Sildenafil and vardenafil in impotent ESRD patients


Effects of sildenafil and vardenafil on erectile dysfunction and health-related quality of life in haemodialysis patients: a prospective randomized crossover study

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Abstract

Background. Erectile dysfunction (ED) is prevalent in end-stage renal disease (ESRD) and has been associated with impaired health-related quality of life (HRQoL). HRQoL, in turn, is related to morbidity and mortality in ESRD patients. Previous studies have shown improved HRQoL with ED treatment using sildenafil and vardenafil. However, no study has examined the effects of sildenafil or vardenafil on HRQoL in impotent ESRD patients. Furthermore, vardenafil has never been tested and its safety profile has not been determined in ESRD patients. The aim of this randomized crossover study was to compare the effects of sildenafil and vardenafil on measures of HRQoL and on ED scores as well as to determine the safety profile of vardenafil in ESRD patients.

Methods. In 32 haemodialysis patients with impotence, ED and HRQoL were evaluated by the International Index of Erectile Function (IIEF-5) and the 36-item Short-Form Health (SF-36) surveys, respectively. Patients were randomized into sildenafil and vardenafil groups. After a 4-week treatment and 2-week washout periods, crossover was performed and an additional 4-week treatment was administered. IIEF-5 and SF-36 surveys were given before and after each treatment period. Adverse effects were evaluated by interview. Friedman tests and Bonferroni-adjusted Wilcoxon signed-rank tests were used to compare groups and for post hoc analysis, respectively.

Results. IIEF-5 and SF-36 scores were significantly improved by both sildenafil and vardenafil compared to pre-treatment values. There were no differences between sildenafil and vardenafil with respect to the studied parameters. Adverse effect profiles were also similar. No patient dropped out because of side effects.

Conclusions. Sildenafil and vardenafil caused similar improvements in ED and HRQoL in haemodialysis patients. Vardenafil was well tolerated in our patient population.

Keywords: erectile dysfunction; haemodialysis; health-related quality of life; sildenafil; vardenafil

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Introduction

Erectile dysfunction (ED) is frequently seen in patients undergoing maintenance haemodialysis; the prevalence may be as high as 71–82% [1]. The cause of ED in end-stage renal disease (ESRD) is primarily organic in nature [2]. In addition to other factors, such as anaemia, age and comorbidities, ED is closely related to quality of life in dialysis patients [3]. Many studies have shown that treatment of depression, ED or both factors can improve health-related quality of life (HRQoL) in patients [4]. Sildenafil, a selective inhibitor of phosphodiesterase type-5 (PDE5), which is the predominant isozyme that inactivates cyclic guanosine monophospate in the corpus cavernosum, has been shown to be an effective and well-tolerated treatment for non-uremic men with ED [5]. Since then, a number of studies have also shown the efficacy and safety of sildenafil in the haemodialysis population [1,6]. Nevertheless, some patients (between 15 and 25% in different series), especially diabetics, do not respond to sildenafil treatment even with dose escalation [6,7]. Vardenafil is an alternate PDE5 inhibitor that is more potent and more selective than sildenafil. The efficacy of this drug also has been established in a number of non-uremic patient populations [8]. Treatment of ED with sildenafil or vardenafil has been shown to improve HRQoL in non-uremic patient populations [9,10].

However, the efficacy and safety of vardenafil have not yet been evaluated in the ESRD population. Furthermore, it is not known whether sildenafil or vardenafil shows efficacy in ED treatment to therefore improve HRQoL in haemodialysis patients. Therefore, we compared the effects of vardenafil and sildenafil on ED and HRQoL, and evaluated the safety profile of vardenafil in maintenance haemodialysis patients in a randomized, crossover study.

Methods

This was an open-label, prospective, randomized crossover study. Forty male patients between 20 and 70 years of age who were undergoing maintenance haemodialysis and were in a stable heterosexual relationship for the previous 6 months with a clinical diagnosis of ED ≥6 months were considered for inclusion in the study. Exclusion criteria were as follows: current treatment of ED regardless of drug or method, alcohol or drug abuse, inability to follow study instructions, major haematologic or hepatic abnormalities, myocardial infarction in the preceding 6 months and concomitant treatment with nitrate or derivatives, uncontrolled hypertension or symptomatic hypotension, penile anatomical deformity, bleeding diathesis and active peptic ulcer disease, and having been scheduled for renal transplantation or alternate surgical procedure. Eight patients were excluded from the study. Reasons for exclusion were scheduling for renal transplantation in one patient, penile prosthesis in one, parathyroidectomy in one and refusal to participate in the study in five patients. As a result, 32 patients were included in the study.

ED was defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse. The diagnosis was confirmed with a score ≥21 in the International Index of Erectile Function (IIEF-5). The study protocol complied with the ethical principles of the Helsinki Declaration and was approved by our institutional review board. All patients were enrolled after signing an informed consent form.

