



Effects of Escitalopram and Citalopram on Semen Parameters in Wistar Albino Rats

Ali Abbas, Kumayl Abbas Meghji, Muhammad Shahab Hanif, Muhammad Saqib Baloch, Shazia Parveen Channar, Ahsan Aslam

ABSTRACT

Objective: To evaluate the effects of citalopram versus escitalopram on semen parameters (count, motility, morphology) in wistar albino rates. **Study Design:** Quasi Experimental Study. **Settings:** Isra University Hyderabad Sindh and Animal Protocol was conducted at Department of Animal Husbandry and Veterinary Sciences, Sindh Agriculture University Tando Jam Pakistan. **Duration:** 6 months from January to June 2017. **Methodology:** Fifty (50) Albino Wistar Rats were divided into five groups namely group A (control) and experimental groups B, C, D and E. Escitalopram (0.4mg/kg P.O) and Citalopram (0.8mg/kg P.O) were given to all experimental groups (B, C, D and E) for six weeks. After six weeks rats of groups A, B and C were sacrificed through cervical dislocation and data was collected. While rats of groups D (citalopram reversal) and E (escitalopram reversal) were treated like control in order to observe the reversal effects of these drugs. Data was recorded in self-made proforma. **Results:** Sperm count in control and experimental groups (B and C) was 3.95 ± 0.64 , 2.43 ± 0.49 , 2.51 ± 0.52 that was decreased in experimental groups. While in reversal groups D and E it was significantly improved 2.82 ± 0.29 and 2.76 ± 0.50 . Between the reversal groups there was no significant difference. Motility among control and experimental (B and C) was 78.9%, 68.7% and 70.4% and in reversal groups D and E it was improved to 74.3% and 73.5%. Normal morphology among control and experimental (B and C) was 92.2%, 74.7% and 76.4% and in reversal groups D and E it was improved to 84.3% and 81.9%. Morphological abnormalities were more common in head as compared to tail.

Conclusion: The present study concludes that Escitalopram and Citalopram both have harmful effects on sperm count, motility and morphology. Whereas Escitalopram is more toxic than Citalopram and on withdrawal of these drugs the semen parameters.

Keywords: SSRIs, Escitalopram, Citalopram, Semen Parameters.

Corresponding Author

Submitted for Publication: 13-11-2019

Accepted for Publication: 06-12-2019

DR. ALI ABBAS, Senior Lecturer, Pharmacology Department, Isra University Hospital Hyderabad-Pakistan.

Contact / Email: +92 335-2641520, alee.abbas@hotmail.com

Citation: Abbas A, Meghji KA, Hanif MS, Baloch MS, Channar SP, Aslam A. Effects of Escitalopram and Citalopram on Semen Parameters in Wistar Albino Rats. APMC 2019;13(4):272-6.

INTRODUCTION

Infertility is defined as inability of couple to conceive after one year of unprotected intercourse. Infertility is a common problem affecting one couple in six.^{1,2}

There are 80 million people in the world that are suffering from infertility.³ Infertility lead to anxiety, depression and negatively affect the relationship of couple.⁴ Recent studies shows that infertile couples have more stress than fertile couple. Stress factor is known to have a negative impact on reproduction system as well.⁵

So things will become further worst. There are many causes of infertility and these causes are divided as causes due to male factor and causes of infertility due female factor. Among females causes these are pelvic inflammatory disease, polycystic ovarian syndrome, endometriosis, hyperprolactinemia, hypothyroidism and idiopathic. Among these causes pelvic inflammatory disease is more common.¹

Among males main causes of infertility are infections, genetic (Klinefelter, Down's syndrome), tumors (pituitary and testicular), hypogonadism (Kallmann syndrome, head injuries). Others anatomical causes include varicocele, hydrocele and damage of the vessels due to obstruction and torsion of testicular sperm passage may lead to infertility among males.⁶

In Pakistan infertility prevalence is 21.9% among this 3.5% accounts for primary infertility and 18.4% accounts for

secondary infertility in Pakistan.¹ Drugs use may be the important cause of infertility in men and drugs includes anabolic androgenic steroids, marijuana, opioid narcotics, cocaine and methamphetamine. Other causes of infertility are hormonal deficits, morphological alteration of gonads, abnormal spermatogenesis and psychological factors.⁷

