Comparison of L-Carnitine vs. CoQ10 and Vitamin E for idiopathic male infertility: a randomized controlled trial

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Abstract. – OBJECTIVE: This study aimed at comparing sperm parameters and hormonal levels with L-carnitine vs. CoQ10 and Vitamin E therapy for patients with asthenozoospermia and teratozoospermia.

PATIENTS AND METHODS: A single-blind randomized controlled trial (RCT) was designed wherein patients were randomly allocated to receive L-carnitine complex nutrient treatment (study group – 15 g/bag, orally one bag at a time, twice a day) or CoQ10 (control group – 10 mg tablet orally, thrice daily) with Vitamin E (100 mg tablet orally, thrice daily) for three months. Outcome variables were sperm concentration, progressive sperm motility, normal sperm morphology, testosterone, follicle-stimulating hormone, luteinizing hormone (LH), and prolactin levels.

RESULTS: 143 patients were analyzed (73 in study and 70 in control group). Compared to baseline, sperm count, progressive sperm motility, and morphology improved significantly in the study group, but only progressive sperm motility and morphology improved in the control group. Serum testosterone levels significantly increased both in the study and control groups, while LH increased only in the study but not in the control group. All sperm parameters showed significantly better improvement in the study group, compared to the control group. Testosterone and LH levels were also higher in the study group compared to the control group.

CONCLUSIONS: L-carnitine significantly improves sperm motility, morphology, and concentration, while also improving testosterone and LH levels. Use of CoQ10 and Vitamin E resulted in improvement of only sperm motility, morphology, and testosterone levels. L-carnitine was found to be superior to the combination of CoQ10 and Vitamin E in improving sperm parameters. Further studies examining clinical pregnancy rates are needed to strengthen the evidence.

Key Words: Asthenozoospermia, Teratozoospermia, Antioxidants, Sperm count, Sperm motility, Testosterone.

Introduction

The World Health Organization (WHO) defines infertility as the inability to conceive after more than one year of regular unprotected intercourse. Indeed, a physician may initiate examination sooner in couples with risk factors for infertility or if the female partner is > 35 years of age. The cause of infertility could be due to male component, dysfunctional ovaries, uterine abnormalities, obstructed tubes, peritoneal, or even cervical factors. According to estimates, around 9% of couples struggle with infertility around the globe, and the malefactor is the reason in 50% of the cases.

Male infertility has several different causes, ranging from genetic alterations to lifestyle choices to general medical diseases, medications, or even drugs. One of the most common causes of male infertility is varicocele wherein factors like oxidative stress, the altered temperature of testicles, and reflux of metabolites lead to Sertoli and Leydig cell dysfunction, thereby affecting germ cell quality and triggering testicular failure. The second leading cause is the accessory gland dysfunction, which is usually due to infections of the seminal vesicles, prostate, or epididymides. Thirdly, around 30% of cases are due to idiopathic causes wherein no etiological factor is recognized. In such cases, semen assessment reveals that the quantitative and qualitative parameters are not within the global reference range, but no other abnormality is detected on full clinical work-up. Idiopathic conditions include oligozoospermia (reduced sperm count), asthenozoospermia (reduced sperm motility), or teratozoospermia (abnormal sperm morphology). Several different theories have been put forward to explain idiopathic male infertility which includes environmental causes like alcohol or tobacco use, high body mass index, unhealthy diet, and exposure to chemicals. These factors may involve a common pathological pathway consisting of damage by oxidative stress.
Indeed, oxidative stress can influence spermatozoal development and function by causing disintegration of the cellular membrane, impairing mitochondrial activity and affecting energy metabolism, or even by causing genetic alterations. Therefore, the role of antioxidants in treating idiopathic male infertility has gained immense attention in recent times.

L-carnitine, or 3-hydroxy-4-N-trimethyl-aminobutyric acid, is an antioxidant that is obtained by humans mostly from the diet, while around 25% is internally synthesized from the amino acids’ lysine and methionine. It was initially isolated from bovine muscle in 1905, but its complete structure was only established in 1927. This antioxidant can be a vital component in protecting the sperm mitochondria from oxidative stress. It can act as a free-radical scavenger, thereby increasing the antioxidative capabilities in spermatozoa, and may improve sperm parameters. In the past few decades, there has been intense research on the ability of supplemental L-carnitine in improving outcomes in patients with idiopathic male infertility. However, to date, only eight randomized controlled trials (RCTs) have been conducted on this topic.

