

Safety and Efficacy of Clomiphene Citrate and L-Carnitine in Idiopathic Male Infertility A Comparative Study

Mahmoudreza Moradi,¹ Asaad Moradi,¹ Mohsen Alemi,¹ Hassan Ahmadnia,² Hossein Abdi,¹ Alireza Ahmadi,³ Shahrzad Bazargan-Hejazi⁴

Purpose: To compare the effects of L-carnitine with clomiphene citrate in idiopathic infertile men.

Materials and Methods: Fifty-two men with idiopathic infertility were recruited in this randomized controlled trial. They were randomly assigned into 2 treatment groups, group 1 ($n = 20$) and group 2 ($n = 32$), who received L-carnitine 25 mg/day and clomiphene citrate 2 gr/day, respectively, for a period of 3 months.

Results: Comparing the effect of L-carnitine and clomiphene on sperm parameters before and after the treatment, both medications had influence on sperm count and motility ($P = .01$). L-carnitine significantly increased the semen volume ($P = .001$), while clomiphene citrate was significantly associated with the motility percentage and normal morphology ($P = .008$).

Conclusion: It seems that the use of clomiphene citrate and L-carnitine, either individually or in combination, as the first step of idiopathic male infertility treatment is reasonable, safe, and effective.

Keywords: semen parameters, male infertility, randomized controlled trial

Urol J. 2010;7:188-93.
www.uj.unrc.ir

¹Fertility-Infertility Research Center, Urology and Nephrology Research Center, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran

²Department of Urology, Mashhad University of Medical Sciences, Mashhad, Iran

³Department of Anesthesiology, Imam Reza Hospital, Kermanshah University of Medical Sciences, Iran-Department of Public Health Sciences, Division of Social Medicine, Karolinska Institute, Stockholm, Sweden

⁴Department of Psychology, College of Medicine, Charles Drew University of Medicine and Science, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA

Corresponding Author:
Mahmoudreza Moradi, MD
Fertility-Infertility Research Center,
Imam Reza Hospital, Kermanshah
University of Medical Sciences, Iran
Tel: +98 918 132 4811
Fax: +98 831 725 9983
E-mail: drmmoradi@yahoo.com

Received July 2009
Accepted November 2009

INTRODUCTION

Infertility is considered as one of the most important issues among married couples. According to the current statistics, about 15% of married couples face with infertility at the end of the first year of their marriage, with male gender implicated in 20% of these cases. Other evidence shows that in 30% to 40% of infertile cases, both man and woman play a role.⁽¹⁾ A male factor, therefore, plays a 50% role in the etiology of infertility.⁽²⁾

Idiopathic male infertility (IMI), with a prevalence of approximately 25%, is a condition where abnormal semen parameters are obtained due to non specific causes. In the

majority of cases, abnormal semen parameters leads to diagnosis of oligoasthenoteratospermia, and in others, it leads to isolated abnormalities of sperm concentration, motility, and morphology. Due to the lack of differentiable or correctable etiology, patients with IMI are often treated by varieties of empirical medications or assisted reproductive technologies. However, the meta-analysis of controlled trials on patients with IMI has revealed that, with a few exceptions, the majority of the trials failed to show the efficacy of treatments. Yet, due to obtained success among small number of

patients with IMI, efforts in medication therapy and technology assisted management of IMI continue.⁽²⁾

Clomiphene citrate, as an anti-estrogen, is the most common prescribed medication for male infertility. However, L-carnitine, which is known to improve semen's parameters, has recently been recognized as the most effective medication. L-carnitine molecule controls the transport of acetyl and acyl groups across the mitochondrial inner membrane and is an essential agent for mitochondrial metabolism. Although the exact function of L-carnitine and acetylated carnitine in the epididymis, where these agents are found in high concentration, is not entirely known, but they seem to have a protective ability against oxidative damages. Both L-carnitine and L-acetyl-carnitine are available as over-the-counter medications in the form of nutritional supplements for the treatment of IMI.⁽²⁾

The anti-estrogenic role of clomiphene citrate and the therapeutic role of L-carnitine in treatment of infertility are well documented;⁽³⁻⁷⁾ however, literature reveals a paucity of research comparing treatment outcome of clomiphene citrate and L-carnitine in infertile men.