Figure 1 depicts a schematic representation of the study design that consisted of two phases. During a 2-week run-in phase, patients were instructed to complete study forms, and blood samples were collected for determination of biochemistry and complete blood counts. Dialysis adequacy (Kt/V) was determined from patient charts. Thirty-two patients were randomized into either sildenafil or vardenafil groups by opening pre-numbered sealed opaque envelopes containing a computer-generated randomization sequence. The patients in each group were instructed to complete the IIEF-5 and SF-36 surveys at baseline. Then, sildenafil 50 mg was administered to one group and vardenafil 10 mg to the other. The study drugs were administered 45 min prior to sexual intercourse once per week. Phase-1 lasted 4 weeks after which patients in each group were asked to complete IIEF-5 and SF-36. Patients were evaluated by complete physical examination and a detailed systems review at each weekly visit to detect any side effects related to the study drugs. After a 2-week washout period, the same forms were completed by each group. We then performed crossover and administered each group the other drug at the same dosage and scheduling as in the first phase of the study. After a second 4-week phase, the same forms were completed by each group for a final evaluation.

Sildenafil and vardenafil were compared for effects on ED and health-related HRQoL via the IIEF-5 and the 36-item Short-Form Health (SF-36) surveys, respectively. The composition and interpretation of each survey are described below.

IIEF-5 to evaluate ED

The IIEF-5 is a widely used, multidimensional self-report instrument for the evaluation of male sexual function [11]. To improve clinical decision making, patient care and practicality, an abridged five-item version of the IIEF (which is known as the IIEF-5) was developed and validated as a brief, easily administered patient-reported diagnostic tool [11]. Diagnostic evaluations of the IIEF-5 have shown it to have high sensitivity and specificity [11]. Responses to each of the five items on the IIEF-5, which are based on a rating scale from 0 to 5 or from 1 to 5 (depending on the item), are summed to arrive at a total score that can range from 1 to 25, with higher scores indicating better sexual health. Patients were instructed to choose the option that best describes their situation. Patients with scores of ≥21 were deemed as having ED.

SF-36 test to evaluate HRQoL

The Medical Outcomes Study 36-Item Short-Form Health Survey (MOS SF-36 Health Survey) is a measure of health status designed for use in clinical practice, research, health policy evaluations and general population surveys. It includes 36 questions in eight scales, which are incorporated into physical and mental component scores (PCS and MCS, respectively) [12]. The test has also been validated in the Turkish population [13].

Statistical analyses

The data were evaluated using the SPSS 15 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) statistical program. Values are expressed as means ± standard deviation. For statistical analysis, the Friedman test was used for four measurements because differences among groups were not normally distributed. In cases of significant differences among measurements, the Bonferroni-adjusted Wilcoxon signed-rank test was used as post hoc analysis. In all analyses, a P-value <0.05 was accepted as statistically significant.

Results

The main result of the present study was the demonstration of equal efficacy and safety profiles for vardenafil and sildenafil in haemodialysis patients. Basic demographic and clinical characteristics of the entire study population are shown in Table 1. Both sildenafil and vardenafil significantly improved IIEF-5 scores and MCS and PCS components of SF-36 compared with pretreatment values. There was no difference in these parameters between sildenafil- and vardenafil-treated patients (Table 2).

Adverse effect profiles were also similar in patients treated with sildenafil and vardenafil. One patient complained of flushing and two others of headache in the vardenafil group, whereas one patient had facial flushing, one had headache and two had dyspeptic complaints in
the sildenafil group. Neither drug was discontinued due to adverse effects.

## Discussion

Aetiologies of sexual dysfunction in haemodialysis patients are myriad and include physiological, psychological and iatrogenic factors [2,14]. Numerous studies have shown that HRQoL is impaired in haemodialysis patients [3], and that there is a direct link between HRQoL and morbidity and mortality [15,16]. Factors associated with impaired HRQoL include but are not limited to age, gender, depression, anaemia and nutritional parameters [3,17]. In addition to these factors, ED has been shown to be an independent variable affecting HRQoL [14]. Previous studies have found associations between ED and different domains of quality of life. For example, while Rosas et al. [18] showed that the emotional domain (MCS) of SF-36 was more profoundly associated with ED than the physical domain (PCS), Turk et al. [3] found a significant association between ED and both MCS and PCS domains. Treatment of different risk factors improved HRQoL in

### Table 1. Demographic characteristics and laboratory data from the entire study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before sildenafil</th>
<th>After sildenafil</th>
<th>Before vardenafil</th>
<th>After vardenafil</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIEF-5 score</td>
<td>13.0 ± 6.1</td>
<td>21.0 ± 3.9</td>
<td>12.7 ± 5.9</td>
<td>20.7 ± 4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical component score</td>
<td>65.2 ± 24.3</td>
<td>83.3 ± 19.0</td>
<td>67.7 ± 22.6</td>
<td>83.6 ± 18.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mental component score</td>
<td>55.0 ± 19.6</td>
<td>71.2 ± 16.6</td>
<td>56.8 ± 18.7</td>
<td>69.6 ± 17.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IIEF-5: International Index of Erectile Function; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey.

*Friedman test.

