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The role of Tadalafil in treatment of infertility

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ABSTRACT

Objective: It was the aim of this research to assess whether Tadalafil 5 mg once daily can improves the sperm count of unexplained infertile males with erectile deficiency induced by the emotional stress of attempting to father children. **Methods:** Two groups, each made up of 30 unexplained infertile males with psychogenic erectile deficiency related to attempts to father children received Tadalafil 5 mg once daily (Group 1) or a placebo (Group 2) for one month. Unexplained infertile men are intended as normospermic men who could not father children over a one year period and whose female partner is free of factors causing infertility. The endpoints were: differences between the groups in restoring erectile response, modifying sperm count, side effects and modifications of sperm analyses with respect to resolution or not of the erectile deficiency irrespective of the substance (Tadalafil or placebo) used. The means were compared using analysis of variance and the percentages using the chi square test. **Results:** The patients who received Tadalafil had their sperm volume, concentration and motility increased, but not the percentage of typical forms. Patients who received a placebo had no significant improvement. Additional analyses indicated that sperm volume, concentration and motility (but not morphology) significantly increased only in the patients who restored erectile response to sexual stimulation, independently of Tadalafil or placebo administration. No significant side effects were present. **Conclusions:** It is thought that therapies aimed at removing emotional stress linked to the performance anxiety of fathering children might improve sperm count in unexplained infertile couples.

1. Introduction

Emotional stress is defined as the poor/absent/difficult adaptation to a circumstance subjectively perceived as dangerous[1]; it affects a number of physiological functions, and is regarded as being linked to unexplained infertility[2]. Unexplained infertility is a diagnosis of exclusion which is made when a couple is involuntarily infertile but no abnormalities are revealed by standard infertility evaluation[2]; unexplained infertility affects about 14% of infertile couples[3]. Stressful life events may be associated with decreased semen quality in fertile men[4]. Social and family issues of reproduction are very strong and may lead to a stress condition[5]; and sexual behaviour in males may be the most vulnerable aspect of male reproduction to acute and chronic stress[6]. In fact, looking for a natural pregnancy might be linked to psychogenic erectile deficiency of various degrees because of the performance anxiety of fathering children[7].

Lilly ICOS registered the use of Tadalafil 5 mg/once daily in Italy in 2007 to restore the erectile response to any stimulation perceived as sexual. All phoshodiesterase-5 (PDE5) inhibitors were tested regarding their ability to improve or affect sperm count and/sperm functions, and the results were contradictory. Some *in vivo* studies in men treated with Tadalafil on a daily basis demonstrated a significant increase in sperm concentration and motility[8]. An increase in the spermatozoa content of c-AMP induced by PDE5 inhibitors has been indicated as the mechanism[8]. An uncontrolled study sustains that PDE5 inhibitors might improve sperm count by removing the psychogenic factors related to the anxiety of achieving a full erection[9].

This prospective placebo-controlled trial was aimed at assessing whether Tadalafil 5 mg once daily improves

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the sperm count of unexplained infertile men affected by pychogenic erectile deficiency.

We chose to test Tadalafil 5 mg from among the different PDE5 inhibitors because, from a theoretical point of view, its daily administration seemed to be the most suitable of the PDE5 inhibitors (characterized by an "on demand administration") for settling the emotional stress linked to performance anxiety[10].

2. Material and methods

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted in Italy. The eligible participants were all unexplained infertile males with psychogenic erectile deficiency linked to attempts to father children. The trial period extended from 10 June 2008 to 30 March 2012. The exclusion criteria were smoking or alcohol habits (6 cases), and X-ray exposure in the previous six months (2 cases), any previous therapy for infertility (5 varicocelectomies, and 6 dietary complement self-administrations) and varicoceles (3 cases).

Unexplained infertile men are intended as normospermic men (ejaculated volume > 2 mL; sperm concentration > 20 millions/mL, class A+B motile sperm > 50%, typical forms [strict criteria] > 14%)[11] who could not father children over a one year period and whose female partner was free of factors of infertility. Normospermia was assessed with two sperm analyses. Semen samples were collected by masturbation at the laboratory after a 72 h abstinence from ejaculation. The two sperm samples were collected at a distance of 7-10 days from one another[11]. Female infertility factors were determined by independent gynecologists with a medical history collection, objective examination, biphasic body temperature recording, progesterone evaluation in luteal phase, ultrasound of the uterus and ovaries, and a hysterosalpingogram to study tubal patency[12]. The psychogenic nature of erectile deficiency and its link to attempts to father children were ascertained with clinical history collection, semistructured interviews, hormonal profile assessment (testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin) and dynamic duplex (i.e. after a 10 μg alprostadil intracavernosal injection).

