A study of the effect of tramadol on testicular functions in adult males

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Abstract: **Objective:** The aim of the study was toelucidate the effects of tramadol addiction on testicular functions of adult males. **Background:** Tramadol is centerally acting atypical opiod analgesic with additional serotonine-norepinephrine reuptake inhibiting effects. Tramadol is used primarily to treat moderate to severe pain. Also, tramadol is used in other uses as post herpetic neuralgia, diabetic neuropathy, antidepressant, acute opioid withdrawal management, obsessive compulsive disorder and premature ejaculation. Long term use of high doses of tramadol may be associated with physical dependence and withdrawal symptoms including numbness, tingling, paresthesia and tinnitus. Many studies were performed on rats for assessment of the effect of tramadol on testis but no studies were performed on humans till now. **Patients and methods:** This study was conducted on 60 patients taking tramadol daily and 30 age matched control. Serum hormones (FSH, LH, prolactine and testosterone) were measured. Semen samples of 30 addicts were analysed. **Results:** Tramadol significantly reduce all measured hormones in comparison to the control groups. Also, tramadol significantly affect the sperm vitality and motility in comparison to the control group. High pus cell in semen of tramadol addicts in comparison to the control group. **Conclusion:** Tramadol affect the hormonal and reproductive functions of the testis.
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Key words: Tramadol, Semen analysis, Hormonal profile

1. Introduction

Tramadol is centrally acting atypical opioid analgesic with additional serotonin-norepinephrine reuptake inhibiting effects (1).

Tramadol is used primarily to treat moderate to severe pain (2).

Also, tramadol is used in other uses as, post herpetic neuralgia (3), diabetic neurapathy (4), antidepressant (5), acute opiod withdrawal management (6), obsessive compulsive disorder (7) and premature ejaculation (8).

Long term use of high doses of tramadol may be associated with physical dependence and withdrawal symptoms including numbness, tingling, paresthesia and tinnitus (9).

Many studies on rats showed that tramadol affects the hormonal and testicular functions, but no studies were performed to see that effects in humans.

2. Patients and Methods

Type of the study: cross sectional study.

Site of the study: the outpatient clinic of Menoufia University Hospital and Meet Khalaf Psychiatric Hospital.

Time of the study: from November 2014 to October 2015.

Aim of the study: Detection of the possible effect of tramadol addiction on testicular functions.

1) Subject:

Patients were chosen from the outpatient clinic according to the following criteria:

-Exclusion criteria:

-patients with any systemic disease affecting testicular functions (i.e.: liver disease, renal disease, respiratory diseases as sinopulmonary infection or C.O.P.D, febrile illness in the last 3 months, surgery as orchiectomy or prostatectomy, neurological diseases as epilepsy or spinal cord trauma, G.I.T diseases as coeliac disease or I.B.D, hematological diseases as thalassemia, hemophilia or megaloplastic anemia, endocrinal diseases as hyperthyroidism, hypercortisolism, DM type 2 and obesity, infections as mumps, AIDS, sexually transmitted diseases and lepromatous leprosy, antiandrogen drugs as finasteride, dutasteride, barbiturates, anticonvulsant, spironolactone, digoxin, cytotoxic drugs, or irradiation and drugs causing hyperprolactinemia as antipsychotic, antidepression, H2 blockers, ca channel blockers, estrogen and antiandrogen.

-patients having varicocele.

-Inclusion criteria

-male.

-taking tramadol for a period not less than 3 months.

-any age.

Method

The selected subjects were submitted to the following procedures:

1) Giving a written consent to be concluded in the study, the advantages he will get of participation, the secrecy of his own data and the destination he can ask for any questions.

2) History taking of: age, job, duration of tramadol daily taking, the daily dose, any other drugs of addiction, smoking and any systemic disease or drugs that mentioned above in the exclusion criteria.

