# Comparing the Efficacy of Tadalafil in Three Groups of Hemodialysis Patients, First Kidney Transplant Recipients, and Second Kidney Transplant Recipients

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## ABSTRACT

Background: The efficacy of phosphodiesterase-5 inhibitors (PDE5Is) on the improvement of erectile dysfunction (ED) in second kidney transplant (KT) recipients has not been well investigated previously.

Objective: We aimed to compare the efficacy of tadalafil in three groups: hemodialysis (HD) patients, first KT recipients (KT1), and second KT recipients (KT2) with bilaterally ligated internal iliac arteries.

Methods: Age-matched men with erectile dysfunction were included in the study. Patients were divided into three groups: HD, KT1, and KT2. The International Index of Erectile Function 15 (IIEF-15) was used to assess baseline erectile function. Tadalafil was administered in a dose-escalation method for three months. Patients were reevaluated by the questionnaire at three months. The mean score evolution was compared between the study groups by one-way ANOVA.

Results: The final analysis included 106 patients in three groups. There was no significant difference between the study groups regarding age, body mass index (BMI), blood pressure, and frequency of smoking, opium, or alcohol use. Tadalafil was safe and effective in all three groups. The mean IIEF score evolution in HD, KT1, and KT2 groups was 16.4 (58.7% increase from baseline), 19.3 (45.0% increase), and 20.4 (52.7% increase), respectively (P= 0.66).

Conclusion: Tadalafil is effective and safe in managing ED after the second kidney transplantation, where the internal iliac arteries are cut bilaterally. The response rate is similar to first kidney transplant recipients and hemodialysis patients.

**KEYWORDS:** PDE5 inhibitors; Erectile dysfunction; Kidney transplantation; Dialysis

## INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to attain or maintain penile erection for satisfactory sexual intercourse [1]. ED is one of the most bothering consequences of end-stage renal disease (ESRD) and is directly related to hemodialysis (HD) duration [2, 3]. The prevalence of ED in patients undergoing hemodialysis is reported to be as high as 70-80% [4-6]. Kidney transplantation (KT) is the lifesaving treatment of ESRD that can also improve the endocrine disturbances of the patients [7-9]. However, the efficacy of kidney transplantation on the improvement of ED depends on multiple parameters and is still unclear. Some studies report that 30-50% of patients still suffer from ED after kidney transplantation [10-12]. Arterial damage is considered to be one of the leading causes of the high prevalence of ED after kidney transplantation. This reason is more prominent when the internal iliac ar-

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tery is used for end-to-end anastomosis to the transplanted renal artery, especially when internal iliac arteries are cut bilaterally during the second KT [13, 14].

Phosphodiesterase-5 enzyme inhibitors (PDE5Is), including sildenafil citrate and tadalafil, are effective and safe in treating ED patients with chronic kidney disease or kidney transplant recipients [15, 16]. PDE5Is require sexual arousal and the production of nitric oxide to be effective [17]. It is unclear whether these drugs would have the same expected effect if the internal iliac artery were cut for kidney transplantation (particularly bilaterally). To the best of our knowledge, no study has examined the efficacy of PDE5Is in patients with second kidney transplantation where the internal iliac arteries are ligated bilaterally. On the other hand, it is unknown whether the efficacy of tadalafil in HD patients and first or second KT recipients are different. Therefore, the current study aimed to compare the efficacy of PDE5Is in ESRD patients on HD, first KT, and second KT recipients.

## MATERIALS AND METHODS

### Study Population

Men undergoing HD or with a history of KT once or twice who had erectile dysfunction were included in the study after obtaining written consent. Erectile dysfunction was defined as a score of less than 25 in the "erectile function" domain of the International Index of Erectile Function-15 (IIEF-15). Patients were 18 years or older and in a stable relationship, as they reported. All patients in the transplanted groups underwent end-to-end anastomosis to the internal iliac artery/arteries. Patients were excluded if they had cognitive or communication impairment; had no tendency to recover from erectile dysfunction; had genital anatomic deformities that could significantly impair erection; were less than six months from last kidney transplantation; have a history of kidney transplantation and are currently undergoing hemodialysis; receive medications that may lead to erectile dysfunction (such as beta-blockers, tricyclic antidepressants); taking nitrite derivatives or nitric oxide-releasing agents in any form; not willing to withdraw any other ED devices or treatments during the study period; and patients with severe hypertension, congestive heart failure, coronary artery diseases and any contraindication for taking PDE5Is.