The patients were randomly assigned to one of the two parallel groups in a 1:1 ratio using, casual number tables[13], and received either active drugs (Tadalafil 5 mg/day) or a placebo (starch) for 30 days. The study investigators and the patients were unaware of the treatment assignments; the patients were informed they might receive a placebo and informed consent for the treatment was obtained. The blinding procedures have previously been presented[12]. Before and after active drug or placebo administration, the following parameters were assessed: erectile function and sperm concentration, motility and morphology and ejaculated volume. Erectile function was assessed with semistructured interviews and categorized as satisfactory or unsatisfactory; ejaculated volume, sperm concentration motility and morphology were assessed with two WHO 1999 sperm analyses for each patient carried out after a 3 day abstinence 7-15 days apart.

An independent Data Monitoring Committee reviewed the unblinded data; two masked interim analyses for efficacy were carried out. The original endpoints with respect to the safety and efficacy of the drugs studied were efficacy in restoring erectile response to sexual stimulation, modifications of the sperm count and side effects.

During the second ad interim masked analysis, the monitoring board noted that sperm count improved when erectile response was restored both when the active drug and the placebo were used. The monitoring committee therefore decided to adopt co-primary endpoints: modifications of sperm analyses with respect to the resolution or not of erectile deficiency irrespective of the substance (tadalafil or placebo) used.

The means were compared using randomized block analysis of variance and the percentages using the chi square test. The analyses of variance were corrected for the number[2] of replicated analyses carried out on the same individual when sperm volume, concentration, motility and morphology were analyzed. The levels of significance maintained an overall P value of 0.01, corrected for the number of interim analyses[13].

3. Results

Thirty-two patients were enrolled in Group 1 (active drug) and 33 in Group 2 (placebo). Two patients dropped out of Group 1 as the result of an insufficient therapeutic effect (1 case) and side effects (1 case of back pain). Three patients dropped out of Group 2 as the result of an insufficient therapeutic effect (2 cases) and protocol violation (1 case). Thus, 30 patients/group were analyzed; their demographic and clinical data are presented in Table 1. No significant difference emerged between the groups.

Table 1

Demographic and clinical data of the patients studied

Data	Group 1 (n=30)	Group 2 (n=30)	P
Duration of symptoms (months)	8.2±4.3	7.6±5.4	0.345
Age (years)	45.2±6.1	44.4±7.2	0.245
Time of attemt to father children (months)	15.3±2.2	16.0±3.7	0.338

Data were expressed as mean±SD.

The effects of Tadalafil or of placebo administration on sperm count, erectile reponse and side effects are presented in Table 2. Patients receiving Tadalafil had their sperm volume, concentration and motility increased, but not the percentage of morphologically typical forms. The patients receiving a placebo had no significant improvement in their sperm analyses. Obviously, the number of patients

who had their erectile response restored was significantly higher in the patients who received Tadalafil than those who received a placebo. No significant difference emerged in side effects between the active drug and the placebo groups, even though a trend emerged of a higher prevalence of side effects in the Tadalafil group.

Table 3 indicates the modifications of ejaculated volume, sperm concentration, motility and morphology of the patients who subjectively achieved (responders) or did not achieve (non-responders) a satisfactory erectile response to sexual stimulation after Tadalafil or placebo administration. Ejaculated volume, sperm concentration and motility significantly increased in responders independently of whether Tadalafil 5 mg daily or a placebo was used. The sperm morphology was not modified.

4. Discussion

Our data indicated that patients who achieved a full erection had their ejaculated volume, sperm concentration and motility increased, independently of whether Tadalafil 5 mg/day or a placebo was administered. The removal of the emotional stress induced by performance anxiety in achieving a full erection should be regarded as the mechanism which improved semen quality.

The association between emotional stress and the quality of semen has been well studied. Psychological stress is a risk factor for semen quality, and health programs focusing on psychological health have been postulated to be helpful for male reproductive health, sustaining that stress is a modifiable factor[4,14]. However, little is known about the reversal of stress conditions and semen quality improvement. Two papers were found in which stress was successfully treated with Conveyer of Modulating Radiance therapy[15] or with plant therapy (Withania somnifera)[16]. Semen quality improved in both. These papers confirmed our data and indicated that the removal of emotional stress improved the sperm count.

