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The Use of Oral Sildenafil Citrate In Hemodialysis Patients: A Multi-Center Double-Blind Placebo-Controlled Study

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Abstract
Efficacy and safety of oral sildenafil citrate use in hemodialysis patients is not very well documented. We undertook a study to evaluate the efficacy and safety of oral sildenafil in treating erectile dysfunction in hemodialysis patients. A total of 50 male hemodialysis patients (mean age 49.2 years) with ED were recruited for this double-blind, placebo-controlled prospective study. Patients were randomized into two groups of 25 patients and received either a placebo or sildenafil. Patients in sildenafil group were started on a 50-mg dose, and the dose was increased to 100 mg if there was no response after 2 doses. Patients were asked to complete the International Index of Erectile Function (IIEF) and a global life-satisfaction questionnaire before and after each dose.
Improvement was observed in 76% of the sildenafil patients compared with 12% of placebo patients using IIEF and global assessment questionnaire. Sildenafil was associated with improvement in the IIEF score in all domains except those related to sexual desire. Sildenafil use resulted in normal EF scores in 36% of sildenafil patients. No correlation was found between sildenafil failure and patient age, duration of ED and the duration and etiology of renal failure. Sildenafil was well tolerated. Side effects were rare but occurred equally in both groups.
Conclusions: Sildenafil is a safe and satisfactory drug for improving erectile function in patients with ESRD without contraindications for this drug. Pretreatment scores on the IIEF may be useful in predicting the success of the treatment.

Keywords:

sildenafil, kidney failure, hemodialysis, erectile dysfunction.

Ethics and Conflict of Interest
This study was approved by the hospital Scientific and Ethics Committee and informed consent was obtained from all patients. The authors did not receive any type of support from the sildenafil (Pfizer, France).

Introduction
Sexual dysfunction is a frequent disorder in men with end stage renal disease (ESRD) (1). Erectile dysfunction is the most common disorder of sexual dysfunction that impairs

the quality of life of such patients, with a prevalence range of 17–82% among dialysis and transplant patients (2,3). Several methods (vacuum devices, intracavernosal injections, transurethral instillation of PGE1 and penile prostheses) have been recommended for treating these patients. But most of them are rejected by the patients due to lack of satisfaction (1).

Since its introduction in 1998, sildenafil citrate has become the main tool for the treatment of ED. However, the evidence about efficacy of sildenafil in patients with ESRD is limited (4).

Only a few other studies have reported the benefits of using sildenafil in hemodialysis (HD) patients (5-7). To our knowledge, there is only one double-blind, placebo-controlled study looking at efficacy and merit of using sildenafil in HD patients (5). We designed this randomized, double-blind, placebo-controlled to confirm the efficacy and safety of sildenafil in patients with end stage renal disease (ESRD).

Materials and Methods

This was a randomized, double-blind, prospective study where H.D patients were randomized to receive either oral sildenafil citrate or placebo. Patients were then followed for one week. The study was started in March 2005 and ended in May 2008. We included patients aged more than 20 years, who were on HD for a minimum of 6 months, who reported ED for more than 6 months and had a stable relationship with a female partner for more than a year. We excluded patients older than 70 years age and those with penile anatomic abnormalities, history of penile surgery(except circumcision), cirrhosis, diabetes, angina (history of precordial pain), severe anemia (hematocrit lower that 21%), patients on nitrate treatment or with a history of recent cerebrovascular accident or myocardial infarction(within past 6 months). In addition, patients currently being treated for ED by sildenafil were excluded.

The qualified patients were asked to complete the 15 questions of the International Index of Erectile Dysfunction (IIEF), a self-administered questionnaire, which has been validated in several languages (8), including French (9). This questionnaire was also professionally translated to Arabic and revalidated through a local epidemiological study (Prevapt study) published in 2007) (10). Patients with a score of 26 or higher on the erectile function domain were considered as not having ED and were excluded.

A total of 50 hemodialysis patients participated in our study. The target population included patients from four dialysis units in the state of Jendouba (Western Tunisia). All selected patients answered a detailed medical and sexual history and had a complete physical examination and psychological assessment. Clinical efficacy of sildenafil was assessed by the IIEF.