### Study Design

This study was a non-randomized three-arm, dose-escalation, single-center, phase IV clinical trial conducted at a tertiary medical Institute. The study population consisted of three groups: the first group included patients with ESRD undergoing HD; the second group consisted of patients with a history of renal transplantation once (KT1), and the third group included patients with a history of renal transplantation twice (KT2). Tadalafil was administered as follows, and patients were evaluated for safety and efficacy at 2, 6, and 12 weeks after treatment. Clinical evaluations at baseline were blood tests including a lipid profile, fasting blood sugar, creatinine level, thyroid-stimulating hormone, and free testosterone levels.

### Drug Dosing

Tadalafil is available as 2.5, 5, 10, and 20 mg film-coated tablets for oral use. The long half-life allows for low-dose daily administration of the drug. At the first visit, all transplanted patients (group II and III) were treated with tadalafil 2.5 mg daily, whereas hemodialysis patients (group I) received tadalafil at a dose of 2.5 mg every 72 hours. On the second visit, patients with well-tolerated doses of 2.5 mg but not having improved erectile function could increase their doses to the maximum dose of 5 mg. Failure to improve was defined as at least two unsuccessful attempts at sexual activity following sexual arousal. Patients who responded well to the initial drug dose were not allowed to receive a higher dose. If an appropriate response to the higher dose was observed, the patients could not take higher doses. In patients receiving the higher dose, the dose of the drug was reduced only in the case of intolerable side effects. If the complication continued using the lower dose, the drug was discontinued, and the patient was excluded.

### Efficacy Parameters

Erectile function and quality of life reported by the patient were measured by the International Index of Erectile Function, translated and validated by Pakpour *et al.* [18]. The questionnaire consists of 15 questions in 5 domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. This questionnaire is designed to assess sexual function in patients who have erectile dysfunction. The primary outcome of this study was the overall IIEF score, which was completed at baseline and again three months after drug administration. Secondary outcomes included information obtained from the IIEF questionnaire on other aspects of sexual function. Clinical efficacy was defined as a 25% improvement in the overall IIEF score.

### Safety Parameters

Patients underwent a thorough physical examination before entering the study and at the end of treatment. Blood pressure and heart rate were measured at each visit. At each visit, the evaluator obtained information about comorbidities or any interfering therapies. All observed or reported adverse events were recorded regardless of the causal relationship with the drug. Serious adverse events are defined as any adverse drug events that occur at any dose that leads to death are life-threatening, lead to a hospital stay or prolonged hospital stay, or cause permanent or significant disability.

### Ethical Considerations

After obtaining the required permissions from the research ethics committee, Isfahan University of Medical Sciences, the current clinical trial was conducted in the urology department between January 2017 to February 2020.

### Statistical Analysis

The population per-protocol included all patients who received regular treatment according to the study protocol and completed the IIEF questionnaire at the beginning and the end of the study. Data were analyzed using IBM SPSS v.23 statistical software. The significance level was fixed at 2.5% for the main efficacy parameter. For secondary outcomes, the significance level was fixed at 5%. A paired t-test was used to compare the results of the IIEF at baseline and post-treatment in each group, and a one-way ANOVA test was used to compare the IIEF score evolution between the three study groups.

## RESULTS

Out of 135 patients assessed for eligibility, 29 patients (21.4%) discontinued the study prematurely: 21 patients did not meet the inclusion criteria, two patients were excluded due to drug side effects, four patients did not return for follow-up, and two patients did not fill out the questionnaire. The study population consisted of 106 male patients with a mean age of 57.5±11.8 years and a mean body mass index (BMI) of 26.1±4.6 kg/m2. On average, systolic blood pressure was 124.3±13.6 mmHg and diastolic blood pressure was 77.7±7.9 mmHg.

