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Tamoxifen as Empirical Treatment in Males with Primary Infertility and Normal Gonadotropic Hormonal Levels: A Prospective Study

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Abstract

Background One of the most commonly employed medical therapies for idiopathic male infertility are antiestrogens. Tamoxifen as estrogen receptor blockers have been used as empiric treatments for male infertility, acting through blocking estrogen receptor at the hypothalamus and pituitary levels and so preventing the important negative feedback of estrogens to the pituitary and hypothalamus as a result that leading to gonadotropin releasing hormone (GnRH) stimulation and pulsatile release of luteinizing hormone (LH)/follicle-stimulating hormone (FSH).

Objective To assess tamoxifen role in the treatment of men with primary infertility who are normogonadotropic. as it is widely prescribed drug for that purpose as well as to evaluate possible patient's criteria for a better response to tamoxifen.

Methods One hundred twenty-three patients with idiopathic primary infertility and normal FSH, LH, and testosterone serum levels were enrolled in this prospective study. All patients received 20 mg tamoxifen daily as a single dose for at least 3 months, and semen analysis (total sperm concentration, total number of progressive motile sperms and percentage of normal sperm morphology) as well hormones levels were evaluated, with the values being compared with those before treatment.

Results Overall, there was no statistically-significant improvement in semen parameters 3 months after treatment (P>0.05); however, patients with pretreatment lower normal FSH level of (1.7-6.85 mIU/ml) and those with pretreatment sperm concentration of (five to ten million per ml) showed statistically significant improvement in sperm concentration after tamoxifen therapy (p=0.044 and p=0.012 respectively).

Conclusion Tamoxifen is an acceptable treatment for idiopathic male infertility. A better response can be expected in patients with pretreatment lower normal FSH level of (1.7-6.85 miu/ml) and sperm concentration of 5-10 million per ml. It might be used as first line treatment to enhance sperm concentration, giving its availability and lower cost in comparison to other hormonal therapies.

Keywords Male Infertility, tamoxifen, empirical treatment

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List of abbreviations: A.Tamox = After tamoxifen treatment, B.Tamox = Before tamoxifen treatment, FSH = Follicle-stimulating hormone, GnRH = Gonadotropin releasing hormone, LH = Luteinizing hormone, SFA = Seminal fluid analysis, SPSS = Statistical package for social sciences

Introduction

Idiopathic male infertility is an idiopathic oligoasthenoteratozoospermia, in another words, the male has an unexplained impairment in semen parameters. On the other hand, unexplained male infertility is recognized

as infertility of unknown origin with normal sperm parameters [1].

Idiopathic male infertility has an effect on nearly 10−15% of men in their reproductive age [2]. Furthermore, the most advantageous strategies for treating idiopathic male infertility have remained unclear [3], as the pathological mechanisms behind this infertility status is unknown.

Various empirical approaches have been applied to treat idiopathic male infertility, which should be evaluated in the context of evidence-based medicine. In general, empirical treatment used in male idiopathic infertility can be divided into two groups depending on their mechanism of action: hormonal treatment and antioxidant supplementation; hormonal medications represented by gonadotropins, estrogen receptor blockers and aromatase inhibitors [4].

One of the most commonly employed medical therapies for idiopathic male infertility are antiestrogens [5]. Tamoxifen as an estrogen receptor blocker has been used as an empiric treatment for male infertility, acting through blocking estrogen receptor at the hypothalamus and pituitary levels, thus preventing negative feedback of estrogens on the pituitary and hypothalamus, leading to gonadotropin releasing hormone (GnRH) stimulation and pulsatile release of luteinizing hormone (LH)/follicle-stimulating hormone (FSH) [6].

However, up to date, there is no universal model to evaluate or identify the ideal patient for such therapy. In addition, there is no agreement regarding the optimal medical therapy and a considerable uncertainty exists as to the perceived effects on fertility [7].

Methods

Prospective study was done in High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, Baghdad for the period from November 2019 to July 2021.

One hundred twenty-three patients were selected as follows:

- Male patient with history of primary infertility.
- Multiple previous seminal fluid analysis (SFA) showed subnormal parameters regarding sperm concentration, sperm motility and sperm morphology, each alone or as combination.
- They should have normal FSH, LH and testosterone levels.
- No history of any chronic disease.
- No history of chronic medication abuse including exogenous testosterone.

All participants agreed and signed an informed consent after sufficient explanations. Physical examination done to ensure presence of testes, confirming normal size, and no clinically significant varicocele is present.

SFA with serum FSH, LH and testosterone levels were collected prior to the treatment.

