoid significant variations in the seminal fluid parameters in both groups.

Table 1. Comparison of pretreatment seminal fluid parameters and age in the studied groups

Parameters (mean±SD)	Carnitine group	Control group	P value
Age	32.35 ± 7.51	31.35 ± 7.78	0.562
Semen volume (ml)	2.767 ± 1.223	2.798 ± 0.965	0.891
Sperm concentration (million/ml)	12.85 ± 8.88	12.99 ± 7.77	0.943
Total sperm motility (%)	35.88 ± 20.16	37.13 ± 22.18	0.211
Progressive sperm motility (%)	18.25 ± 12.78	20.85 ± 18.37	0.104

Table 2 shows the comparison of seminal fluid parameters in carnitine group and the control group before and after treatment. In carnitine group, the seminal volume didn't show significant increase (*P* = 0.57) but the sperm concentration increased significantly (*P* = 0.001). There was a highly significant increase in total sperm motility (grade A+B) and rapid progressive motility (grade A) after carnitine treatment (*P* = 0.0001). In the control group, no significant increase noticed in any of the seminal fluid parameters, however, a significant drop of total and progressive sperm motility observed (*P* = 0.014, 0.011, respectively).

Table 2. Comparison of pre and post treatment seminal fluid parameters in the carnitine and control groups

Semen Parameters	Carnitine group			Control group		
	Pre treatment	Post treatment	P value	Pre treatment	Post treatment	P value
Volume (ml)	2.77 ± 1.22	2.88 ± 1.22	0.57	2.8 ± 0.97	2.66 ± 1.01	0.42
Concentration (million/m)	12.85 ± 8.88	17.55 ± 11.97	0.001	12.99 ± 7.8	13.36 ± 14.9	0.83
Motility (%)	35.88 ± 20.1	47.39 ± 23.06	0.0001	47.13 ±22.2	40.43 ± 32.2	0.014
Progressive Motility (%)	18.25 ±12.78	29.56 ± 20.15	0.0001	27.85 ±18.4	23.1 ± 18.2	0.011

A comparison of seminal fluid parameters was made between carnitine group and the control group before and after treatment in patients with primary infertility, as shown in table 3. Those patients who received carnitine showed a highly significant increase of sperm concentration (*P* = 0.013) with a similar increase in total and progressive sperm motility (*P* =

0.001 and 0.0001, respectively). Seminal parameters in the control group of primary infertility didn't show significant changes.

Table 3. Comparison of pre and post treatment seminal fluid parameters in patients with primary infertility (carnitine and control groups)

Semen Parameters	Carnitine group			Control group		
	Pre treatment	Post treatment	*P* value	Pre treatment	Post treatment	*P* value
Volume (ml)	2.54 ± 1.14	2.6 ± 0.92	0.76	2.6 ± 0.77	2.5 ± 0.9	0.58
Concentration (million/m)	12.3 ± 7.95	17.4 ±12.1	0.013	13.6 ± 6.57	11.8 ± 7.3	0.186
Motility (%)	33.8 ± 21.3	48.1 ± 25.3	0.001	44.4 ± 21.9	39.6 ± 25.1	0.187
Progressive Motility (%)	17.6 ± 13.7	31.1 ± 22.1	0.0001	24.1 ± 17.34	20.9 ± 19.4	0.212

Table 4 shows comparison of seminal parameters in patients with secondary infertility in carnitine group and the control group before and after treatment. Patients on carnitine therapy showed significant increase in sperm concentration only (*P* = 0.034). Seminal parameters didn't improve in the control group after treatment, however, significant drop noticed in total and progressive sperm motility.

Table 4. Comparison of pre and post treatment seminal fluid parameters in patients with secondary infertility (carnitine and control groups)

Semen Parameters	Carnitine group			Control group		
	Pre treatment	Post treatment	*P* value	Pre treatment	Post treatment	*P* value
Volume (ml)	3.1 ± 1.3	3.2 ± 1.5	0.620	3.1 ± 1.14	2.9 ± 1.12	0.576
Concentration (million/ml)	13.5 ± 10.1	17.75 ± 12.1	0.034	12.2 ± 9.2	15.4 ± 21.1	0.378
Motility (%)	38.5 ± 18.6	46.4 ± 20.34	0.126	50.6 ± 22.54	41.3 ± 21.1	0.032
Progressive Motility (%)	19.1 ± 11.8	27.5 ± 17.6	0.100	32.7 ± 18.9	25.8 ± 16.6	0.016

Semen volume was included in the analysis of results because a significant number of patients with primary infertility had their semen volume within the lower normal level (WHO guidelines) [2] prior to the onset of the study (equal or less than 1.7 ml), therefore, we aimed to test the antioxidant ability of L-carnitine to improve the functions of the seminal vesicle and prostate gland which contribute to the bulk of ejaculated volume of semen. Also we aimed to compare the results of the effect of L-carnitine on semen volume in this study with the results of past studies [16].