The specific aim of this study was to compare treatment outcome of L-carnitine with the standard treatment, clomiphene citrate, in infertile men with oligoasthenoteratospermia.

MATERIALS AND METHODS

This randomized longitudinal study was carried out on 107 patients who presented with idiopathic infertility to the urology clinics of Kermanshah University of Medical Sciences between January 2006 and January 2008.

Of 107 patients, those who met the following inclusion criteria of: 1) a history of infertility for at least one year 2); and semen parameter abnormalities, including sperm concentration or count less than 20×10^6 spermatozoa/mL, motility less than 50% with grade "a + b" or 25% with grade "a", and morphology less than 50%, for which no specific causes were identified, were enrolled in this study. Then, a written informed consent was obtained from each patient.

On the other hand, patients who presented with symptoms of hypogonadism or sperm count less than 10 million/mL, and/or any hormonal disorder detected by hormonal tests, including testosterone, prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were excluded from the study. Furthermore, patients with an inguinal operation, infectious or venereal diseases, testicular atrophy, hypogonadism, varicocele, and disorders of the vas deferens and the epididymis were also excluded from the study. The study protocol was approved by the ethics committee of Kermanshah University of Medical Sciences.

The remaining 52 patients were randomly assigned into 2 groups in a double blind manner by the sealed opaque envelope technique; group 1 ($n = 20$) and group 2 ($n = 32$) who received clomiphene citrate 25 mg/day (Tab. 50 mg/Iran Hormone Co.) and L-carnitine 2 gr/day (Tab. 250 mg/Shahre Daru Co.), respectively, for 3 months. Post treatment semen analyses were performed twice, within a window period of 5 days, for all the subjects who completed the 3-month treatment, to increase the accuracy of the test results and reduce test bias.

The mean score for semen parameters analysis was calculated for each participant in both treatment groups. Using paired sample *t* test, parameters, including sperm count, semen volume, motility, and morphology were compared between two groups before and after the treatment assignments.

Using an independent sample *t* test, post treatment semen measures of the subjects in both treatment groups were compared with each other. These tests allowed us to see if there were any detectable differences between the means of the study measures between and across the groups, and if the differences were statistically significant. All statistical analyses were performed using SPSS software (Statistical Package for the Social Science, version 14.0, SPSS Inc, Chicago, Illinois, USA).

RESULTS

The mean age of the patients was 28.46 ± 2.67 years (range, 22 to 35 years). Of a total of 52,

32 patients with the mean age of 28.44 ± 2.34 years (range, 22 to 35 years) and 20 patients with the mean age of 28.5 ± 3.21 years (range, 26 to 31 years) were treated by clomiphene citrate and L-carnitine, respectively. The mean period of infertility was 2.98 ± 4.11 years (range, 1 to 14 years) for all the patients; 3.12 ± 3.52 years (range, 1 to 7 years) in clomiphene citrate group and 2.87 ± 4.7 years (range, 1 to 14 years) in L-carnitine group.

Table compares changes of the semen parameters before and after the treatment with clomiphene citrate and L-carnitine. In clomiphene citrate group, the average values of semen volume, sperm counts, motility percentage, and normal morphology before the treatment were 3.21 ± 1.3 mL, 20.38 ± 16.2 million/mL, $23.78 \pm 17.5\%$, and $45.06 \pm 20.8\%$, respectively, which changed to 3.36 ± 1.3 mL, 42.51 ± 29.4 million/mL, $43.38 \pm 20.1\%$, and $58.44 \pm 19.3\%$ after the treatment. Our results revealed that clomiphene citrate had considerable influence on sperm count, morphology, and motility ($P = .01$), but not much effect on the semen volume ($P = .57$).