Patients then fallowed up for at least 6 months, regular checkup was arranged with time interval of 3 months. All patients received 20 mg tamoxifen daily as a single oral dose. Semen analysis (sperm concentration, total progressive motile of sperms and percentage of normal sperm morphology according to WHO 2010 standards) as well as hormones levels were evaluated, with the values being compared with those before treatment by calculating mean value and P value which was estimated by utilizing paired t-test using statistical package for social sciences (SPSS) version 27 (2019).

Results

In general, there was an improvement in the mean values of seminal fluid parameters (sperm concentration, total progressive motile sperms and percentage of normal sperm morphology), however, improvement was not statistically significant as shown in table (1), but it was near significant in regard to sperm concentration parameter.

Table 1. Mean of seminal fluid parameters before and after treatment

SFA parameters (n=123)	B.Tamox Mean±SD	A.Tamox Mean±SD	P value
Sperm concentration (million/ml)	6.35±2.8	7.36±2.3	0.054
Total motile sperm per ejaculate	4.5±1.6	4.75±2.37	0.080
Normal sperm morphology percentage	15.4±0.06	16.0±0.05	0.963

B.Tamox= before tamoxifen treatment, A.Tamox= after tamoxifen treatment

Since the results showed an improvement in sperm concentration with tamoxifen that approached statistical significance, secondary analysis was performed by sub classification of the studied group according to sperm concentration prior to treatment into 3 subgroups; from 1 sperm to 5 million, from 5 million and one to 10 million and from 10 million and one to 15 million sperm concentration per ml. It has been found that the second group (5 million and one to 10 million sperm concentration per ml) got statistically significant improvement as illustrated in table (2).

Table 2. Response of studied group participants according to their baseline sperm concentration levels

Sperm concentration (million/ml)	B.Tamox Mean±SD	A.Tamox Mean±SD	P value
<5 (n=34)	2.64±0.9	2.63±0.75	0.960
5 to >10 (n=45)	8.4±1.3	10.08±2.8	0.012
10 to15 (n=44)	11.84±1.4	12.08 ±1.4	0.260

B.Tamox= before tamoxifen treatment, A.Tamox= after tamoxifen treatment

When hormonal levels were compared before and after tamoxifen for the 3 subgroups, there was an increase in serum levels of FSH, LH and testosterone following tamoxifen treatment by 19.4%,17.8% and 29.4% respectively, but yet all remained within normal ranges, none of these increments was statistically significant as demonstrated in table (3).

Table 3. Response of studied group participants according to their initial serum hormones levels

Hormone	B.Tamox Mean±SD	A.Tamox Mean±SD	P value
FSH (mIU/ml)	5.90±1.2	7.05±1.1	0.570
LH (mIU/ml)	5.65±0.9	6.73±1.4	0.200
Testosterone (ng/ml)	3.83±1.1	4.95±0.9	0.080

B.Tamox= before tamoxifen treatment, A.Tamox= after tamoxifen treatment

For more a precise evaluation, seminal fluid parameters before and after treatment were gauged against the baseline FSH, LH and testosterone level, which were divided into two categories, lower and upper normal levels.

Regarding serum testosterone and LH there was no significant difference in seminal fluid parameters for those of initial lower normal levels in comparison to patient with initial upper normal levels as shown in table (4) and table (5) respectively. Although patients with upper normal LH levels showed an increase in sperm concentration and total motility that approached statistical significance.

Table 4. Response of studied group participants according to their initial serum testosterone levels

SFA parameters	Testosterone level					
	2.27-6.29 ng/ml (n=69)		P value	6.3-10.3 ng/ml (n=54)		P value
	B.Tamox Mean±SD	A.Tamox Mean±SD		B.Tamox Mean±SD	A.Tamox Mean±SD	
Sperm concentration (million/ml)	7.56±1.9	9.13±1.5	0.150	7.45±2.1	7.9±2.0	0.100
Total motile sperm per ejaculate	3.38±0.8	4.2±0.75	0.100	4.25±0.9	4.51±1.0	0.240
Normal sperm morphology percentage	14.9±2.1	16.2±1.9	0.130	15.0±1.4	15.2±1.75	0.360

B.Tamox= before tamoxifen treatment, A.Tamox= after tamoxifen treatment

Table 5. Response of studied group participants according to their initial serum LH levels

SFA parameters	Serum LH level					
	1.1-4.0 mIU/ml (n=57)		P value	4.1-7.0 mIU/ml (n=66)		P value
	B.Tamox Mean±SD	A.Tamox Mean±SD		B.Tamox Mean±SD	A.Tamox Mean±SD	
Sperm concentration (million/ml)	8.04±2.9	9.37±2.3	0.080	7.05±1.9	8.1±2.1	0.060
Total motile sperm per ejaculate	3.4±0.9	4.0±0.6	0.210	4.0±0.6	4.45±0.9	0.070
Normal sperm morphology percentage	14.1±2.2	14.45±1.9	0.850	15.1±2.0	16.0±2.6	0.360

B.Tamox= before tamoxifen treatment, A.Tamox= after tamoxifen treatment

On the other hand, subgroup of patients with initial lower normal serum FSH levels showed a significant improvement in concern to sperm concentration but not for the other parameters as demonstrated in table (6).