CoQ10 or ubiquinone is another antioxidant that is structure-wise isoprenylated benzoquinone. It is involved in electron transport in the mitochondria during the respiratory cycle and functions as a membrane stabilizer and a regulator of mitochondrial permeability transition pores. The presence of CoQ10 has been reported in the seminal fluid and is related to several different sperm parameters like count and motility. Similarly, Vitamin E is also an antioxidant that has been used to improve sperm counts. However, to the best of our knowledge, there has been limited comparative research on the efficacy of these antioxidants in improving outcomes in male infertility. Given such deficiency in literature, we herein report the results of an RCT comparing the efficacy of L-carnitine vs. CoQ10 and Vitamin E in improving outcomes in patients with idiopathic asthenozoospermia or teratozoospermia.

**Eligibility Criteria**

The inclusion criteria were as follows:

1. Adult males between 20-40 years of age with infertility for > 1 year having regular sexual intercourse with fertile females;
2. Normal rheological characteristics of semen (appearance, consistency, and liquefaction) with normal volume and pH;
3. No female component in infertility with a female partner having undergone workup for infertility (biphasic basal body temperature, luteal phase progesterone evaluation).
4. No temporary improvement of semen features.
5. Any varicocele or testicular hypotrophy noted on USG or Doppler.
7. Smokers, alcoholics, and drug users.

All eligible patients underwent full work-up before the trial to look for any abnormalities that could have excluded the patients from the study.

**Study Design**

The trial consisted of one month of run-in, followed by 3 months of treatment. Semen analysis was carried out one month before the trial and just before the trial to exclude patients with any transient decrease in sperm quality or patients with any temporary improvement of semen features. Semen analysis was carried out by the same pathologist following WHO criteria. Patients allotted to the study group were administered L-carnitine complex nutrient treatment (Shandong Sincean Pharmaceutical Co. Ltd., Shandong, China), 15 g/bag, orally one bag at a time, twice a day. The control group was administered CoQ10 (Shanghai Xudong Haiipu Pharmaceutical Co. Ltd., Shanghai, China), 10 mg tablet orally thrice daily with Vitamin E (Hainan Haishen Pharmaceutical Co. Ltd.), 100 mg tablet

**Patients and Methods**

This RCT enrolled 143 patients with male infertility due to idiopathic asthenozoospermia or teratozoospermia reporting to our institute between November 2019 and October 2021. The study was approved by the Institutional Ethical Committee (No. ZZSFYBJY-2022-006) and informed written consent was obtained from all study participants.

Additionally, patients were randomized using a computer-generated random number table. The randomization code was kept with the hospital pharmacist who was not involved in any part of the study. Patients allotted to the study group were administered L-carnitine complex nutrient treatment (Shandong Sincean Pharmaceutical Co. Ltd., Shandong, China), 15 g/bag, orally one bag at a time, twice a day. The control group was administered CoQ10 (Shanghai Xudong Haiipu Pharmaceutical Co. Ltd., Shanghai, China), 10 mg tablet orally thrice daily with Vitamin E (Hainan Haishen Pharmaceutical Co. Ltd.), 100 mg tablet
orally thrice daily. All patients were asked to follow a regular standard diet to avoid variability in L-carnitine uptake from food.

**Data Collection**

All patients underwent semen analysis at baseline and three months after therapy. Additionally, we also carried out a serum hormonal analysis consisting of testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin levels before and after treatment. Samples were collected by a single investigator who was blinded to the randomization protocol. Semen samples were obtained by masturbation post sexual abstinence of 3-5 days. Semen variables included in the analysis were: sperm concentration, progressive sperm motility, and normal sperm morphology.

**Statistical Analysis**

All continuous data were reported as mean ± standard deviation. The normality of data was judged using the Shapiro-Wilk test. Baseline and outcome data between the study and control groups were compared using the student’s t-test. p-values lower than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS for Windows 19.0 software (IBM Corp., Armonk, NY, USA).

**Results**

A total of 170 patients were assessed for eligibility for the trial. 24 patients were excluded for various reasons (Figure 1). A total of 146 patients were then randomized. 3 patients allocated
to the control group withdrew consent and hence were not administered any therapy. A total of 73 patients in the study group and 70 patients in the control group underwent treatment. No patient was lost to follow-up.

The baseline details of the included patients are presented in Table I. The mean age of patients in the study group was 31.6 ± 5.61 years, while that of the control group was 30.9 ± 4.87 years. Time since infertility was 3.22 ± 1.84 in the study group and 3.29 ± 1.74 in the control group. There was no statistically significant difference in the serum levels of testosterone, FSH, LH, and prolactin between the study and control groups at baseline.

Outcome data after 3 months of treatment is presented in Table II. Compared to baseline, serum testosterone levels significantly increased both in the study and control groups. LH increased only in the study, but not in the control group. Sperm count, progressive sperm motility, and morphology improved significantly in the study group, but only progressive sperm motility and morphology improved in the control group.