3) Blood sample: a 5 ml blood sample from the cubital vein was taken from each patient for detection of the levels of LH, FSH, prolactin and testosterone. The sample was centrifuged for 10 min at a speed of 3000 ram/ sec for separation of the serum. Each sample was divided into 4 Eppendorf and frozen at a temperature of -20^{o}C until all samples were completed. The detection of the hormones mentioned above was done by ELISA (enzyme linked immunosorbent assay).

4) Semen: the semen was taken from patients by masturbation and sent immediately to lab for analysis. The semen analysis was done based on WHO 2010 Guidelines.

3. Results

The study was conducted on 60 patients of mean age of 27.05 -+ 7.74 years. Forty four patients (73.3%) were heavy smokers, three patients (5 %) were moderate smokers, eight patients (13.3 %) were mild smokers and five patients (8.3%) were nonsmokers. The dose of tramadol daily taking was of mean of 1127.9 mg -+ 878.34. The duration of addiction was of mean of 4.61 years -+ 2.95. Thirty nine patients (65%) were taking tramadol only, eleven patients (18.3%) were taking cannabis with tramadol, two patients (3.3%) were taking cannabis and alcohol with tramadol, four patients were taking heroin with tramadol, one patient (1.7%) was taking heroin and morphine with tramadol, one patient (1.7%) was taking apytral with tramadol. **(Table 1).**

The mean of age of the control group was 32.73± 7.76 years old. One (3.3%) of the control group was heavy smoker. Three (10%) of the control group were moderate smokers. Seven (23.3%) of the control group were mild smokers. Ninteen (63.3%) of the control group were nonsmokers. **(Table 2)**

Serum level of LH hormone was statistically reduced with increasing duration of tramadol addiction. **(Table 3)**

With increasing the dose of tramadol, all of sperm count, sperm vitality and abnormal sperm forms were significantly affected. **(Table 4)**

Comparing tramadol only addicts and the control group, all of these parameters are significantly affected: decreased sperm linear progressive motility, increased abnormal forms and decreased all measured serum hormones. Comparing other dugs addicts and the control group, all of these parameters are significantly affected: increased spermatogenic cells, decreased sperm vitality, decreased sperm progressive motility, increased sperm abnormal forms, decreased serum levels of prolactine, fish and testosterone. comparing tramadol only addicts and other drug addicts no significant differences were detected. **(Table 5)**.

Table (1): Demographic and clinical characteristics of cases.

	Cases (N=60)	
Age		
Mean±SD	27.05±7.74	
Median	25.00	
Range	18-55	
Duration of addiction (years)		
Mean±SD	4.61±2.95	
Median	4.00	
Range	0.33-12	
Dose (mg)		
Mean±SD	1127.9±878.34	
Median	787.5	
Range	50.00-3375.00	
	No	%
Smoking habits		
Heavy smoker	44	73.3
Moderate smoker	3	5.0
Mild smoker	8	13.3
Non smoker	5	8.3
Other drugs		
Hashish	11	18.3
Hashish & alcohol	2	3.3
Heroin	4	6.7
Heroin & morphine	1	1.7
Shisha & Goza	2	3.3
Apytral	1	1.7
No drugs	39	65

Table (2):-Demographic and clinical characteristics of control group

	Control N=30	
Age		
Mean±SD	32.73±7.76	
Median	32.5	
Range	22-60	
Smoking habits	No	%
Heavy smoker	1	3.3
Moderate smoker	3	10
Mild smoker	7	23.3
Non smoker	19	63.3

Table (3): Correlation between duration of Tramadol intake and some measured parameters:

Parameters	Duration of Tramadol intake	
	R	P value
Sperm count	0.01	0.93
Spermatogenic cells	0.11	0.56
Sperm vitality	-0.35	0.06
Prolactin	-0.05	0.65
FSH	0.02	0.85
LH	0.28	**0.03 S**
Testesterone	0.04	0.73

r=correlation coefficient

Table (4): Correlation between dose of Tramadol and some measured parameters:

Parameters	Dose of Tramadol	
	R	P value
Sperm count	-0.45	**0.01 (S)**
Spermatogenic cells	-0.03	0.87
Sperm vitality	-0.41	**0.02 (S)**
Abnormal sperm forms	0.37	**0.04 (S)**
Prolactin	-0.21	0.10
FSH	0.11	0.36
LH	0.04	0.73
Testesterone	-0.05	0.71

r=correlation coefficient

Table (5):- Comparison between **Controls**, **All addicts**, **Tramadol only addicts** and **Other drugs addicts**.