The number of patients in the HD, KT1, and KT2 groups was 31, 48, and 27, respectively. The basic characteristics of the patients are given in Table 1. One-way ANOVA test showed no statistically significant difference between the three study groups regarding age, BMI, and systolic and diastolic blood pressures. There was no significant difference between the study groups regarding the frequency of smoking, opium, and alcohol consumption.

The average duration of kidney transplantation in the KT1 group was 50.6±52.8 months and in the KT2 group was 76.6±78.6 months. Initial nephropathy was due to diabetes mellitus or hypertension in 54 patients (50.9%). The mean length of dialysis in the HD group was 83.7±83.5 months, in KT1 was 27.5±20.2 months, and in KT2 was 21.7±18.8 months. At the end of the study, 26 patients (24.5%) took a dose of 2.5 mg/day, and 80 patients (75.5%) took a dose of 5 mg/day.

Table 2 shows the mean scores of different domains of the IIEF questionnaire before and after the treatment and score evolution in the three study groups. One-way ANOVA

**Table 1:** Characteristics of the study population.

| Variables | HD (n= 31) | KT1 (n= 48) | KT2 (n= 27) | P-value |
|---|---|---|---|---|
| Age (years) | 58.2±13.1 | 57.6±11.7 | 54.7±10.5 | 0.324[a] |
| BMI (kg/m$^2$) | 26.4±6.1 | 26.1±4.1 | 26.0±3.0 | 0.950[a] |
| Systolic blood pressure (mmHg) | 12.2±2.0 | 12.3±1.1 | 13.0±1.1 | 0.208[a] |
| Diastolic blood pressure (mmHg) | 7.7±0.9 | 7.7±0.7 | 7.8±0.7 | 0.910[a] |
| Smoking: yes/no | 8/23 | 4/44 | 5/22 | 0.091[b] |
| Opium: yes/no | 5/26 | 2/46 | 4/23 | 0.332[b] |
| Alcohol: yes/no | 4/27 | 1/47 | 2/25 | 0.072[b] |
| Married/single | 30/1 | 47/1 | 25/2 | 0.714[b] |
| Testis exam: Normal/unilateral atrophy/unknown | 25/2/4 | 41/4/3 | 19/4/4 | 0.473[b] |
| Fasting blood sugar (mg/dL) | 94.7±12.3 | 129±94.5 | 103.8±14.2 | 0.147[a] |
| Hemoglobin A1c (%) | 6.1±1.9 | 6.3±1.6 | 6.8±2.7 | 0.768[a] |
| Triglyceride (mg/dL) | 133.1±52.1 | 193.8±109.5 | 164.6±84.5 | 0.050[a] |
| Total cholesterol (mg/dL) | 126.6±37.3 | 203.8±163.7 | 170.2±44.0 | 0.074[a] |
| TSH (mIU/L) | 2.3±1.7 | 1.6±1.6 | 1.7±1.4 | 0.292[a] |
| Total testosterone (ng/mL) | 3.3±1.8 | 4.7±2.4 | 4.6±2.3 | 0.082[a] |
| Free testosterone (ng/mL) | 6.4±4.2 | 8.7±6.2 | 7.7±4.2 | 0.281[a] |

Data present as Mean±SD. Abbreviations: BMI: body mass index, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TSH: thyroid-stimulating hormone.

a. One-way ANOVA test, b. chi-square test

showed that at baseline, there was a significant difference between the mean scores of the three study groups in the overall score and all the domains except for sexual desire. Tukey's posthoc test showed that before starting the treatment, the overall IIEF score in KT1 was significantly different from the HD group (P= 0.007), but the overall IIEF score in the KT2 group was not significantly different from HD and KT1 groups (P= 0.777 and P= 0.259, respectively).