In L-carnitine group, the average values of semen volume, sperm counts, motility percentage, and normal morphology before the treatment were 2.50 ± 1.2 mL, 44.75 ± 18.1 million/mL, $38.82 \pm 15.5\%$, and $48.40 \pm 37.9\%$, respectively. After the treatment, these parameters altered to 4.03 ± 0.8 mL, 73.25 ± 18.5 million/mL, $48.03 \pm 19.7\%$, and $49.45 \pm 32.2\%$. There was a statistically significant association between L-carnitine

and semen volume, sperm count, and motility ($P = .01$), but not with the sperm morphology ($P = .698$).

Comparing the effect of L-carnitine and clomiphene on sperm parameters before and after the treatment, both had influence on sperm count and motility ($P = .01$). The effect on sperm counts was not significant ($P = .376$). L-carnitine significantly increased the semen volume ($P = .001$), while clomiphene citrate was significantly associated with the motility percentage and normal morphology ($P = .008$).

DISCUSSION

Clomiphene citrate is one of the most common experimental medications used for treatment of idiopathic infertility. As an anti-estrogen, clomiphene citrate links to the receptors of estradiol in the hypothalamus and stimulates the gonadotropin secretion. Anti-estrogens increase the pituitary gonadotropin secretion by blocking feedback inhibition, thus, increasing both serum FSH and LH levels as well as the testicular production of testosterone. Clomiphene citrate with the dosage of 25 mg per day is the standard recommended treatment for IMI. Higher doses of clomiphene citrate, however, may cause down-regulation of the system.^(1,2)

In the present study, we anticipated noticing an overall improvement in the sperm count, semen volume, motility percentage, and morphology in the group receiving L-carnitine

Comparison between changes of the semen parameters before and after the treatment with clomiphene citrate and L-carnitine

Parameters	Clomiphene Citrate		L-Carnitine		<i>P</i>
	Before Treatment	After Treatment	Before Treatment	After Treatment	
Sperm Count	20.38 ± 16.2	42.51 ± 29.4	44.75 ± 18.1	73.25 ± 18.5	= .01* = .01† = .376‡
Semen Volume	3.21 ± 1.3	3.36 ± 1.3	2.50 ± 1.2	4.03 ± 0.8	= .57* = .01† = .001‡
Motility	23.78 ± 17.5	43.38 ± 20.1	38.82 ± 15.5	48.03 ± 19.7	= .01* = .01† = .008‡
Morphology	45.06 ± 20.8	58.44 ± 19.3	48.40 ± 37.9	49.45 ± 32.2	= .01* = .698† = .008‡

*Clomiphene citrate

†L-carnitine

‡Comparison of two drugs with each other

compared to the group that received clomiphene citrate. Comparing baseline measures of semen parameters with that of the follow-ups, our data showed an increase in the sperm motility and count in both groups; clomiphene citrate and L-carnitine ($P = .01$). However, no meaningful association was observed between semen volume and clomiphene citrate ($P = .57$) as well as morphology and L-carnitine ($P = .698$). This finding is not compatible with the finding of Mićić and colleagues.⁽⁸⁾ They randomly divided 101 patients with a history of 2-year infertility into 2 groups. Fifty-six patients received 50 mg/day clomiphene citrate for 6 to 9 months and 45 patients as the control group received no medication. In that study, sperm parameters such as semen volume and sperm motility were treated with clomiphene citrate compared to the control group ($P \leq .05$).⁽⁸⁾

Khademi and coworkers studied 48 smokers and 122 non-smokers with abnormal sperms after receiving L-carnitine 3 times per day for 3 months. They observed that L-carnitine was effective in improving sperm mobility percentage, grade A sperms, and normal-shaped sperms. Improvements in the non-smokers were even more noticeable. They concluded that a smoker should not be excluded from the treatment with L-carnitine.⁽⁶⁾