The IIEF is an instrument used for the clinical assessment of ED and treatment outcomes in clinical studies. It evaluates several aspects of sexual performance. The total IIEF score was computed as the sum of the final score of each domain (8). The total score ranges from 5 to 75. Treatment efficacy was evaluated through the scores for the five separate response domains of male sexual function of the IIEF: erectile function (questions 1 to 5 and 15, total score 1 to 30), overall satisfaction (questions 13 and 14, total score 2 to 10), intercourse satisfaction (questions 6 to 8, total score 0 to 15), orgasmic function (questions 9 and 10, total score 0 to 10), and sexual desire (questions 11 and 12, total score 2 to 10) (8). The erectile function domain scores (11) were also used to classify patients according to ED severity levels: absence of ED (score 26 or higher), mild (score 22 to 25), mild to moderate (score 17 to 21), moderate (score 11 to 16), or severe (score 6 to 10).

Both the placebo and sildenafil were placed in identical capsules. Each patient was given 6 capsules of either placebo or sildenafil. Patients were instructed to take one capsule an hour before sexual activity, two to three hours after a meal. The protocol involved increasing the dose to two capsules next day if there was an inadequate response but not exceeding two capsules per day. The use was allowed only on non-dialysis days. The patients were instructed to record their sexual activity as well as any adverse effect before and after each dose and were required to fill out an IIEF questionnaire one week after the first evaluation. The questionnaire also required reporting the number of capsules used by each patient during the treatment period. After using medication an erectile function score of ≥ 26 indicated restored erectile function. Patients with post-treatment improvement of at least 10 points for the total IIEF score were considered as responders. Medical and epidemiologic data of our patients were obtained for each patient from the monthly dialysis records and included age (years), time on dialysis (months) and etiology of ESRD.

Statistical Analyses

Paired t-test and wilcoxon test were used to compare the

parametric and nonparametric data, respectively in placebo and sildenafil groups. Mean and standard deviation (S.D) was calculated for each IIEF question and domain. The p-value <0.05 was considered to indicate significance.

Results

The study patients (n=50) had following characteristics: mean age of 49.2 years (22 - 70), mean duration of ED of 34.2 months (6 - 102) and the mean duration of hemodialysis of 50 months (6 - 180). Renal failure was attributed to nephrolithiasis (n= 31, 62%), hypertension (n= 8, 16%), glomerulonephritis (n= 6, 12%), urinary tuberculosis (n= 3, 6%), and other rare etiologies in 2 patients. The etiology of ED was multifactorial (age, drugs, psychological). A total of 37 patients were on antihypertensives including α-blockers, β-blockers, calcium channel blockers and angiotensin converting enzyme inhibitors.

The baseline characteristics of patients in placebo vs. sildenafil group are shown in Table 1. There were 25 patients in each group. No difference was found between the groups in terms of age, time on dialysis, ED duration, hematocrit and urea levels before and after treatment.

The initial E.D IIEF score did not differ between patients in the placebo and sildenafil group in any domain (p = 0.24). One week post treatment, a significant number of patients in sildenafil group reported an improvement in erectile function (total IIEF score > 10) versus the patients in the placebo group (19 out of 25, [76%]) versus 3 of 25 [12%], p<0.001)(Table 2). In sildenafil group, 5 patients noticed improvement with the use of 50 mg dose whereas 14

Table 1. Baseline parameters in the placebo and sildenafil groups (mean ± SD)

Parameters	Sildenafil (n = 25)	Placebo (n = 25)	P value
Demographic features			
Age	52.9 ±8.2	47.6 ± 10.4	0.51
Alcohol	28%(5)	24%(6)	1
Cigarette smoking, years > 20	28%(7)	56%(14)	0.085
Nephrectomy	8%(2)	12%(3)	1
Mean time on dialysis (mo)	57.36	42.46	0.74
Mean duration of ED	25	19.8	0.78
Haemoglobin (g/L)	8.3 ± 1.4	9.7 ± 2.5	0.86
Urea (mg/dl)	149 ± 31	154 ± 30	0.75