	Controls	All addicts	Tramadol only addicts	Other drugs addicts	Test of significance	P value
Sperm countx10³ Mean±SD	49566± 23717	46933± 26948	45945± 31176	48416± 20210	U1=0.51 U2=0.54 U3=0.26 U4=0.36	P1=0.60 P2=0.58 P3=0.79 P4=0.72
Spermatogenic Cells Mean±SD	2.8±0.41	3.13±0.93	3.00±1.14	3.33±0.49	t1=1.78 t2=0.87 t3=3.61 t4=0.95	P1=0.07 P2=0.38 P3=0.001 P4=0.35
Sperm vitality % Mean±SD	72.16±8.87	50.66±29.44	55.27±32.4	43.75±23.9	U1=2.68 U2=2.71 U3=3.74 U4=1.27	P1=0.007 P2=0.01 P3=0.000 P4=0.21
After 30 min vitality% Mean±SD	72.17±8.88	50.57±29.45	54.56±32.1	44.58±25.1	U1=2.62 U2=2.84 U3=3.28 U4=1.06	P1=0.009 P2=0.007 P3=0.001 P4=0.31
After 1st hr vitality % Mean±SD	58.5±10.35	46.8±29.36	51.06±31.1	40.42±26.4	U1=0.67 U2=0.28 U3=3.22 U4=0.95	P1=0.50 P2=0.77 P3=0.003 P4=0.34
After 2nd hr vitality % Mean±SD	49.83±8.55	39.83±26.98	43.89±28.2	33.75±24.9	U1=0.71 U2=0.18 U3=3.14 U4=0.78	P1=0.47 P2=0.85 P3=0.003 P4=0.43
After 3rd hr vitality % Mean±SD	35.17±7.59	34.5±25.67	38.06±26.5	29.17±24.3	U1=0.36 U2=1.17 U3=0.83 U4=0.68	P1=0.71 P2=0.24 P3=0.41 P4=0.51
Rapid linear progressive motility % Mean±SD	19.67±4.72	15.33±17.61	20.56±19.9	7.5±9.41	U1=1.42 U2=0.61 U3=3.52 U4=2.02	P1=0.15 P2=0.54 P3=0.000 P4=0.04
moderate linear progressive motility % Mean±SD	28.0±6.05	17.07±16.35	18.22±16.6	15.33±16.3	U1=3.55 U2=2.63 U3=3.29 U4=0.27	P1=0.000 P2=0.008 P3=0.001 P4=0.78
Sluggish linear progressive motility % Mean±SD	28.5±7.56	14.5±9.69	12.61±10.2	17.33±8.41	U1=5.09 U2=4.73 U3=3.51 U4=1.47	P1=0.000 P2=0.000 P3=0.000 P4=0.15

