



ORIGINAL ARTICLE

Effects of three-times-per-week versus on-demand tadalafil treatment on erectile function and continence recovery following bilateral nerve sparing radical prostatectomy: Results of a prospective, randomized, and single-center study



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Abstract Erectile dysfunction (ED) and urinary incontinence after bilateral nerve-sparing radical prostatectomy (BNSRP) still remain major causes of morbidity. Phosphodiesterase type 5 inhibitors (PDE5-Is) have a role in the treatment of ED after BNSRP. Several studies in patients with ED and lower urinary tract symptoms demonstrated that PDE5-Is could improve both erectile function and urinary symptoms. The aim of this study was to compare the efficacies of two dosing regimens of 20 mg tadalafil (on-demand and 3 times per week) and to assess the role of tadalafil in recovery of erectile function and continence after BNSRP. We conducted a single-center, prospective, randomized controlled trial of three times per week versus on-demand tadalafil 20 mg and a control group after BNSRP. A total of 129 preoperatively potent and continent patients were included in the study. The patients were evaluated at 6 weeks and 12 months postoperatively for erectile function and continence status. There was no significant difference between all three groups with respect to erectile function at 6 weeks after the surgery. Twelve months after the surgery, the International Index of Erectile Function score was significantly higher in the group using tadalafil 20 mg three times per week. However, there was no significant difference between the treated groups and the control group with respect to the continence status at 12 months after the surgery. There was no correlation between incontinence and ED after the surgery in all groups. Tadalafil 20 mg three times per week is an efficacious and well-tolerated treatment option for ED after BNSRP. Treatment with 20 mg

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tadalafil either three times per week or on demand cannot improve continence recovery after BNSRP compared with the control group.

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Introduction

Radical prostatectomy (RP) is a commonly performed procedure for patients with clinically localized prostate cancer and a life expectancy of at least 10 years [1]. The number of RPs has been increasing annually, and currently many patients are treated at younger ages. The most common long-term complications of this procedure are urinary incontinence (UI) and erectile dysfunction (ED), which significantly affect quality of life after surgery [2].

Phosphodiesterase type 5 inhibitors (PDE5-Is), such as tadalafil, sildenafil, and vardenafil, are the recommended first-line treatment for ED [3] and are currently used to repair erectile dysfunction after RP; nevertheless, a treatment for continence rehabilitation is still lacking.

Several studies have demonstrated that cyclic guanosine monophosphate (cGMP) and the cGMP-dependent protein kinase-1 are expressed in the prostate, bladder, and urethra [4,5]. Currently, the anatomical site of action of PDE5-Is in the urinary system is unknown. Evaluation of urinary function in patients treated with tadalafil after RP allows us to assess whether or not positive activity of PDE5-Is on the lower urinary tract can be increased even in the absence of the prostate gland. Management of PDE5-Is may increase pelvic blood flow and oxygen supply, with a beneficial effect on sphincter function. There are few data on the possible effects of PDE5-Is on continence recovery after bilateral nerve-sparing radical prostatectomy (BNSRP) in the literature [6].

The aim of our study is to evaluate the influence of three times per week and on-demand tadalafil administration to analyze rehabilitation of erectile function and continence after BNSRP.

Materials and methods

Patients were enrolled between June 2006 and September 2010 in one center in Turkey. All patients signed written informed consent forms prior to the study; this study was conducted in accordance with the ethical principles of the Declaration of Helsinki (1996) and Good Clinical Practice guidelines (1997), and was approved by the local ethics committee.

The present study included 129 patients with prostate cancer who underwent retropubic BNSRP with or without lymph node dissection. Indication for preservation of neurovascular bundles was based on the characteristics at diagnosis [prostate-specific antigen (PSA) < 10 ng/mL, cT1-T2a disease, and a biopsy Gleason score $\leq 3 + 4$].