Table 2. Change in ED severity using IIEF scores in placebo vs. sildenafil group

Parameters	Sildenafil (n = 25)		Placebo (n = 25)	
	Initial	Final	Initial	Final
ED severity:				
Absence of ED: score ≥ 26	0	36%(9)	0	0
Mild : score 22 - 25	28%(7)	44%(11)	44%(11)	40%(10)
Mild to moderate: score 17 – 21	12%(3)	4%(1)	4%(1)	12%(3)
Moderate: score 11 – 16	12%(3)	8%(2)	24%(6)	28%(7)
Severe: score 6 - 10	48%(12)	8%(2)	28%(7)	20%(5)
P value	p = 0.001		p = 0.69	

patients had to use 100 mg dose. Patients who benefitted in the sildenafil group also reported an increased frequency of intercourse. 9 (36%) patients in the sildenafil group achieved a score above 26, thus achieving a complete resolution of the ED. 6 patients had a change of the total IIEF score of less than 10 and stopped treatment despite using maximum allowed dose (100 mg).

After treatment, patients receiving sildenafil had a better score in 13 of 15 questions compared with the placebo group. Only the questions related to the frequency of sexual desire (p=0.81), and level of sexual desire (p=0.77) did not differ significantly. In the intra-group longitudinal analysis, the placebo group showed an improved score in only three questions (8: How much have you enjoyed sexual intercourse, 13: How satisfied have you been with your overall sex life? and 14: How satisfied have you been with your sexual relationship with your partner?), regarding intercourse satisfaction and overall satisfaction ($p<0.05$). Treatment with placebo had no significant impact on the scores.

Table 3: Side effects in placebo vs. sildenafil group

Parameters	Sildenafil (n = 25)	Placebo (n = 25)
Patient's number	32%(8)	24%(6)
Headache	20%(5)	20%(5)
Flush	16%(4)	12%(3)
Palpitation	8%(2)	0%
Paresis	8%(2)	0%
Dyspepsia	0%	8%(2)
Visual disturbances	4%(1)	0%

The initial mean score for the erectile function domain was higher in patients who responded than in those who did not (23.6 and 17.9 respectively) (p=0.03). 15 out of the 25 patients in group Sildenafil reported a complete sexual intercourse (one or more) during the study period. Patient's age, etiology of ED, the duration and severity of ED and the duration and etiology of renal failure did not predict the response to sildenafil. (Table 1)

Side effects related to study drugs were reported in both groups with no significant difference (p= 0.38) (Table 3). Headaches and flushing were the most frequently reported side effects. Dyspepsia was reported by two patients in the placebo group only. One patient in the sildenafil group complained of blurred vision. Only one patient in the sildenafil group discontinued the drug because of intense headache.

Discussion

Erectile dysfunction (ED) is defined as the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity (12). It is a common condition in middle-aged and older men and frequently occurs in association with various illnesses, such as cardiovascular disease, hepatic failure and renal failure (13). The incidence of ED among patients with renal failure is significantly higher than that in the general population (1,2,14). Rodger et al found that 79% of patients on chronic dialysis complained of sexual dysfunction and 61% reported ED (2). Others have reported the prevalence of ED in these patients in between 71 and 82% (3,15).

The cause of ED in renal failure is primarily organic related to multiple factors: Hormonal disturbances, zinc deficiency, medications, peripheral neuropathy, biochemical imbalances from dialysis, autonomic insufficiency and peripheral vascular pathologies have been all suggested to be involved in pathogenesis of ED (1).

The psychogenic component of ED seems to arise from chronic illness and lifestyle limitations. Patients with ESRD have chronic fatigue, anxiety and a decline in self-esteem, which not surprisingly result in a decrease in sexual interest. In our study, we excluded diabetic patients to minimize the risk of bias (a major independent cause of ED). These patients usually have high co-morbidities and complications and all these factors could have significantly altered the quality of our study (heterogeneous group of patients). The main cause of renal failure in this study was urinary stones, which is also the most common cause of ESRD in our population. Treatment of ED in ESRD patients in our clinical setting typically involves optimization of dialysis

dose (1), anemia correction with recombinant erythropoietin (16), discontinuing possible culprit medications, using oral or injection form of testosterone, applying external vacuum device (17), intracavernosal injection of vasoactive agents, transurethral delivery of alprostadil (18), implantation of penile prosthesis (19) and venous or arterial surgery (20).