Comparing the study and control groups at 3 months, the serum testosterone levels increased to 4.31 ± 0.78 ng/ml in the study group and 3.76 ± 0.74 ng/ml in the control group (p < 0.0001). Similarly, there was a statistically significant difference in the levels of LH between the study and control groups (5.65 ± 1.73 mIU/ml vs. 4.88 ± 1.78 mIU/ml, p = 0.009) after 3 months of therapy. There was no statistically significant difference in the levels of prolactin and FSH between the two groups.

We noted a statistically significant higher concentration of sperms in the study group (40.51 ± 18.66 x 10^6/ml), as compared to the control group (30.3 ± 17.5 x 10^6/ml) after three months (p = 0.001). The percentage of progressive sperm motility was also significantly higher in the study group (32.29 ± 10.25%), as compared to the control group (25.64 ± 9.55%, p < 0.0001). The percentage of normal sperm morphology was significantly higher in the study group (4.15 ± 2.12%), as compared to the control group (3.33 ± 1.93%, p = 0.01).

### Discussion

Oxidative stress is an important mechanism involved in the pathophysiology of idiopathic male infertility. Excessive production of free radical and reactive oxygen species can affect both the anatomy and function of sperm. While the precise mechanism is yet to be elucidated, it is postulated that reduced intracellular ATP levels, lipid peroxidation of the cell membranes, and inadequate axoneme phosphorylation could impact the fertilizing ability of the sperm. The vulnerability to damage by oxidative stress is high in the case of sperm since it has limited cytoplasm and endogenous antioxidant protection. Free radicals cause the formation of malondialdehyde and 4-hydroxynonenal which lead to lipid membrane oxidation and disintegration of mitochondrial, as well as nuclear DNA in the sperm. Smoking, high body mass index, environmental factors like pollution, and an unhealthy diet have been recognized as key contributors to oxidative stress in males.

Given much research on the role of oxidative stress in male infertility, the next obvious step would be to assess if antioxidants could improve outcomes in such patients. Few antioxidants like vitamin C, folic acid, selenium, zinc, carotenoids, and carnitines are naturally occurring in semen.
and they prevent damage by reactive oxygen species. But several other antioxidant supplements have also been investigated for the treatment of male infertility. Indeed, the increased availability and marketing of antioxidants are based on patients’ demand. A survey suggests that 58.3% of males would prefer medications and achieve natural conception rather than treatment (24.6%) to improve the success of assisted reproductive technology.

In this context, we designed an RCT to examine the effects of L-carnitine complex nutrient supplements vs. CoQ10 and vitamin E in improving outcomes of patients with idiopathic asthenozoospermia or teratozoospermia. The study and control groups were matched at baseline due to the randomized nature of the trial. After 3 months of treatment, we noted a statistically significant improvement in the sperm parameters with both L-carnitine and CoQ10 and vitamin E, except for sperm concentration with the latter. On comparing the two treatment modalities, the improvement was significantly better with L-carnitine as compared to CoQ10 and vitamin E for all three sperm parameters (concentration, progressive motility, and normal morphology). Also, we noted a significant increase in the levels of testosterone and LH levels in patients on L-carnitine therapy, but only testosterone levels increased with CoQ10 and vitamin E.

The results of our study are supported by outcomes of previous RCTs. Moslemi Mehni et al in a study on the Iranian population have compared the use of L-carnitine and placebo in 51 and 59 patients, respectively. The authors reported a statistically significant improvement in sperm count and motility in the L-carnitine group after three months of therapy. On the other hand, Tsounapi et al, in another RCT involving 86 patients in the L-carnitine and placebo groups, have noted significant improvement only in progressive sperm motility but failed to demonstrate any improvement in total sperm motility, sperm concentration, or normal sperm morphology with the supplement therapy. In a small four-arm RCT of 60 patients, Balercia et al have reported significant improvement in sperm motility and sperm morphology with L-carnitine, L-acetyl-carnitine, and combination therapy as compared to placebo, but no improvements in sperm counts with either therapy. In a systematic review and meta-analysis, Khaw et al combined data of 8 RCTs to show that L-carnitine complex therapy significantly improves total sperm motility, progressive sperm motility, and semen morphology, but had no effect on sperm concentration. The variability in the results of individual RCTs could be due to the variability in the baseline patient characteristics, different dosing strategies, and follow-up between the studies. Literature on the effect of L-carnitine on hormonal levels is scarce. However, in line with our results, Rezaei et al have found in an animal study that L-carnitine administration significantly increased FSH, LH, and testosterone.