After catheter removal, 2 weeks after surgery, patients were divided into three groups: patients using Tadalafil 20 mg three times per week (Group 1), patients using tadalafil 20 mg on demand (Group 2), and patients not using PDE5-Is (Group 3). For randomization, the Number Cruncher

Statistical System 2007 program (Istanbul, Turkey) was used. All patients were strongly recommended to attempt sexual intercourse as soon as possible after catheter removal, and all patients were strongly encouraged to start pelvic floor muscle exercise in order to improve urinary continence. Patients in Groups 1 and 2 received the protocols for 12 months following the removal of the urethral catheter. Patients were instructed to take their 'on-demand' dose 1 hour before sexual activity and 'three times a week' dose 1 hour before bedtime.

All patients were stratified by complete preoperative clinical and functional data, including age, body mass index, preoperative PSA, smoking, alcohol consumption, and presence of comorbidities (e.g., diabetes mellitus, hypertension, and coronary arterial disease) (Table 1). Preoperatively, all patients were evaluated for erectile function based on the International Index of Erectile Function (IIEF-6) [7]. Urinary function was evaluated by the International Prostate Symptom Score [8,9], and continence status was evaluated by the International Consultation on Incontinence Questionnaire–Short Form (ICIQ-SF) [10,11]. The Beck Depression Index (BDI) form was used for psychological evaluation [12]. Patients were evaluated at 6 weeks and 12 months after the surgery.

Patients with moderate or severe ED prior to the surgery were excluded from the study, and all patients had a steady sexual partner. Patients were fully continent prior to the surgery. Other exclusion criteria were as follows: any disorder that could affect the individuals' ability to have sexual intercourse, history of other malignancy, and a history of pelvic surgery or pelvic radiotherapy. In addition, the patients who had received any treatment for ED or incontinence, such as androgens, antiandrogens, 5 α -reductase inhibitors, and anticholinergic medications, were excluded. Other exclusion criteria included hypersensitivity to tadalafil and being unable to complete the questionnaires.

SPSS version 17 for Window (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Demographic factors and potential confounding variables were compared between treatment groups using Chi-square tests for categorical variables. Preoperative urinary, erectile, and continence functions were analyzed according to different treatment arms such as analysis of variance (ANOVA) and Kruskal–Wallis test. We assessed the significance of erectile function and continence decline (preoperative) and subsequent recovery (6 weeks vs. 12 months) by *t* test for paired samples. Differences between the three groups were calculated by an ANOVA test.

Results

During this study period, 152 patients were operated, 129 screened, and 112 randomized: 38 (33.9%) patients to

Table 1 Baseline data of groups.

	Group 1 (n = 38)	Group 2 (n = 40)	Group 3 (n = 34)	p
Age (y)	62.63 (50–72)	62.95 (54–72)	63.52 (52–74)	0.888 ^a
Total PSA (ng/mL)	7.26 ± 2.41	6.20 ± 1.97	6.19 ± 2.48	0.237 ^b
BMI (kg/m ²)	27.6 ± 3.4	26.3 ± 3.1	26.7 ± 2.9	0.367 ^b
Diabetes mellitus (n)	6	6	6	0.665 ^c
Hypertension (n)	6	4	8	0.665 ^c
Cardiovascular disorder (n)	12	6	4	0.665 ^c
Smoker (n)	16	16	12	0.665 ^c
Alcohol consumption (n)	3	7	14	0.665 ^c

ANOVA = analysis of variance; BMI = body mass index; PSA = prostate-specific antigen.

^a ANOVA test.

^b Kruskal–Wallis test.

^c Chi-square test.

tadalafil three times per week (Group 1), 40 (35.7%) patients to tadalafil on demand (Group 2), and 34 (30.3%) patients to the control group (Group 3). Overall, eight (21.05%) patients in Group 1, four (10%) patients in Group 2, and five (14.7%) patients in Group 3 discontinued the study.