More recently, sildenafil, a selective inhibitor of phosphodiesterase type-5(an isozyme that inactivates cyclic guanosine monophosphate [cGMP]), has been shown to be an effective, oral, first-line, well-tolerated treatment for non-uremic men with ED (21). Its use results in increased nitric oxide synthesis which causes smooth muscle relaxation and increased blood flow in the corpus cavernosum, improving erection. Although sildenafil has been used for over 10 years, there are only few studies specifically investigating its use in HD patients. Data on the use of sildenafil in patients on dialysis are limited. To our knowledge, only one randomized, double-blind, placebo-controlled study involving dialysis population has been reported (5).

Rosas et al. (22) conducted a 4 week open-label study in which 15 dialysis patients were treated with sildenafil. Using the global efficacy question of the IIEF, those authors reported an improved erection with sildenafil in 66.7% of the patients. Türk et al (15) treated 20 HD patients with ED, and the response rate was 60%. Chen et al. (4) treated 34 HD patients in a 6-mo open-label study and treatment was effective in 80% of the patients, a result that is comparable with our own experience.

Sildenafil pharmacokinetics does not appear to be influenced by mild to moderate renal impairment, although clearance is significantly reduced with severe renal impairment. In our study, a starting dose of 50 mg was administered to all of our patients with ESRD but a higher dose of 100 mg was allowed since all study patients were on regular dialysis, and sildenafil is cleared during dialysis (23).

Mohamed et al (24) have recommended that sildenafil be used on non dialysis days to prevent intradialytic hypotension. Fatigue is also a common symptom in patients after HD (25). Fluid and electrolyte imbalance caused by the HD, medications and depression are reported reasons. This was our reason of allowing use of sildenafil in this study only on non dialysis as well.

The response rate to sildenafil was 76% in this study which was better than reported in few previous studies (15, 22). Taking sildenafil on non-dialysis days could have resulted in improved efficacy and this should be assessed in a further study.

Aside from our study, only one other double-blinded trial (5) has reported an improvement in sexual function with sildenafil in dialysis patients. The authors in that study reported an efficacy of 85%, the results similar to our findings as well, despite a reported greater degree of ED in the Seibel study). Juergensen et al (26) reported that only 2 out of 6 (33%) peritoneal dialysis reported a satisfactory response with sildenafil. However, the small number of patients completing that study makes it difficult to compare results with other studies.

The response rate to sildenafil in our study however concurs with those reported in most other studies (21). Our results confirm that sildenafil is an effective and safe treatment for selected ESRD patients with ED. Treatment was associated with significant increases in mean scores for the IIEF domains and global assessment question that assessed the ability to achieve and maintain erections for sexual intercourse, although sexual desire was not improved. These results are in aggrement with previously reported studies. Sildenafil improves erectile response to sexual stimulation, but it does not have an effect in the absence of such stimulation (21). Moreover, sildenafil improves the quality of life of patients with ED and various comorbid diseases, including ESRD (4, 9,15,22,26).

As reported by YeniçerioGlu et al (27), it seems that pretreatment scores on the IIEF may be useful in predicting the success of treatment. The higher the pretreatment score, the higher is the chance of treatment efficacy. This is an important consideration for starting sildenafil in patient with ED much earlier.

Most of the reported adverse effects of sildenafil are considered mild and rarely result in discontinuation of treatment (15,28). The severity and frequency of the adverse effects of sildenafil in patients with ESRD are similar to those reported in the general population (3,21, 27). Headache and flushing are the most common adverse effects in non-uremic patients (21). In general, most studies suggest good tolerability to sildenafil in HD patients.

Conclusions

Sildenafil is an effective and safe treatment for ED in

selected HD patients. We recommend it to be taken on non-hemodialysis days. Pretreatment scores on the IIEF may be useful in predicting the success of the treatment. Further large studies would be helpful to confirm our results.

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