The mean IIEF score evolution was 48.8% in the study population. The increase in different domains of the questionnaire and the overall score after receiving tadalafil was clinically and statistically significant, except for the sexual desire, in which the difference was not clinically but statistically significant. The rate of score evolution following the use of tadalafil in all domains of the questionnaire was calculated and compared between the three study groups. The rate of change in all questionnaire domains and the overall score after treatment with tadalafil was not different between the three groups, indicating similar response rates.

## DISCUSSION

The most striking result from the data is that tadalafil has favorable and similar efficacy in improving ED in patients on HD or KT recipients. Although patients with second KT had lower IIEF scores before treatment, the response rate to the drug was comparable with the other groups. To the best of our knowledge, this is the first study to evaluate the efficacy of PDE5Is in second KT recipients.

There is a growing body of literature that reports the safety and efficacy of PDE5Is in patients with ESRD, in whom the administration of these drugs was cautioned previously [19, 20]. Similarly, we found that patients on HD had a mean IIEF score evolution of 58.7% and we did not note a significant adverse effect.

**Table 2:** IIEF domains at baseline and after treatment in the study groups in addition to P-values representing inter-group and intra-group analysis.

| Variables | HD (n= 31) | KT1 (n= 48) | KT2 (n= 27) | Total | P-value[a] |
|---|---|---|---|---|---|
| Erectile function score | | | | | |
| Before treatment | 10.1±9.0 | 15.8±8.0 | 14.1±8.6 | 14.1±8.6 | 0.040 |
| After treatment | 17.9±8.7 | 26.4±5.4 | 24.2±8.9 | 23.9±7.7 | <0.001 |
| Evolution | 7.7±8.2 | 10.5±6.4 | 10.0±7.5 | 9.7±7.1 | 0.328 |
| P-value[b] | <0.001 | <0.001 | 0.001 | <0.001 | |
| Orgasmic function score | | | | | |
| Before treatment | 4.0±3.2 | 6.7±2.8 | 5.6±3.3 | 5.8±3.2 | 0.004 |
| After treatment | 6.0±2.6 | 8.4±1.9 | 7.6±2.7 | 7.7±2.4 | <0.001 |
| Evolution | 2.0±2.8 | 1.6±2.4 | 2.0±2.0 | 1.8±2.4 | 0.836 |
| P-value[b] | 0.004 | <0.001 | 0.009 | <0.001 | |
| Sexual desire score | | | | | |
| Before treatment | 5.6±2.6 | 6.4±2.2 | 6.4±2.9 | 6.2±2.4 | 0.487 |
| After treatment | 6.9±2.3 | 8.1±1.4 | 7.9±2.2 | 7.7±1.8 | 0.035 |
| Evolution | 1.2±1.2 | 1.7±2.1 | 1.4±2.3 | 1.5±1.9 | 0.632 |
| P-value[b] | <0.001 | <0.001 | 0.046 | <0.001 | |
| Intercourse satisfaction score | | | | | |
| Before treatment | 3.5±4.3 | 7.5±4.5 | 6.9±5.3 | 6.4±4.8 | 0.005 |
| After treatment | 6.5±3.6 | 10.9±3.0 | 11.6±4.1 | 9.9±3.8 | <0.001 |
| Evolution | 3.0±3.5 | 3.3±3.3 | 4.7±4.0 | 3.4±3.4 | 0.419 |
| P-value[b] | 0.001 | <0.001 | 0.003 | <0.001 | |
| Overall satisfaction score | | | | | |
| Before treatment | 4.6±2.2 | 6.2±2.4 | 5.5±3.1 | 5.7±2.5 | 0.050 |
| After treatment | 6.9±2.3 | 8.2±1.7 | 7.7±2.5 | 7.8±2.0 | 0.058 |
| Evolution | 2.3±1.6 | 2.0±1.9 | 2.1±2.6 | 2.1±1.9 | 0.834 |
| P-value[b] | <0.001 | <0.001 | 0.019 | <0.001 | |
| Overall IIEF score | | | | | |
| Before treatment | 27.9±19.2 | 42.8±17.3 | 38.7±20.3 | 38.3±19.1 | 0.010 |
| After treatment | 44.3±17.6 | 62.2±11.3 | 59.1±19.7 | 57.1±16.2 | <0.001 |
| Evolution | 16.4±15.2 | 19.3±13.3 | 20.4±14.6 | 18.7±13.9 | 0.662 |
| P-value[b] | <0.001 | <0.001 | 0.001 | <0.001 | |