In the study by Cavallini and colleagues,⁽⁷⁾ the effect of cinnoxicam supplement and L-carnitine on idiopathic infertility and varicocele was examined in 3 groups: placebo group; L-carnitine (2 gr/day) + acetyl-L-carnitine (1 gr/day) group; and L-carnitine + cinnoxicam (30 mg) group. After 6 months, sperm count, sperm motility and morphology, the amount of fertility (pregnancy rate), and complications were recorded. In placebo group, no change was observed in sperm parameters. In the group that received L-carnitine + acetyl-L-carnitine, sperm parameters increased significantly at 3 and 6 months in idiopathic infertile patients with minor varicoceles, but no improvement was observed in idiopathic infertile patients with severe varicoceles. But all the patients in group 3 had significantly increased sperm parameters with the exception of very severe varicoceles. Pregnancy rates were 1.7%

(group 1), 21.8% (group 2), and 38.0% (group 3) ($P \leq .01$). Cavallini and colleagues concluded that combination of L-carnitine and cinnoxicam could be a reliable treatment for low-grade varicoceles and idiopathic oligoasthenospermia.⁽⁷⁾

In spite of positive effect of L-carnitine on sperm motility in the present study, Sigman and colleagues did not find such statistically significant association.⁽⁹⁾ Sigman and coworkers compared the effects of L-carnitine, ie, 2000 mg/day L-carnitine and 1000 mg/day L-acetyl-carnitine for 24 weeks, with placebo on idiopathic asthenospermic patients. Sperm motility and the number of mobile sperms were measured at the baseline, 12 weeks, and 24 weeks post treatment. No statistically or clinically significant differences were found between the two groups at any of the measured points.⁽⁹⁾

However, our results regarding the effect of clomiphene citrate and L-carnitine on the sperm count and sperm motility are consistent with several studies.⁽³⁻⁷⁾ In the study by Patankar and colleagues,⁽³⁾ clomiphene citrate 25 mg/day was administered for 2 groups for 25 days, including 5 days resting period for duration of 3 months. First group included 25 men with extreme oligospermia and the second group composed of 40 men with moderate oligospermia. Results of seminal fluid analysis at the end of the treatment period were as follows: the mean sperm count in the first and second group increased from 3.84 to 8.2 million/mL and from 13.05 to 24.55 million/mL, respectively. The mean motile sperms in the first group increased from 1.74 to 3.92 and in the second group from 8.27 to 10.05. The researchers concluded that the medication was more effective when there was no end-organ pathology.⁽³⁾

Zhou and associates in a systematic review of 9 studies reported the effects of L-carnitine on male infertility. The meta-analysis compared L-carnitine and/or L-acetyl-carnitine therapy with placebo treatment. They found significant improvement in pregnancy rate, total sperm motility, forward sperm motility, and atypical sperm cell.⁽⁵⁾ In a study including 30 men with oligospermia, Rönnberg observed that in the group who received clomiphene citrate 50 mg

per day for 3 months, the average sperm count increased from 13.3 to 28.5 million/mL ($P \leq .05$). Moreover, in clomiphene citrate group, 3 cases of pregnancy were observed; while none were observed in the control group.⁽⁴⁾

Still others claim that there is yet no acceptable empirical treatment for IMI.⁽⁹⁻¹¹⁾ Reviewing 20 years of medication therapies for IMI, Kumar and colleagues found no clear advantage for any of the medications used by the patients.⁽¹¹⁾ Vandekerckhove and associates reviewed 10 studies consisting of 738 infertile men, to evaluate the effect of anti-estrogens like clomiphene citrate and tamoxifen on idiopathic oligoasthenospermia. They concluded that anti-estrogens appeared to have a beneficial effect on endocrines, but there was not enough evidence to evaluate the use of anti-estrogens for increasing the fertility of men with idiopathic oligoasthenospermia.⁽¹⁰⁾

Limitations and Future Directions

We view this to be an incipient project and recognize its limitations. Small sample size with limited statistical power, lack of placebo group, failing to consider pregnancy rate as the ultimate measure of treatment outcome, and short-term follow-up period (3 months) were the flaws of this study. However, to the best of our knowledge, it is amongst the first studies that has compared the effect of clomiphene citrate and L-carnitine regarding semen parameters abnormalities in idiopathic infertile men.