At present, the mechanism which affects sperm count in the course of emotional stres is unknown s; hormonal imbalance modifications are likely to occur. Gonadotropins and testosterone are regarded as linked to semen alterations in the course of stress. Non-obstructive azoospermic men had their follicle-stimulating hormone and luteinizing hormone positively associated with anxiety in contrast to testosterone which was inversely associated with anxiety[17]. Anxiety strongly depresses serum testosterone, but not luteinizing hormone[18]. It has also been sustained that emotional stress increases the activity of seminal superoxide-dismutase which, in turn, affects sperm concentration and motility[19].

Ejaculated volume, sperm motility and concentration significantly increased in our study while sperm morphology did not. Thus, it is unlikely that some kind of physical mechanism improving the emission of the ejaculate and related to a firmer erection (i.e. urethral firmness) might improve sperm count. It is unknown why the sperm morphology was not significantly modified while ejaculated volume, sperm concentration and motility improved; we can only speculate that this occurred because morphology is

Table 2
Effects of Tadalafil or of placebo administration on erectile function and sperm count.

Item	Group 1 (Tadalafil 5 mg/day)		Group 2 (Placebo 5 mg/day)		*P*	
	Before Tadalafil administration (a)	After Tadalafil administration (b)	Before placebo administration (c)	After placebo administration (d)	a *vs.* b	c *vs.* d
Ejaculated volume (mL)	2.5±0.5	3.2±0.6	2.6±0.4	2.8±0.5	0.009	0.101
Sperm concentration (millions/mL)	36.1±14.0	45.4±14.0	37.0±16.2	40.3±18.2	0.008	0.181
% Motility (classes a+b)	60.3±9.2	70.3±16.4	58.3±7.4	60.2±9.2	0.007	0.132
% Typical forms (strict criteria)	16.3±2.1	17.4±3.1	16.6±2.2	16.8±2.2	0.198	0.232
Number of patients who suffered from side effects (%)	6^{A} (20%)		1^{B} (3.3%)		0.072	
Number of patients who had their erectile response restored (%)	25/30 (83.3%)		6/30 (20%)		0.008	

Data were expressed as Means±SD. The side effects are also presented: [A]3 patients had back pain, 2 patients had cutaneous rashes and head ache, 1 patients had head ache; [B]1 patient had epigastric pain.

Table 3
Ejaculated volume, sperm concentration, and sperm motility of patients with psychogenic erectile deficiency who subjectively had (responders) or did not have (non responders) a satisfactory erectile response to sexual stimulation after administration of the placebo or of Tadalafil 5 mg once daily for 30 days (active drug).

Groups	Ejaculated volume (mL)		Sperm concentration (millions/mL)		Sperm motility (class A+B) (%)	
	Responders	Non responders	Responders	Non responders	Responders	Non responders
Group 1	3.8±0.6	2.7±0.5*	47.9±15.0	37.6±16.0*	71.0±15.6	60.3±10.0*
Group 2	3.7±0.4	2.6±0.5	48.9±16.0	36.7±15.4*	70.3±16.0	60.6±9.6*
P (columns)	0.342	0.265	0.228	0.339	0.328	0.342

Group 1: 25 responders and 5 non responders; Group 2: 6 responders and 24 non responders; *$P<0.05$ non-responders *vs.* responders.

relatively independent of concentration and motility[20].

This study has the following limitations. The first is the low number of responders to the placebo and of non responders to Tadalafil. We feel that this bias might be relatively compensated because responders to the placebo and non responders to Tadalafil agreed that the presence or the absence of a suitable erectile response to sexual stimulation was critical regarding whether or not there was an improvement of the sperm count. Furthermore, pregnancies cannot be included in the endpoints because the follow-up was deliberately short. An attempt to use a longer period of study in the course of preliminary tests induced the majority of the candidates to refuse to participate. In any case, pregnancies occurred in two Tadalafil-responder patients.

A number of *in vivo* and *in vitro* studies have been carried out to examine whether PDE5 inhibitors positively or negatively affect sperm parameters and sperm fertilizing capacity, but the results are controversial. Some of these studies have not demonstrated any significant effects of PDE5 inhibitors on the motility, viability and morphology of the spermatozoa collected from men who have been treated with PDE5 inhibitors. On the other hand, several studies have demonstrated a positive effect of PDE5 inhibitors on sperm motility both *in vivo* and *in vitro*; activity of sildenafil on PDE5 isoforms and of Tadalafil on PDE11 isoforms has been reported[8,21]. These data do not contradict our results because these studies were conducted on sexually active patients without erectile deficiency, i.e. different populations were studied.

As a conclusion, it is thought that educational and/or counseling programs and/or therapies aimed at removing emotional stress linked to performance anxiety of fathering children might improve fertility in some unexplained infertile couples.

Conflict of interest statement

We declare that we have no conflict of interest.

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