*a Compared with before sildenafil P < 0.05.

b Compared with after sildenafil P < 0.05.

c Compared with before vardenafil P < 0.05 (with Bonferroni-adjusted Wilcoxon signed-rank tests).

### Fig. 1. Schematic representation of the study design.
dialysis patients [4,18]. Because of its high prevalence and close relationship with other determinants of HRQoL, ED should always be incorporated into daily evaluation of haemodialysis patients.

Sildenafil is a less potent selective inhibitor of PDE5 than vardenafil [19]. In fact, the failure rates for sildenafil exceed 50% in patients who have concomitant diabetes and vascular disease. Because haemodialysis patients have multiple comorbidities, even at the start of dialysis treatment, it is likely sildenafil will be ineffective in a subset of patients.

The effectiveness of sildenafil citrate in patients with ED of various aetiologies was confirmed in numerous large-scale prospective randomized trials [5,20]. Sildenafil was the first drug tested in ESRD patients and was found to be effective and safe in this population [21]. The average response rate for sildenafil in these studies was about 70–80%. However, subgroup analyses showed that sildenafil treatment was ineffective for patients with severe uncontrolled diabetes and vascular complications. A number of management strategies have been proposed to overcome sildenafil non-response including switching to other PDE5 inhibitors [22]. In sildenafil non-responders at 100 mg dose, increasing the dose improves the rate of response at the expense of increasing side effects [23]. Thus, administering a more potent drug such as vardenafil can be recommended. To date, no study has performed a head-to-head comparison between sildenafil and vardenafil. In fact, only indirect comparisons have been made between vardenafil and sildenafil in a systematic review of individual trials that tested sildenafil or vardenafil for the treatment of ED [24]. In their placebo-controlled trial, Carson et al. [25] randomized sildenafil non-responders into either vardenafil 10 mg or placebo. Compared with placebo, vardenafil significantly improved ED. In our study, a lack of severe complicated diabetes may have accounted for the high response rates and the failure to demonstrate any difference between the study drugs. Further studies with sildenafil non-respondent haemodialysis patients are needed to clarify the role of vardenafil in this special patient group.

Adverse effect profiles of sildenafil and vardenafil are similar. Morales et al. [26] evaluated the safety profile of sildenafil in 3700 patients and reported that the most frequently encountered adverse events were headache (16%), flushing (10%) and dyspeptic complaints (7%). Importantly, all of the adverse effects were of mild to moderate severity and did not lead to treatment discontinuation in any of the patients. The most frequent adverse events with vardenafil were headache, flushing, dyspepsia and rhinitis, which occurred at comparable rates [27]. Although sildenafil has been shown to have a similar safety profile in impotent uraemic patients as in other populations, the safety profile of vardenafil has never been tested in uraemic patients. Results from the current study demonstrated in ESRD patients that vardenafil is safe and well tolerated. No patient was dropped from the study because of adverse effects.

Because ED and HRQoL have been shown to be closely interrelated, it was not surprising that treatment of ED with sildenafil produced improved HRQoL in treated patients. In agreement, a number of studies have demonstrated improved HRQoL with treatment of ED during sildenafil in non-uraemic cohorts [9,10]. A favourable effect of ED treatment on HRQoL was also confirmed with vardenafil [10]. However, this relationship has not been previously investigated in ESRD patients while testing sildenafil or vardenafil.

Our study had several limitations. We did not use diagnostic or physical tests to confirm the diagnosis of ED; all our measures of ED were self-reported. We used the IIEF-5 survey to standardize the presence and severity of ED. Despite our longitudinal and randomized design, this was an open-label study that lacked a blinded design as well as placebo controls. Sample sizes were relatively small to detect subtle differences between the study drugs and to determine whether vardenafil was absolutely safe in ESRD patients. In addition, fixed-dose studies may not be the ideal method for comparing two impotence drugs. An escalation of doses to the highest recommended dose would be more appropriate.

In conclusion, despite some limitations, this study was the first to show beneficial effects of sildenafil and vardenafil on ED and HRQoL in haemodialysis patients. Interestingly, and in contrast to previous studies [1,4], sildenafil improved both the PCS and MCS domains of SF-36. There was no difference between sildenafil and vardenafil in terms of efficacy against ED. Both drugs were well tolerated. Further prospective studies with larger sample sizes are warranted to investigate effects of vardenafil in sildenafil non-respondent ESRD patients.

Conflict of interest statement. None declared.

References
Background. Dialysis patients and patients with chronic kidney disease (CKD) experience a substantial risk for abnormal autonomic function and abnormal heart rate variability (HRV). It remains unknown whether HRV changes across sleep stages in patients with different severity of CKD or dialysis dependency. We hypothesized that high-frequency (HF) HRV (vagal tone) will be attenuated from wakefulness to non-rapid eye movement (NREM) and then to rapid eye movement (REM) sleep in dialysis patients as compared to patients with CKD.

Methods. In-home polysomnography was performed in 95 patients with stages 4–5 CKD or end-stage renal disease (ESRD) on haemodialysis (HD) or peritoneal dialysis.