

Can Clomiphene Citrate Improve the Quality of Seminal Fluid Parameters in Idiopathic Oligoasthenoteratozoospermic Males

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Abstract

Introduction: Male infertility is a rising problem worldwide. Idiopathic male infertility is responsible for 31% of all male infertility. Among them 44% is due to Idiopathic Oligo Astheno Teratozoospermia (iOAT) syndrome. The role of medical treatment in managing iOAT syndrome is controversial. But there are accumulating evidence of the efficacy of Clomiphene citrate on treating iOAT syndrome.

Objective: To determine the efficacy of Clomiphene Citrate therapy in improving seminal fluid parameters of a group of male patients with iOAT syndrome.

Study type: a comparison study was done using retrospective data.

Method: This study was conducted in the Reproductive biology laboratory of the Faculty of Medicine, Galle. Medical records of 52 patients presented with iAOT syndrome, treated with clomiphene citrate were screened using the exclusion and inclusion criteria. The pre-treatment and post-treatment seminal fluid analysis of the patients were compared using the paired t- test. All the patients were given clomiphene citrate 50mg per day in divided doses for minimum of 3 months. Post-treatment seminal fluid analysis were done at the end of the 4th month of commencing the treatments.

Results: Sperm concentration, sperm total count, normal morphology, motility and viability are improved significantly ($p < 0.001$). The improvement of the volume is not significant ($p > 0.001$)

Conclusion: Clomiphene citrate improves the sperm concentration, total count, normal morphology, motility and viability in a group of selected male patients with iOAT syndrome but the volume.

Keywords— Clomiphene citrate, iOAT, Male infertility

I. INTRODUCTION

Infertility, a rising global problem affected 48.5 million couples in reproductive age worldwide in 2010 (Mascarenhas et al. 2012) (Winters and Walsh 2014). Though the recent demographic data on this issue is not available, the prevalence of subfertility among Sri Lankan couples in reproductive age is about 15% (Winters and Walsh 2014) (Farouk Mahmoud 2011).

In General the male factors contribute to about 50% of all infertility cases (A. Jungwirth et al. 2013) (Irvine 1998). The common causes of male infertility are Idiopathic oligoasthenoteratozoospermia (iOAT), Varicocele, Hypogonadism and genetic disorders, mal-descended testes, Autoimmune antibodies and urogenital infections (A. Jungwirth et al. 2013). However iOAT is considered as the major cause of male infertility worldwide and its prevalence is about 30% of all male infertility (A. Jungwirth et al. 2013) (Gudeloglu, Brahmabhatt, and Parekattil 2014).

Though the medical or surgical management for male infertility is very time consuming, the success rates are fairly good if the causes for the infertility is known (Gudeloglu, Brahmabhatt, and Parekattil 2014). But the majority of male infertility is either due to idiopathic causes (30%) or due to multiple causes (A. Jungwirth et al. 2013). The outcome of the medical management for these cases is not promising (Gudeloglu, Brahmabhatt, and Parekattil 2014). Therefore the outcome of medical management for male factor infertility, as a whole has a fairly low success rate which discourages not only patients but also physicians. Further more, in most of the instances, the availability of modern

Advanced Reproductive Technologies (ART) which have more reliable and better success rates has become the first line of the management of male infertility which is not rational when social and economic impacts are considered.

Though several drugs are available in the market for male factor infertility, Food and Drug Authority (FDA) has approved only Gonadotrophin Releasing Hormone (GnRH), Human chorionic-gonadotropin (hCG), Human menopausal Gonadotropin (hMG), Highly purified or recombinant human Follicle-Stimulating Hormone (rhFSH) and Dopamine agonist (Gudeloglu, Brahmbhatt, and Parekattil 2014) (A. Jungwirth et al. 2013) . The other drugs such as Aromatase inhibitors, anti oxidants, Co-Enzym Q, Selective estrogen receptor modulators (Clomiphene Citrate) have been categorized as remedies or empirical and are being used as off label drugs (A. Jungwirth et al. 2013).

However some recently published literature has shown that clomiphene citrate (beta-diethyl aminoethoxy) can improve seminal fluid parameters and pregnancy rates in males with iOAT. Though there are several protocols of administration of clomiphene citrate, the widely used protocol is 25mg per day as a single dose (Patankar et al. 2007) (Hayashi et al. 1988). Though it has not been clearly documented, the duration of clomiphene citrate treatment is thought to be more than three (03) months to have a detectable response (Patankar et al. 2007) (Hayashi et al. 1988)

Clomiphene is an estrogen receptor inhibitor at the level of hypothalamus, inhibiting the negative feedback of estrogen on GnRH release. Clomiphene can up-regulate the hypothalamic-pituitary-gonadal axis in males increasing the serum Follicular stimulating Hormone (FSH) and testosterone levels("DrugBank: Clomifene (DB00882)" 2014) .

In 1988, Hayashi N et.al, noticed statistically significant improvement of sperm motility and sperm count in a group of Japanese males with idiopathic infertility with clomiphene citrate treatment. But they haven't recorded an improvement of sperm morphology. However four (04, 10%) spontaneous pregnancies have been recorded in their study sample (n=40) (Hayashi et al. 1988).

According to findings of Patankar SS et al., in 2007, clomiphene citrate has ability to improve sperm count, sperm motility but sperm morphology to certain extent in a group of oligozoospermic patients (Patankar et al. 2007) .