Among Anti-depressant drugs SSRI (selective serotonin reuptake inhibitors) are most commonly used. SSRI includes fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram and escitalopram.⁸ SSRIs act by the blocking the uptake of serotonin into pre synaptic neuron and causing increased concentration in the synaptic space, resulting in the stimulation of post synaptic receptors.⁹

Escitalopram is enantiomer of citalopram.¹⁰ The primary indication of the SSRIs is depression and anxiety. Off label uses of SSRIs has become commonest for premature ejaculation management.^{11,12} To the best of knowledge, there are only few studies present on escitalopram and citalopram effects on testicular tissue but no work has been done in Pakistan regarding SSRI effects on testis and testicular histology as well as there is no any study for the comparative effects of escitalopram and citalopram.

Purpose of this study was to assess the effects of citalopram versus escitalopram on semen parameters (count, motility) in wistar albino rates. This study is going to add knowledge

regarding the association between SSRIs use and infertility. This will also help to find out which of the two commonly prescribed drugs is more toxic at therapeutic doses, which will be helpful to both, Physicians and Patients.

METHODOLOGY

Study Design: Quasi Experimental Study.

Settings: Pharmacology department of Isra University Hyderabad/ Animal House, Sindh Agricultural University Tando Jam Pakistan.

Duration: 6 months from January to June 2017.

Total fifty Normal, Healthy Albino Wistar adult Male Rats with weight of 200-300 gm were included. These 50 albino rats will be divided into the 5 groups.

1. Group A : Control
2. Group B : Escitalopram 0.4mg/kg P.O
3. Group C : Citalopram 0.8/kg P.O
4. Group D : Reversal group of citalopram
5. Group E : Reversal group of escitalopram

All the albino Male Wistar rats were purchased from Karachi and were placed at department of animal husbandry and veterinary sciences, SAU Tando Jam. Rats were placed in the separate cages having the access to tap water and chow ad libitum. Drugs were purchased from local pharmacy and were grinded and diluted in distilled water.

Group A serves as control it was given normal chow diet ad libitum. Escitalopram was given to the rats at 0.4mg/kg orally to groups B and E for 6 weeks. Groups C and D were given citalopram 0.8mg/kg for 6 weeks. The drugs were administered by oral gavage.

After 6 weeks, testes were harvested after cervical dislocation of groups A, B and C. Epididymis was separated and transferred to petri dish and macerated to have an epididymal suspension. And that was used for evaluation of semen parameters including sperm count, morphology and motility were examined under the light microscope.

After 6 weeks drugs of Groups D and E were stopped for 4 weeks. Then the testes of group D and E were harvested after 4 weeks and same procedure were repeated in order to see either the effects produced by drugs are reversible or not. All the information was recorded in the profroma.

Statistical Analysis: After the collection of data the analysis was conducted by using statistical package for social sciences (SPSS) software version 21. ANOVA and student t-test were used to evaluate statistical significance.

RESULTS

The present experimental study showed the effects of Escitalopram and citalopram therapy on semen in albino wistar rat model. Mean of sperm counts in Group A control was $3.95 \pm 0.64 \times 10^6/\text{ml}$, in Group B (Escitalopram) it was observed as $2.43 \pm 0.49 \times 10^6/\text{ml}$ and in group C (Citalopram) $2.51 \pm 0.52 \times 10^6/\text{ml}$. Two group i-e Group D and Group E which were kept on drug free regimen for 4 weeks to see the reversal effects of citalopram and escitalopram respectively, after that mean of

sperm count in group D (Citalopram Reversal) was 2.82 ± 0.29 and in group E (Escitalopram Reversal) was 2.76 ± 0.50 .

Sperm motility decreased in experimental groups as in group A sperm motility was 78.9%, in group B 68.7% and in group C it was 70.4%, whereas on reversal results were better with Group D showing 74.3% motile sperms and Group E showing 73.8% sperm motility.

