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Original Research Article

Effects of clomiphene citrate on seminal parameters in idiopathic oligospermia: a single blinded prospective randomized controlled trial

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ABSTRACT

Background: About 15% married couples face problem of infertility of which male factor is implicated in 20% of them. In about 30% infertile men no causative factor is found and the condition is termed “Idiopathic”. They are often treated by empirical medications or Assisted Reproductive Technologies (ART) although success in few; our present study is carried on effects of clomiphene citrate on seminal parameters in idiopathic oligospermia.

Methods: This single blinded prospective randomized controlled trial was conducted at the infertility clinic with 200 idiopathic oligospermic men (sperm count <15 millions/ ml of ejaculate) after fulfilling inclusion and exclusion criteria and were alternately allocated into two equal groups - “Group C” receiving clomiphene citrate tablets and “Group P” receiving placebo after concealment. Semen analysis data were collected at baseline and every month and three months of completion of treatment and were summarized by routine descriptive statistical analysis.

Results: The demographic characteristics like mean age is comparative in both groups but duration of infertility of >2 years is more in group C than group P (4.3±3.06 versus 4.1±2.57). The semen volume, spermatozoa count, sperm motility and not normal form are all increased after three months of treatment in group C as are biochemical parameters like total testosterone and serum FSH, LH and also pregnancy rate (22% versus 4%).

Conclusions: This study showed clomiphene citrate treatment protocol is inexpensive, relatively safe and easy to administer and improves semen volume, sperm count and sperm motility but not sperm morphology by increasing serum testosterone, FSH and LH in male and resulting in improved pregnancy rate in female partners.

Keywords: Clomiphene citrate, Idiopathic oligospermia, Male factor infertility, Pregnancy rate, Semen analysis, Sperm count

INTRODUCTION

Infertility remains a serious socio- medical problem worldwide and is defined as inability to conceive after one year of unprotected intercourse by couples of reproductive age group. About 15% of married couples face the problem with male gender implicated in 20% of them.¹ In fact male factor plays more role in the etiology of infertility.² These male infertility factors are almost

always defined by finding of an abnormal semen analysis according to WHO criteria, although other factors play a role even when the semen analyses are normal.³ In male dominant societies particularly where illiteracy and poverty are more prevalent like in our country, man hardly agree to get investigated for infertility.⁴ According to WHO criteria (2010), Normozoospermia is defined as an ejaculate with sperm concentration of $> 20 \times 10^6$ spermatozoa/ml, progressive sperm motility of $> 50\%$ or

at least 25% of spermatozoa with linear progressive motility and $\geq 30\%$ morphologically normal spermatozoa. Oligozoospermia or oligospermia is defined when sperm concentration is <15 million/ml or motility $< 40\%$ or normal form $<4\%$.⁵ In about 30% of infertile men no causative factor is found for their decrease in sperm concentration or quality by common clinical, instrumental or laboratory means, and the condition is termed "Idiopathic".⁶ They are often treated by varieties of empirical medications or assisted reproductive technologies (ART) although success in few.² In this context authors intended to perform the present study on the "Effects of clomiphene citrate on seminal parameters in idiopathic oligospermia".

METHODS

This study was conducted at the infertility clinic in our department of gynecology and obstetrics at NRSMC, Kolkata for one year between January 2017 to December, 2017 with 200 idiopathic oligospermic men (sperm count < 15 million/ml of ejaculate) after fulfilling the inclusion criteria (healthy males 20-45 years of age marrying for > 1 year with no issue giving informed written consent who were willing for treatment for 3 months with monthly follow-up and semen examination, serum testosterone (total), FSH and LH estimation and no past history of renal, hepatic or any other chronic illness like chronic sinusitis) and the exclusion criteria (azoospermia, obesity, male reproductive accessory gland infections, any recent medical or surgical illness, hypertension, oligospermia of definitive pathology, ejaculatory and erectile dysfunctions). Institutional Ethical Committee permission was taken. They were alternatively allocated into two equal groups - "Group C" receiving clomiphene citrate tablets 25 mg/day for 25 days with 5 days rest for 3 months and "Group P" receiving placebo after concealment. Data were collected for this single blinded prospective randomized controlled trial at baseline, every month during treatment and after completion of 3 months of treatment from subjects of both the groups. Semen samples were collected from subjects by masturbation following strict abstinence of 3 days from intercourse with a clean sterile wide mouthed jar of 20 ml and analyses were performed within an hour of receiving the samples for semen volume, semen density, motility and morphology according to the WHO protocol: semen volume was measured directly on a graduated pipette after giving 20-30 minutes for liquefaction; sperm density was determined by using haemocytometer (Neubauer counting chamber); the percentage of mobile spermatozoa was taken as the proportion of progressive spermatozoa moving either slowly or rapidly relative to the hundred successive sperms under microscope. Two samples of 5 ml blood were taken from antecubital vein from each subject before administration of first dose of clomiphene citrate and at the end of each month 24 hours after the last dose and analyzed by using standard ELISA method at the department of biochemistry at NRSMCH, Kolkata. Effects of clomiphene citrate were measured by