Table II. Outcomes after three months of treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study</th>
<th>Control</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma testosterone (ng/ml)</td>
<td>4.31 ± 0.78</td>
<td>3.76 ± 0.74</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0002</td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>12.04 ± 3.3</td>
<td>12.56 ± 3.72</td>
<td>0.37</td>
</tr>
<tr>
<td>p-value</td>
<td>0.66</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>5.65 ± 1.73</td>
<td>4.88 ± 1.78</td>
<td>0.009</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.0004</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Progesterone (ng/ml)</td>
<td>27.93 ± 5.04</td>
<td>28.42 ± 5.46</td>
<td>0.57</td>
</tr>
<tr>
<td>p-value</td>
<td>0.53</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Prolactin (pg/ml)</td>
<td>7.62 ± 2.32</td>
<td>7.21 ± 3.47</td>
<td>0.46</td>
</tr>
<tr>
<td>p-value</td>
<td>0.65</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Sperm concentration (x10^9 /ml)</td>
<td>40.51 ± 18.66</td>
<td>30.30 ± 17.5</td>
<td>0.001</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.0001</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Progressive sperm motility (%)</td>
<td>32.29 ± 10.25</td>
<td>25.64 ± 9.55</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.0001</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Normal sperm morphology (%)</td>
<td>4.15 ± 2.12</td>
<td>3.33 ± 1.93</td>
<td>0.01</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.0001</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

FSH: Follicle stimulating hormone; LH: luteinizing hormone. *study vs. control at 3 months of therapy. ^as compared to baseline values.
Comparison of L-Carnitine vs. Coq10 and Vitamin E for idiopathic male infertility

levels. While we noted a significant improvement only in testosterone and LH levels, further studies are needed to explore the association between carnitines and hormonal levels.

The scientific rationale behind the effect of carnitine can be explained by its essential role during spermatogenesis. It acts as a co-factor for long-chain fatty acid transport in the mitochondria, thereby facilitating the oxidative process to enhance cellular energy production. In addition to its central role in energy metabolism, evidence suggests that the initiation of sperm motility is due to the increase of carnitines in the epididymis and sperm cells. Indeed, carnitines are found in high concentrations in epididymal luminal fluid while individuals with poor sperm parameters are known to have low concentrations. Balercia et al. have found in an RCT that administration of carnitines significantly improved the scavenging capacity of seminal fluid for hydroxyl and peroxyl radicals. Since the scavenging capacity is directly related to the kinetic parameter of sperm cells, it is not surprising to note significant improvements in sperm motility in our, as well as in previous trials on L-carnitine.

We also noted that progressive sperm motility and normal sperm morphology significantly increased in the control group, while there was no significant difference in other outcomes. However, the improvement was significantly better with L-carnitine, as compared to CoQ10 and vitamin E. Unlike carnitines, CoQ10 has received limited attention for the management of male infertility. In a recent meta-analysis of three double-blind placebo-controlled trials, Vishvakarma et al. have demonstrated that CoQ10 has a profound effect on total sperm motility and progressive motility. However, it had limited beneficial effect on sperm count, sperm morphology, and ejaculate volume. The authors suggested that CoQ10 may be used for asthenozoospermia but not for oligozoospermia, and that combination therapy, together with other antioxidants, may be beneficial in improving outcomes. In congruence with these results, we also noted a significant improvement in progressive sperm motility with CoQ10 therapy but no impact on sperm counts. Despite a combined therapy with Vitamin E, the effects were not very encouraging. The effect of only Vitamin E supplementation has been studied by Sabetian et al. in a double-blind RCT, only to note no improvement in sperm parameters after 8 weeks of therapy.

Our study has some limitations. Firstly, our trial was a direct comparative study of two antioxidants and there was no placebo group. Secondly, patient blinding was not possible due to the two different drug regimens which have introduced bias. Third, we focused only on sperm parameters and hormonal levels but did not assess clinical pregnancy rates. Thus, while the improvement in sperm parameters leads to significant improvement, the improvement in the fertility rate is still unclear.

The strengths of the study include the large sample size, the rigorous randomization process, and the blinding of outcome assessment to reduce bias. To the best of our knowledge, this is the first RCT to compare outcomes of L-carnitine with CoQ10 and Vitamin E; therefore, it would be a valuable addition to the literature.

Conclusions

L-carnitine significantly improves sperm motility, morphology, and concentration, while also improving testosterone and LH levels. Use of CoQ10 and Vitamin E resulted in improvement of only sperm motility, morphology, and testosterone levels. L-carnitine was found to be superior to the combination of CoQ10 and Vitamin E in improving sperm parameters. Further studies examining clinical pregnancy rates are needed to strengthen the evidence.

Conflict of Interest

The authors declare that they have no competing interest.

Acknowledgments

Not applicable.

Informed Consent

Informed written consent was obtained from all study participants.

Ethical Approval

Study was approved by the Institutional Ethical Committee (No. ZZSFYBJY-2022-006).

Authors’ Contribution

L.-Ma conceived and designed the study. L.-Ma and Y.-Sun collected the data and performed the analysis. Y.-Sun was involved in the writing of the manuscript and is responsible for the integrity of the study. All authors contributed to the article and approved the submitted version.
References