The effect of L-carnitine on improving sperm morphology was not included in this study because all the patients had their normal sperm morphology within the accepted levels prior to the onset of the study. Also the previous studies didn't showed any effect of L-carnitine on sperm morphology [16,17].

Pregnancy was not a target point in this study but we observed conception in the partners of two (out of 48) patients after L-carnitine therapy (one patient has primary infertility and the other has secondary infertility) but this didn't occur with the 48 patients in the control group.

Discussion

Human semen quality and fertility rates have been declining during the last decades [18-20]. This might be related to environmental and occupational pollutants, lifestyle changes, exposure to toxins and changes in dietary habits [21]. The dietary factors are of concern, they

include a lower intake of antioxidant nutrients such ascarnitine, vitamin A, E and C, folate, zinc and selenium [22,23]. Reactive oxygen species (ROS), at physiologic levels, are essential for normal reproductive function, however, at higher levels, they exert a negative effect [24]. The seminal plasma has a high concentration of antioxidants, which protect gametes from ROS. Depending on these facts, oxidative stress occurs when there is an excess of ROS or decrease of antioxidant levels or both which is found in most patients with iOAT [25,26]. Oxidative stress can impair sperm motility and morphology and may lead to sperm cell death [27,28]. The dose of L-carnitine used in this study is similar to that used in past trials on this subject [15], however, other studies used higher doses for longer periods with no superior results [15,17]. Up to date, it is unknown if higher doses can yield a difference in outcome.

This study is a randomized controlled clinical study in which two groups of infertile males received either multivitamin or carnitine but not both drugs. This is similar to the study of Sigman et al [29] but unlike the study of Lenzi et al [16] who used a placebo-controlled double-blind cross over design in which two groups of patients received both placebo and carnitine at intervals separated by washout periods to observe the effect of both carnitine and placebo. This design was not applied in our study because the length of any residual drug effect is unknown, therefore, the needed length of a washout period can't be predicted.

In this study, the seminal volume showed no significant increase after carnitine therapy. This is comparable to the results of Lenzi et al [16]. The sperm concentration showed a highly significant increase after carnitine therapy). This was also observed in both groups of primary and secondary infertility. This was also comparable to the results of past studies [15-17] but the later results of Sigman et al [29] and Lenzi et al [30] showed no significant changes in sperm concentration. The effect of carnitine on sperm concentration was unexpected because the intracellular metabolic action of carnitine and its posttesticular (epididymal) effect might contribute to the effect on sperm motility, however, Lenzi et al [16] suggested that this might be due to an improvement in the epididymal microenvironment which reduces gamates phagocytosis and increases ejaculated sperms.

This study included four azoospermic patients (zero sperm concentration) who received carnitine, one of them showed increased sperm concentration. The effect of L-carnitine on azoospermia had not been studied in the past trials; therefore, further studies are needed on a larger number of azoospermic patients.

The most prominent effect of L-carnitine was on total sperm motility and progressive sperm motility. Both of these parameters increased to a highly significant value after carnitine therapy but on reviewing the results of those patients, we observed that only patients with primary infertility showed this significant raise while patients with secondary infertility didn't show significant raise of these two parameters. These results are more significant than the corresponding results of Lenzi et al [16] but comparable to the results of Costa et al [15], however, these studies used higher doses of L-carnitine for a longer period. The study of Sigman et al [29] used a similar higher dose of carnitine for a long period but showed no significant improvement in sperm motility; however, only 12 patients were included in this study.

In our study, the effect of L-carnitine on sperm concentration and sperm motility was assessed in patients with primary and secondary infertility, however, this was not observed in the past studies. Although conception was not a target point in this study because of the many possible interfering factors , we observed two pregnancies in the partners of two infertile males who received carnitine (out of 48 patients) while no conception observed in those who received multivitamin. The effect of carnitine on improving the conception rate needs a larger sample of patients, a longer follow up period and possibly larger doses of L-carnitine.

In conclusion, L-carnitine is an effective therapy for infertile males to improve sperm concentration and more importantly, sperm motility, which improves significantly in patients with primary infertility, therefore, we recommend its use for infertile men with oligoasthenozoospermia. Further studies are needed to assess the efficacy of L-carnitne in patients with non-obstructive azoospermia and patients with very low sperm motility. The conception rate is another target, which needs further evaluation in a larger number of infertile men using L-carnitine.

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