comparing the changes in above parameters in the two groups. Pregnancies were documented in those patients who conceived during the three months of therapy using urinary rapid-kit test (Nischay kit supplied by the dept. of Health and Family Welfare, Govt. of India).

Statistical analysis

The sample size was calculated by taking α - error as 0.05 with power of 80% (β - error as 0.2) and degree of variance of mean of 15% of primary outcome measures with standard statistical formula showing the minimum number to be 70 in each group. All statistical analyses were carried out using Statistica version 6 (Tusla, Oklahoma: Statsoft Inc., 2001), www.medcalc.org and Graph Pad Prism Version 5 (San Diego, California: Graph Pad Software Inc., 2007) software's. Data had been summarized by routine descriptive statistics. Mean values of semen parameters and hormonal levels were compared between two groups using Student's unpaired t-test. Non- parametric numerical variables were compared between groups by Mann - Whitney U test. For intragroup comparison of changes of semen and hormonal parameters Repeated Measures ANOVA was employed followed by Tukey's Multiple Comparison Test where Repeated Measure ANOVA returned p- value <0.05 . Fishers exact test was used to compare pregnancy rate between the two groups. Analyses were 2 - tailed and p - value of <0.05 was considered as statistically significant.

RESULTS

It is seen from the data through Table 1 (demographic variables), Table 2 (primary outcome measures) and (secondary outcome measures) depicted below that mean age in both groups are comparable (29.9 ± 8.64 in group C versus 28.7 ± 7.25 in group P) but the duration of infertility of >2 years is more in group C than group P (4.3 ± 3.06 versus 4.1 ± 2.57).

Table 1: Demographic variables, (age groups in infertile couples and duration of infertility in infertile couples).

Characteristics	p-value		
	Group C (%) (n = 100)	Group P (%) (n = 100)	
Age (years)			
21 -25	32	34	
26 -30	28	40	0.2887; 95% CI (-3.4242 to 1.0242), t = -1.064
31 -35	26	16	
36-40	14	10	
Mean \pm SD	29.9 \pm 8.64	28.7 \pm 7.25	
Duration of infertility (years)			
≤ 2	32	52	0.6173; 95% CI (-0.9880 to 0.5880), t = -0.500
3 - 5	56	42	
≥ 6	12	6	
Mean \pm SD	4.3 \pm 3.06	4.1 \pm 2.57	

Table 2: Outcomes.

Characteristics	Group C (Mean±SD)	Group P (Mean±SD)	p-value*	Within group p-value **	
				Group C	Group P
Primary outcomes					
Semen volume (ml)					
Baseline	2.4±0.57	2.2 ± 0.57	0.101		
After 1 month	2.6±0.57	2.2± 0.49	0.003	< 0.001	0.078
After 2 months	2.7±0.51	2.3±0.47	0.000		
After 3 months	3.1±0.58	2.3± 0.50	0.000		
Spermatozoa count (mil/ml)					
Baseline	11.2±2.64	11.4±4.02	0.747		
After 1 month	13.8±3.99	12.1±3.99	0.036	< 0.001	< 0.001
After 2 months	17.3±5.88	12.9±4.21	0.000		
After 3 months	25.6±8.89	14.2±5.50	0.000		
Sperm motility (%)					
Baseline	46.7±9.74	45.9±8.23	0.666		
After 1 month	48.9±9.56	47.1±8.31	0.318	< 0.001	< 0.001
After 2 months	50.9±9.56	47.9±8.33	0.100		
After 3 months	53.8±10.17	49.0±8.05	0.000		
Sperm morphology - normal form (%)					
Baseline	33.0±14.66	35.0±13.98	0.474		
After 1 month	34.1±14.68	35.5±13.80	0.605	< 0.001	< 0.001
After 2 months	35.1±14.77	36.2±13.81	0.706		
After 3 months	36.6±15.11	37.1±13.67	0.873		
Secondary outcomes					
Serum testosterone (ng/ml)					
Baseline	4.1±0.75	4.1±0.70	0.701		
After 1 month	4.4±0.76	4.2±0.72	0.245	< 0.001	< 0.001
After 2 months	4.9±0.69	4.2±0.73	0.000		
After 3 months	5.6±0.81	4.3±0.73	0.000		
Serum FSH (mIU/ml)					
Baseline	5.6±1.33	5.3±0.80	0.139		
After 1 month	6.2±1.30	5.4±0.77	0.000	< 0.001	< 0.001
After 2 months	6.7±1.35	5.5±0.77	0.000		
After 3 months	7.6±1.58	5.6±0.79	0.000		
Serum LH (mIU/ml)					
Baseline	5.7±1.10	5.8±1.30	0.691		
After 1 month	6.3±0.97	5.8±1.26	0.029	< 0.001	< 0.001
After 2 months	7.2±0.95	5.9±1.20	0.000		
After 3 months	8.1±1.00	6.0±1.21	0.000		
Pregnancy rate after 3 months of treatment					
Positive urinary kit test (%)	22	4	0.0002; 95% CI*** (8.8866 to 27.3912); chi -squared **** = 14.252; DF = 1.		
Side effects of clomiphene citrate					
Nausea	5	1	0.0981(95% CI: -1.2809 to 10.2297) 0.3136 (95% CI: -2.8671 to 7.5137) 0.3149 (CI*****: 0.24 to 7.04; z = 1.005) 1 (CI*****: 0.03 to 5.45; z = 0.000)		
Hypertension	3	1			
Blurred vision	2	0			
Psychotic reaction	1	0			