	Controls	All addicts	Tramadol only addicts	Other drugs addicts	Test of significance	P value
Dead sperm % Mean±SD	23.5±6.84	44.27±34.46	42.22±34.9	47.33±34.9	U1=3.23 U2=2.86 U3=3.62 U4=0.08	P1=0.002 P2=0.006 P3=0.001 P4=0.95
Abnormal forms% Mean±SD	16.67±5.14	23.72±7.32	23.47±8.66	24.08±5.21	t1=3.66 t2=3.39 t3=4.21 t4=0.22	P1=0.000 P2=0.001 P3=0.000 P4=0.83
Prolactin Mean±SD	4.94±3.18	13.73±5.83	12.41±4.46	16.17±7.27	U1=6.72 U2=6.23 U3=5.2 U4=2.48	P1=0.000 P2=0.000 P3=0.000 P4=0.01
FSH Mean±SD	11.48±3.96	17.28±4.53	17.02±4.59	17.76±4.47	t1=5.96 t2=5.27 t3=5.28 t4=0.59	P1=0.000 P2=0.000 P3=0.000 P4=0.55
LH Mean±SD	10.26±4.31	15.27±6.08	15.96±5.74	14.00±6.61	U1=3.93 U2=4.23 U3=2.11 U4=1.09	P1=0.000 P2=0.000 P3=0.03 P4=0.27
Testesteron Mean±SD	5.81±2.17	2.17±1.04	1.99±0.98	2.5±0.97	U1=6.93 U2=6.52 U3=5.18 U4=1.59	P1=0.000 P2=0.000 P3=0.000 P4=0.11

U= Mann-Whitney test t=student t test P1=between ***control*** and ***all addicts*** P2= between ***control***and ***tramadol only addicts***
P3= between ***control*** and ***other drugs addicts*** P4=between ***tramadol only addicts*** and ***other drugs addicts***

4. Discussion

The wide use of narcotic drugs among young people's especially tramadol led me to run out this work to illustrate the dramatic effects in the male reproductive organs.

Our study detected significant association between tramadol administration and impaired quality sperm parameters. The results of sperm quality analysis showed a significant decrease in sperm motility and vitality that indicate the possibility of adverse effects of long term administration of tramadol. The observed findings revealed marked deterioration of the hormonal profile also. The observed findings supported the recent work carried out following tramadol-treatment by Ahmed and Kurkar [10] and Abdellatief et al. [11]. The authors revealed that tramadol-treatment led to a decrease of testosterone and total cholesterol and increased level of the the testicular levels of nitric oxide and lipid peroxidation, and decreased the anti-oxidant enzymes activities significantly compared with the control group. These may facilitate the damage of spermatogenic cells via increase of reactive species. Also similar Cannabis is the most commonly abused drug in the world. Its administration led to disruption of the spermatogenic cells from the membranes [12].

Finally, the author concluded that chronic administration of tramadol lead reproduction dysfunction and increased average of infertility.

Another study was done by Heba Atef El Ghawet (13) showed that in tramadol-treatment, the testis showed focal disorganization of seminiferous tubules with marked depletion of the spermatogenic cell populations. Many of the seminiferous tubules lacked sperm, spermatids and secondary spermatocytes. Exfoliation of the damaged spermatocytes and spermatids were detected within the tubular lumina of many seminiferous tubules. The intertubular connective tissue become hyalinized and showed comparative reduction of interstitial cells.

A study done by Mohammed A. Hussein (14) revealed that tramadol significantly reduced serum LH, FSH and testosterone levels. The histopathological examination of testes revealed severe diffused testicular degeneration, the histopathological lesions were aggravated till testicular tissues calcification according to the dosing of tramadol (40, 80, 120, 160 and 200 mg/ kg.b.wt.).

Another study carried by Essam_Eldien Mohamed Mohamed (11) revealed that tramadol induced a decrease in LH, FSH and testosterone serum levels. Histologically, degenerative changes in the seminiferous tubules were observed. They showed

shrinkage, separation of tubular basement membrane, disorganization and vacuolization of spermatogenic layers. Morpho-metric analysis revealed significant decrease in the mean values of the tubular diameter and epithelial height. Ultrastructural abnormalities were detected in all cells of spermatogenic lineage in addition to the appearance of apoptotic cells. Sertoli cell vacuolation, huge lipid droplets and disrupted Sertoli cell junctions were observed. Leydig cells showed euchromatic nuclei and dilated smooth endoplasmic reticulum. In view of these findings, it is concluded that tramadol induces alterations in sex hormonal levels in conjunction with disruption of the normal histological structure of rat testis. This might lead to the risk of male infertility.

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