Based on the review study done by Willets AE, in 2012, " there is insufficient evidence to indicate that clomiphene is effective for the treatment of male infertility". However the author agreed that the majority of the studies have demonstrated a statistically significant increase in sperm concentrations (Willets AE, Corbo JM, and Brown JN 2013).

In 2012, Iqbal Mirza has recorded an improvement of semen volume, sperm count, sperm motility and to a certain extent sperm morphology in his study group after treating with clomiphene citrate. It was a quasi-experimental study and the study population was 50 males with iOAT (Zahoor Iqbal Mirza).

The objectives of the present study were to study the effect of Clomiphene Citrate on patients with iOAT syndrome. This study was carried out in the Reproductive Biology Laboratory (RBL) of the Faculty Of Medicine, University of Ruhuna. RBL of the Ruhuna Medical Faculty is a center of excellence in the management of male factor infertility. It has the country's first sperm bank and it caters to patients who seek help from all over the country.

II. PATIENTS AND METHODS

This was a retrospective study conducted in the Reproductive Biology Laboratory (RBL), Faculty of Medicine, Karapitiya. Medical records of the males treated with clomiphene citrate, 25 mg daily for more than 3 months, between 2009 and 2012 were selected from the data base. The medical records were carefully evaluated and screened by an Andrologist and the records that are complying with the following inclusion and exclusion criteria were included for the analysis.

Inclusion Criteria:

1. Males, who's Basic Seminal fluid Analysis (SFA) assessments were done in the RBL.
2. Males who had pre and post treatment SFA assessments.

3. Infertile men having OTS (Sperm concentration < 15X10⁶ per ml., Morphology <30% using standard protocol, Motility (a+b) < 50%)
4. Otherwise healthy males aged 25-45 having coital frequency more than 4 times/week with the married partner.
5. Normal levels of serum FSH, LH, and testosterone.
6. Married and having a stable relationship for more than 3 years.

Exclusion criteria:

1. Males who were on long term (more than 6 months) medical treatment.
2. Males with past history of any surgical intervention related to scrotum or testes.
3. Previous history of mumps, orchitis, trauma to testes, cryptorchidism or varicocele.
4. Previous history of STD.
5. Previously treated for infertility.

The data was analyzed by Epi Info 7. Two tailed P test was used to compare pre – treatment and post – treatment groups.

III. RESULTS AND DISCUSSION

Fifty one (51) patients were in the study. The mean age of the study population was 33 (SD ± 3.5). The mean FSH, LH and testosterone values of the study sample prior to treatment were 2.7 (SD ± 1.32), 3.5 (SD ± 1.6) and 4,6 (SD ± 2.3) respectively. The mean testicular volume was 28 ml.

The mean semen volume of the pre-treatment phase was 2.15 ±1.3 ml. After treating with clomiphene it was 2.42 ± 0.89 ml. It doesn't show any significant improvement.

The mean concentration of the pre – treatment group was 6.17 X 10⁶ (SD ± 5.59)per/ ml . It showed a statistically significant improvement (p<0.001) after clomiphene treatment. The mean concentration of the post – treatment group was 18.18 X 10⁶ (SD - ± 11.1).

Morphology also showed a significant improvement (p < 0.001) with clomiphene treatment. Prior to the treatment the mean morphology was 22.4 ± 8.8 and it was 29.5 ± 10.7 after the treatment.

The mean motility of the pre-treatment group was recorded as 32.5 ± 14.9. In post-treatment group the mean motility was 45.3 ± 14.7. It showed a statistically significant improvement (p < 0.001).

In the post-treatment group, the mean viability was 56.9 ± 12.6. It too showed a statistically significant improvement (P < 0.001) when compared to the mean viability of the pre-treatment group, 44.6 ± 14.

Table 1: Summary of the statistical analysis of the various Seminal Fluid (SF) parameters in pre and post study groups

Parameter	Pre Treatment		Post Treatment		P Value
	Mean	SD	Mean	SD	
Volume	2.15	1.13	2.42	0.89	> 0.5
Concentration	6.17	4.59	18.18	11.1	< 0.001
Total Count	13	12.2	48.6	18.5	< 0.001
Morphology	22.4	8.8	29.5	10.7	< 0.001
Motility	32.5	14.9	45.3	14.7	< 0.001
Viability	44.6	14	56.9	12.6	< 0.001

The results showed significant improvements of concentration (pre treatment 6.17 ± 4.59 and post treatment 18.18 ± 11.1), total count (pre treatment 13 ± 12.2 and post treatment 48.6 ± 18.5), morphology (pre treatment 22.4 ± 8.8 and post treatment 29.5 ± 10.7), motility (pre treatment 32.5 ± 14.9 and post treatment 45.3 ± 14.7) and viability (pre treatment 44.6 ± 14 and post treatment 56.9 ± 12.6). But volume has not showed a significant improvement (pre treatment 2.15 ± 1.13 and post treatment 2.42 ± 0.89).

Our results are compatible with the results of Mahmoudreza Moradi et. al. 2010 (Mahmoudreza Moradi et al. 2010). They have reported statistically significant improvements in concentration, total count, morphology, motility and viability but the volume.

In 2012 Zahoor Iqbal Mirza et. al. Recorded a significant improvement of the the SF volume after clomiphene treatment (Zahoor Iqbal Mirza) which we could not observe.

IV. CONCLUSION AND RECOMMENDATIONS

Clomiphene citrate can improve the sperm concentration, total count, normal morphology, motility and viability in a group of selected male patients with iOAT syndrome. A well designed randomized clinical trial is recommended to study the effects of clomiphene citrate on iOAT.

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