Data present as Mean±SD. Abbreviations: IIEF: International Index of Erectile Function.

a. One-Way ANOVA test, b. Paired t-test

The efficacy of PDE5Is has also been shown in kidney transplant recipients by some authors. These studies were focused on patients who have had a KT once. Barrou *et al.* [21] studied 46 first KT recipients and 7 second KT recipients and showed the efficacy and safety of sildenafil for the treatment of erectile function in these patients. The mean IIEF score was increased by 16.4, showing a score evolution of 51.5%. In the study by Sharma *et al.* [22], sildenafil citrate effectively improved all domains of IIEF except for sexual desire. The mean IIEF score was increased by 19.4, showing a score evolution of 56.0%. In the current study, patients in the first KT group improved by 19.4 in IIEF score after tadalafil consumption, comparable with previous studies results.

We found that in patients with second KT recipients in whom internal iliac arteries were cut bilaterally, tadalafil is as effective as patients with first KT recipients or HD patients. The mean IIEF score was increased by 18.7, showing a score evolution of 48.8%. There was no significant difference between the study groups regarding the mean IIEF score evolution. To the best of our knowledge, this is the first study to assess the efficacy of PDE5Is in second KT recipients.

It is assumed that internal iliac arteries are responsible for the blood supply of genital organs, including the cavernosal artery, and hence when this artery is ligated in kidney transplantation, ED would be inevitable. But this theory has been rejected in several investigations. There are contradictory data about the impact of kidney transplantation on erectile function. Cummings *et al.* are skeptical about any positive effect, and Fanbin et al. have reported the destructive impact of kidney transplantation on erectile function [23, 24]. Several reasons may be considered for the absence of positive response in erectile function after kidney transplantation, including preexisted risk factors such as DM, HTN, and smoking, side effects of medications, and violating the blood supply of genital organs during surgery. On the other hand, some studies have reported improved erectile function after kidney transplantation [25-28]. In our study, the data gathered before treatment showed that first KT recipients had better IIEF scores than HD patients, but second KT recipients had worse IIEF scores than first KT recipients.

Atherosclerosis is one of the main consequences of ESRD and KT that gradually increases and leads to hypoxemia in these patients. It can be presumed that patients with second KT have had this condition for a more extended period. On the other hand, organ transplantation is associated with inflammation and immune system responses. The role of monocytes and growth factors, such as the granulocyte colony-stimulating factor (G-CSF), can increase endothelial shear stress and stimulate the emergence of collateral arteries [29, 30].

It seems that the collateral circulation for genital organs in ESRD and KT patients is the reason for a favorable response to PDE5Is. A more extended period of ESRD and, consequently, atherosclerosis and immune system reaction to KT in second kidney transplantation patients have expanded the collateral circulation [31]. Therefore, we can conclude that the destructive effect of penile devascularization due to bilateral ligation of the internal iliac on drug effectiveness is reversed by the development of arterial collaterals.

Several caveats need to be noted regarding the present study. First, there was no placebo-controlled group to compare the efficacy of the drug with patients with well-functioning native kidneys. Second, randomization between groups was not feasible. To neutralize the effect of age on drug efficacy on erectile quality, we matched samples on age. However, comprehensive group matching was not possible.

In conclusion, although ED is a common problem in ESRD and, in many cases, persists after kidney transplantation, it can be treated effectively by tadalafil even after the second kidney transplantation, where the internal iliac arteries are cut bilaterally.

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**CONFLICTS OF INTEREST:** None declared.

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