Table 1: Sperm count comparison between study groups n=50

Groups	Total sperm count (Mean± S.D)		P-value
(group A) vs (group B)	$3.95 \pm 0.64 \times 10^6/\text{ml}$	$2.43 \pm 0.49 \times 10^6/\text{ml}$	0.001
(group A) vs (group C)	$3.95 \pm 0.64 \times 10^6/\text{ml}$	$2.51 \pm 0.52 \times 10^6/\text{ml}$	0.001
(group B) vs (group C)	$2.43 \pm 0.49 \times 10^6/\text{ml}$	$2.51 \pm 0.52 \times 10^6/\text{ml}$	0.026
(group D) vs (group E)	$2.82 \pm 0.29 \times 10^6/\text{ml}$	$2.76 \pm 0.50 \times 10^6/\text{ml}$	0.942

In group A control 92.2% normal morphology and 7.8% as abnormal morphology, in Group B 74.7% were normal and 25.3% as abnormal, among abnormal head abnormality was seen in 10% and tail abnormality in remaining 15.3%. In group C 76.4% were normal and 23.6% were abnormal, similarly in abnormal cases 16.3% showed tail abnormality and 7.4% showed head abnormality. In both reversal groups results were better with Group D showing 84.3% normal and 15.7% as abnormal, in abnormal 4.5% head and 11.2% tail abnormality.

Table 2: Comparison of sperm motility between control and experimental groups

Groups	Sperms motility (frequency (%))		P-value
(group A) vs (group B)	78.9 %	68.7%	0.001
(group A) vs (group C)	78.9 %	70.4%	0.001
(group B) vs (group C)	68.7%	70.4%	0.026
(group D) vs (group E)	74.3%	73.5%	0.942

Group E showed similar improved results in terms of morphology, 81.9% normal and 17.1% as abnormal, among abnormal 5.1% head and 12% tail abnormality.

Table. 3: Comparison of sperm morphology between control and experimental groups

Groups	Sperms motility (frequency (%))		P- value
(group A) vs (group B)	7.8%	25.3%	0.001
(group A) vs (group C)	7.8%	23.6%	0.001
(group B) vs (group C)	25.3%	23.6%	0.026
(group D) vs (group E)	15.7%	81.9%	0.942

DISCUSSION

The present study has reported the effects of two of the most popular and commonly prescribed SSRI escitalopram and citalopram on sperm count, sperm morphology and sperm motility along with histological changes, the present study has focused on the comparative effects of both SSRI's

To the best of knowledge, the present research study is the first comparing the effects of Escitalopram and Citalopram on semen parameters and testicular histology in an experimental rat model in Pakistan. The study evaluated the main variables of male infertility by estimating and comparing the sperm count, sperm motility, sperm morphology and testicular histology creatinine in controls and intervention receiving rats. The Null hypothesis was rejected and alternative hypothesis was proved in the present research, as both the SSRI's had a negative effect on semen parameters and testicular histology. However, escitalopram was found to be more toxic as compared to citalopram.

G Kilic et al (2017) conducted a study on effects of citalopram on semen parameters and testicular histology in rats. He reported that citalopram decreases both the sperm count and motility. They also reported degenerative changes in seminiferous tubules and decreased spermatogenesis on histological examination. The present study is consistent with above study.¹³

AAA Galal et al (2016) reported that SSRIs decrease count, motility and normal morphology of sperms. But these effects were reversible after withdrawal drug. They also distorted seminiferous tubules on histological examination. The present study is consistent with above study.¹⁴

HY Elnazer et al (2014) reported that there was a decrease in count, motility and morphology in a patient on citalopram treatment for 3 years. These findings were reversed after 4 months when citalopram was stopped. Present study is consistent with above study as the changes in the semen parameters were reversed after the discontinuation of drug.¹⁵

H Koyuncu et al (2011) carried a study on escitalopram and they observed that escitalopram decreased semen parameters: sperm count, motility and morphology significantly over a time period of 3 months. The present study is consistent with above study.¹⁰