Table 6. Response of studied group participants according to their initial serum FSH levels

SFA parameters	Serum FSH level					
	1.7-6.85 mIU/ml (n=60)		P value	6.85-12.0 mIU/ml (n=63)		P value
	B.Tamox Mean±SD	A.Tamox Mean±SD		B.Tamox Mean±SD	A.Tamox Mean±SD	
Sperm concentration (million/ml)	7.74±1.3	9.66±1.9	0.040	7.38±1.2	7.9±1.3	0.075
Total motile sperm per ejaculate	3.75±0.5	4.0±0.7	0.780	4.25±0.4	4.45±0.3	0.310
Normal sperm morphology percentage	15.3±3.1	17.2±2.8	0.180	14.7±2.9	16.9±1.3	0.210

B.Tamox= before tamoxifen treatment, A.Tamox= after tamoxifen treatment

In addition, the response to treatment was gauged against patients age; younger patients (20-30 years old) having a better response, the difference between the two age groups was not statistically significant as seen in table (7).

Table 7. Response of studied group participants according to their age

SFA parameters	Patients' age					
	20-30 years (n=66)		P value	31-40 years (n=57)		P value
	B.Tamox Mean±SD	A.Tamox Mean±SD		B.Tamox Mean±SD	A.Tamox Mean±SD	
Sperm concentration (million/ml)	7.85±1.2	9.25±0.9	0.167	7.45±1.4	8.0±1.2	0.660
Total motile sperm per ejaculate	3.38±1.1	4.25±1.3	0.090	4.13±1.1	4.58±1.4	0.070
Normal sperm morphology percentage	15.4±2.1	16.6±2.2	0.140	15.1±1.9	16.3±1.8	0.480

B.Tamox= before tamoxifen treatment, A.Tamox= after tamoxifen treatment

Discussion

Tamoxifen by acting as antiestrogens is frequently recommended medical treatment in idiopathic male infertility [(5)]. Kotoulas et al. concluded that tamoxifen is a valuable effect on sperm density was associated with tamoxifen treatment but no considerable effect was found in regard sperm motility and morphology [(8)]. Even more, Moein et al. showed that sperm recovery in testis samples can be enhanced by treating patients diagnosed with nonobstructive azoospermia with anti-oestrogenic drugs like tamoxifen and also can increase the chance of pregnancy by microinjection [(9)]. In contrast, more recent study may not agree with that as concluded by Sadeghi et al. [(10)]. Because of that, controversy re-evaluation of tamoxifen as empirical therapy is common research filed, some researchers suggested even an adverse effect of tamoxifen

on sperm quality and sexual accessory glands as Motrich et al. found [11]. The current study did not become aware of measurable adverse effect of tamoxifen on seminal fluid parameters.

Dabaja and Schlegel observed a significant increase in sperm concentration and percent of sperm motility along with significant elevation in the serum FSH and testosterone levels [12]. Kadioglu TC et al experimented a similar result regarding FSH and testosterone levels [13], in the existing study improvement in sperm concentration was observed as well in some patients and it seems to be related to pretreatment serum FSH level, while it is correct that increment in serum FSH level was noticeable but it was not statistically significant.

Kadioglu et al. noticed that patients presented with initial lower FSH levels had a significant improve concerning sperm counts in comparison to those of initial higher FSH levels [13]. A finding that goes hand by hand with present study but no significant improvement in sperm motility was established as they did. Limitations include that it is non-randomized, non-blinded, short follow-up study that is done in single center

In conclusion, tamoxifen is an acceptable treatment for idiopathic male infertility. A better response can be expected when the patient presented with pretreatment FSH level of (1.7-6.85) mIU/ml as well as in those patients of pretreatment sperm concentration of five to ten million per ml. A better response might be expected in younger patients as well. And Tamoxifen might be used as first line improve sperm concentration, giving its availability and lower cost in comparison to other hormonal replacement therapies.

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Conflict of interest

Author declare there is no conflict of interest.

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