L-carnitine in this study had a significant effect on improving semen parameters; it has few side-effects and seems to be an appropriate choice for idiopathic infertile men when taken in combination with clomiphene citrate. Therefore, findings of this study are encouraging enough to stimulate further similar investigations to expand our findings with the use of larger samples, inclusion of placebo/control group, and consideration of pregnancy rates as the ultimate treatment outcome measure.

CONCLUSION

Clomiphene citrate and L-carnitine are among the most administered, available, and effective

medications for male infertility, while offering fewer complications. Results of this study suggest that the treatment outcome of clomiphene citrate and L-carnitine on the sperm count is nearly equal. However, the effect of L-carnitine on the semen volume is more meaningful than clomiphene citrate ($P = .001$) and the effect of clomiphene citrate on motility and morphology is more meaningful than L-carnitine ($P = .008$). It seems that the use of clomiphene citrate and L-carnitine, either individually or in combination, as the first step of idiopathic male infertility treatment is reasonable, safe, and effective.

ACKNOWLEDGEMENT

The authors would like to thank all who participated in this study. Financial support for this project was provided by Kermanshah University of Medical Sciences.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Guyton AC, Hall JE. *Textbook of Medical Physiology*. Philadelphia: WB Saunders; 2000:996-1009.
2. Sigman M, Jarow JP. Male Infertility. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, eds. *Campbell-Walsh Urology*. Vol 1. Philadelphia: Saunders 2007:609-53.
3. Patankar SS, Kaore SB, Sawane MV, Mishra NV, Deshkar AM. Effect of clomiphene citrate on sperm density in male partners of infertile couples. *Indian J Physiol Pharmacol*. 2007;51:195-8.
4. Rönnberg L. The effect of clomiphene citrate on different sperm parameters and serum hormone levels in preselected infertile men: a controlled double-blind cross-over study. *Int J Androl*. 1980;3:479-86.
5. Zhou X, Liu F, Zhai S. Effect of L-carnitine and/or L-acetyl-carnitine in nutrition treatment for male infertility: a systematic review. *Asia Pac J Clin Nutr*. 2007;16 Suppl 1:383-90.
6. Khademi A, Alleyassin A, Safdarian L, Hamed EA, Rabiee E, Haghanezhad H. The effects of L-carnitine on sperm parameters in smoker and non-smoker patients with idiopathic sperm abnormalities. *J Assist Reprod Genet*. 2005;22:395-9.
7. Cavallini G, Ferraretti AP, Gianaroli L, Biagiotti G, Vitali G. Cinoxicam and L-carnitine/acetyl-L-carnitine treatment for idiopathic and varicocele-associated oligoasthenospermia. *J Androl*. 2004;25:761-70; discussion 71-2.

8. Mićić S, Dotlić R. Evaluation of sperm parameters in clinical trial with clomiphene citrate of oligospermic men. *J Urol.* 1985;133:221-2.
9. Sigman M, Glass S, Campagnone J, Pryor JL. Carnitine for the treatment of idiopathic asthenospermia: a randomized, double-blind, placebo-controlled trial. *Fertil Steril.* 2006;85:1409-14.
10. Vandekerckhove P, Lilford R, Vail A, Hughes E. Clomiphene or tamoxifen for idiopathic oligo/asthenospermia. *Cochrane Database Syst Rev.* 2000;CD000151.
11. Kumar R, Gautam G, Gupta NP. Drug therapy for idiopathic male infertility: rationale versus evidence. *J Urol.* 2006;176:1307-12.