*The p- value for intergroup comparison is by Student's unpaired t- test; ** The p- value for within group comparison is from Repeated Measures of Analysis of Variance (ANOVA); ***The confidence interval (CI): recommended method by Altman et al; ****The "N-1" Chi - Squared test: by Campbell (2007) and Richardson; *****The "exact" Clopper - Pearson confidence interval. (Clopper and Pearson, 1934; Fleis et al, 2003).

The semen volume, spermatozoa counts, sperm motility and normal sperm are all increased in group C than group

P after 3 months of treatment as depicted in Table 2. Total testosterone level, serum FSH and LH are all

increased also; Pregnancy rate with positive urine for pregnancy test are significantly more in group C than group P (22% versus 4%) while side effects occurred slightly more in group C as observed in Table 2.

DISCUSSION

Inability to conceive in an eligible couple at their starting of married life is a social and psychological stigma still today in modern days and blaming female partner ignoring male counterpart has resulted in higher treatment cost to overcome.⁷ Clomiphene citrate, 1-[p-(beta-diethylaminoethoxy)phenyl]-1,2-diphenyl chloroethylene, is an orally active non-steroidal agent distantly related to diethylstilbestrol and it acts by stimulating pituitary gonadotrophin release and increased testosterone released by the Leydig cells.^{8,9} Many doses and protocols of using clomiphene citrate are reported while 25 mg daily for 25 days followed by a drug free interval of 5 days for 3 months is studied.¹⁰ Increase endogenous testosterone is related to seminal vesicle functions. Clomiphene citrate also stimulates sertoli cells resulting in more spermatocytes.^{11,12} Like our study, Fuse H et al; Simantini et al; Zaman et al; Moradi et al, have shown increase in semen volume, sperm count and motility whereas Ronnberg et al; Ghanem et al showed diminished motility and no improvement in morphology.¹³⁻¹⁷ Increase in the serum testosterone, FSH and LH levels after treatment are corroborated well in studies by Fuse H et al; Zaman et al; AT Guay et al and Da Ros CT et al.^{13,15,19,20} Higher pregnancy rates in group C than in group P are also observed in studies by Ronnberg L et al, and Wang et al.^{17,21} The minor side effects of clomiphene citrate occurred during treatment and are subsided with time and no patient needed drug discontinuation. Siddiq et al also reported side effects are usually mild and occur in less than 5% of patients.²²

CONCLUSION

Patients with idiopathic oligospermia not only are frustrated by having no explanation for their problem but also are surprised by the scarcity of effective medical treatments to improve upon the production and quality of their sperm. This study shows clomiphene citrate improves semen volume, sperm count and sperm motility but not sperm morphology by increasing serum testosterone, FSH and LH with improved pregnancy rate in female partners. This treatment protocol is inexpensive, relatively safe, easily accepted and easy to administer. Although clomiphene citrate is used as first-line therapy in idiopathic oligospermia for many years, its effectiveness is not yet well established. Further clinical studies with large number of patients with a longer follow-up period are needed on a multicentric basis to substantiate in Indian perspective.

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