O Atli et al (2017) conducted the research on the effects of SSRI on semen parameters albino rats, he found that there was no significant effect on sperm motility between control and experimental group. That is inconsistent with the present study. Reason for the inconsistency may be the use of different technique for the evaluation of semen parameter.¹⁶ Fikret Erdemir et al (2014) observed the effects of different SSRIs on testicular tissue and found SSRIs have an adverse effect on testicular histology. These findings are consistent with the present study.⁸ In a Clinical trial reported by Akasheh et al (2014) it was observed that SSRI have a detrimental effect on semen parameters. SSRI. There was a decrease in the sperm count and percentage of normal morphology which is consistent with the current study.¹⁷ Tanrikut et al (2007) studied the effect of anti-depressant associated alteration in sperm's motility and concentration. They observed decreased sperm count, Impaired motility and abnormal morphology in patients while they were on SSRI's which improved after cessation of drug therapy. These findings are consistent with the current study in which sperm count, motility and histology were improved after discontinuation of SSRI therapy.¹⁸

Safarnejad et al (2008) observed the SSRI's groups were significantly decreased in the SSRI group as compared to control group. These findings are consistent with the present study.¹⁹ Korshunov et al (2016) studied the effects of SSRI use on semen parameters. They observed reduction in semen parameters after SSRI use which reverted back to normal after cessation of drug therapy. These findings are also consistent to the current study as the semen parameters were altered by SSRI use and a reversal was noted in all the parameters in the reversal groups.²⁰

Inass et al (2005) studied the effects of SSRI's on male fertility and semen parameters.²¹ They found that SSRI use had deleterious effects on semen parameters such as reduced sperm count and altered sperm morphology. SSRI use also caused alterations in the normal shape of seminiferous tubules. These findings are consistent to the current study.²¹⁻²³

CONCLUSION

The present study concludes that Escitalopram and Citalopram both have harmful effects on semen parameters. Whereas Escitalopram is more toxic than Citalopram. On withdrawal of these drugs the semen parameters show sign of recovery.

RECOMMENDATION






Similar studies should be carried on the other SSRIs at larger scale.

The subjects that are trying to conceive, should be prescribed alternative therapies (SNRIs, TCA and Atypical Antidepressant). Further studies are recommended to find the exact mechanism responsible for these effects that can be by measuring FSH, Testosterone, Prolactin, Gonadotropin releasing hormone and some oxidative stress assessment is also recommended

REFERENCES

1. Arain F, Arif N, Halepota H. Frequency and outcome of treatment in polycystic ovaries related infertility. *Pakistan journal of medical sciences*. 2015;31(3):694.
2. Dam P, Dasgupta S, Das N, Chakravorty PS. Evaluation of role of intrauterine insemination in infertility in a tertiary care hospital. *Journal of Evolution of Medical and Dental Sciences*. 2014;3(16):4336-49.
3. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. *Human reproduction update*. 2015;21(4):411-26.
4. Cserepes RE, Kollár J, Sápy T, Wischmann T, Bugán A. Effects of gender roles, child wish motives, subjective well-being, and marital adjustment on infertility-related stress: a preliminary study with a Hungarian sample of involuntary childless men and women. *Archives of gynecology and obstetrics*. 2013;288(4):925-32.
5. Rooney KL, Domar AD. The impact of stress on fertility treatment. *Current Opinion in Obstetrics and Gynecology*. 2016;28(3):198-201.
6. Masoumi SZ, Parsa P, Darvish N, Mokhtari S, Yavangi M, Roshanaei G. An epidemiologic survey on the causes of infertility in patients referred to infertility center in Fatemeh Hospital in Hamadan. *Iranian journal of reproductive medicine*. 2015;13(8):513.
7. Fronczak CM, Kim ED, Barqawi AB. The insults of illicit drug use on male fertility. *Journal of andrology*. 2012;33(4):515-28.
8. Erdemir F, Atilgan D, Firat F, Markoc F, Parlaktas BS, Sogut E. The effect of sertraline, paroxetine, fluoxetine and escitalopram on testicular tissue and oxidative stress parameters in rats. *International braz j urol*. 2014;40(1):100-8.
9. Koyuncu H, Serefoglu EC, Ozdemir AT, Hellstrom WJ. Deleterious effects of selective serotonin reuptake inhibitor treatment on semen parameters in patients with lifelong premature ejaculation. *International journal of impotence research*. 2012;24(5):171.
10. Koyuncu H, Serefoglu EC, Yencilek E, Atalay H, Akbas NB, Sarica K. Escitalopram treatment for premature ejaculation has a negative effect on semen parameters. *International journal of impotence research*. 2011;23(6):257.
11. Nørr L, Bennedsen B, Fedder J, Larsen ER. Use of selective serotonin reuptake inhibitors reduces fertility in men. *Andrology*. 2016;4(3):389-94.
12. Kassan M, Lasker GF, Sikka SC, Mandava SH, Gokce A, Matrougui K et al. Chronic escitalopram treatment induces erectile dysfunction by decreasing nitric oxide bioavailability mediated by increased nicotinamide adenine dinucleotide phosphate oxidase activity and reactive oxygen species production. *Urology*. 2013;82(5):1188-e1.
13. Ilgin S, Kilic G, Baysal M, Kilic V, Korkut B, Ucarcan S, Atli O. Citalopram Induces Reproductive Toxicity in Male Rats. *Birth defects research*. 2017;109(7):475-85.
14. Galal AA, Alam RT, Abd El-Aziz RM. Adverse effects of long-term administration of fluvoxamine on haematology, blood biochemistry and fertility in male albino rats: a possible effect of cessation. *Andrologia*. 2016;48(9):1002-10.
15. Elnazer HY, Baldwin DS. Treatment with citalopram, but not with agomelatine, adversely affects sperm parameters: a case report and translational review. *Acta neuropsychiatrica*. 2014;26(2):125-9.
16. Atli O, Baysal M, Aydogan-Kilic G, Kilic V, Ucarcan S, Karaduman B, Ilgin S. Sertraline-induced reproductive toxicity in male rats: evaluation of possible underlying mechanisms. *Asian Journal of Andrology*. 2017;19(6):672.
17. AKASHEH, Goudarz, et al. Comparison of the effect of sertraline with behavioral therapy on semen parameters in men with primary premature ejaculation. *Urology*, 2014;83(4):800-804.
18. TANRIKUT, Cigdem; SCHLEGEL, Peter N. Antidepressant-associated changes in semen parameters. *Urology*. 2007;69(1):185.
19. Safarinejad MR. Sperm DNA damage and semen quality impairment after treatment with selective serotonin reuptake inhibitors detected using semen analysis and sperm chromatin structure assay. *The Journal of urology*. 2008;180(5):2124-8.
20. Korshunov MN, Korshunova ES. Selective serotonin reuptake inhibitor and fertility potential of the men. *Psychiatry and Urology. At the junction of related disciplines. Urologicheskie vedomosti*. 2016;6(3):19-25.
21. Aggarwal A, Jethani SL, Rohatgi RK, Kalra J. Effects of fluoxetine on testis of albino rats—a histological assessment. *Int. J. Sci. Eng. Res*. 2012;3:1-5.
22. Soliman ME, Mahmoud BL, Kefafy MA, Yassien RI, El-Roghy ES. Effect of antidepressant drug (fluoxetine) on the testes of adult male albino rats and the possible protective role of omega-3. *Menoufia Medical Journal*. 2017;30(4):1135.
23. Inass EG, Hassan M, Fouad G, El-Komey F. Toxic effects of paroxetine on sexual and reproductive functions of rats. *Egyptian Journal of Hospital Medicine*. 2005;21:16-32.

AUTHORSHIP AND CONTRIBUTION DECLARATION

AUTHORS	Contribution to The Paper	Signatures
Dr. Ali Abbas Senior Lecturer, Pharmacology Department, Isra University Hospital Hyderabad	Research idea and data collection	
Dr. Kumayl Abbas Meghji Senior Lecturer, Physiology Department, Isra University Hospital Hyderabad	Contribution in manuscript writing	
Dr. Muhammad Shahab Hanif Senior Lecturer, Anatomy Department, Isra University Hospital Hyderabad	Contribution in data analysis	
Dr. Muhammad Saqib Baloch Senior Lecturer, Anatomy Department, Isra University Hospital Hyderabad	Contribution in manuscript writing	
Dr. Shazia Parveen Channar Senior Lecturer, Pharmacology Department, Isra University Hospital Hyderabad	Manuscript writing and data collection	
Dr. Ahsan Aslam Medical officer, Isra University Hospital, Hyderabad	Contribution in data analysis	