The mean age was 63 years (range: 50–74 years), and the mean preoperative PSA was 6.55 ng/mL (range: 3.8–9.7 ng/mL). A total of 24 patients were pT2a, three were pT2b, and 85 were pT2c in the definitive pathologic stage. The definitive Gleason score was 5 in 11 cases, 6 in 36 cases, 7 in 57 cases, and 8 in eight cases. Baseline characteristics were similar between the three groups, and regarding the parameters that might be associated with ED (body mass index, smoking and alcohol consumption, and presence of comorbidities including diabetes mellitus, hypertension, and coronary arterial disease) we found no statistically significant difference between all three groups (Table 1). The preoperative mean IIEF-6 score, mean International Prostate Symptom Score, mean ICIQ-SF score, and mean BDI score are demonstrated in Table 2. The three groups did not show any significant difference for all preoperative scores.

There were no significant differences between all three groups with respect to the IIEF-6 scores at 6 weeks after the surgery. However, 12 months after the surgery, the IIEF-6 score was significantly higher in Group 1. There were no significant differences between Groups 2 and 3 in the 12th month. Urinary continence analysis results of Group 1 were statistically significantly different from those of the other groups at 6 weeks after the surgery; the ICIQ-SF score was

significantly higher in Group 1. Nevertheless, there were no significant differences among the groups at 12 months after the surgery. When erectile function and continence status were evaluated together, there were no correlation at 6 weeks and 12 months after the surgery. Psychological analysis indicated that the BDI score was not different among the groups (Table 3).

In none of the groups, medication was required to be stopped due to adverse events. The most frequently reported treatment-emergent adverse events include flushing, headache, dizziness, and dyspepsia (Table 4).

Discussion

ED and UI continue to be significant complaints among men undergoing RP, despite using the nerve-sparing technique. The incidence of complete ED has been reported to be 26–100% and partial ED 16–48% [13]. The most appropriate preservation of erectile function after RP represents one of the major difficulties for practicing urologists [14]. PDE5-Is are more commonly used in penile rehabilitation programs than in other treatment alternatives [15]. The influence and adverse events of PDE5-Is used to treat ED after BNSRP have been largely studied. However, varying efficacy has been reported, with no final evidence to promote the optimal treatment strategy. There is no consensus or guidelines on their use at present.

Penile rehabilitation therapy has become a subject of intense concern over the past decade. Schwartz et al [16]

Table 2 Preoperative IIEF, ICIQ-SF, IPSS, and BDI scores of groups.

	Group 1 (n = 38)	Group 2 (n = 40)	Group 3 (n = 34)	p
IIEF score	26.15 ± 2.79	24.75 ± 4.02	24.76 ± 3.38	0.362 ^a
ICIQ-SF score	0	0	0	^b
IPSS score	14 ± 5.4	17.93 ± 5.19	16 ± 10.86	0.571 ^a
BDI score	3.21 ± 2.76	2.80 ± 2.09	2.11 ± 2.26	0.276 ^c

ANOVA = analysis of variance; BDI = Beck Depression Index; ICIQ-SF = International Consultation on Incontinence Questionnaire—Short Form; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score.

^a ANOVA test.

^b All patients were fully continent.

^c Kruskal–Wallis test.

Table 3 Postoperative 6th week and 12th month IIEF, ICIQ-SF, and BDI scores of groups.

	Group 1 (n = 38)	Group 2 (n = 40)	Group 3 (n = 34)	p
6 th wk IIEF score	15.52 ± 7.49	15.35 ± 6.08	14.76 ± 5.29	0.933 ^a
12 th mo IIEF score	19.89 ± 5.90	15.8 ± 6.97	13.47 ± 5.66	0.011 ^a
6 th wk ICIQ-SF score	7.15 ± 5.41	3.85 ± 2.75	3.35 ± 2.17	0.006 ^b
12 th mo ICIQ-SF score	4.26 ± 3.88	3.25 ± 3.22	2.94 ± 1.91	0.766 ^b
6 th wk BDI score	4.31 ± 3.26	3.70 ± 1.65	3.52 ± 2.21	0.625 ^b
12 th mo BDI score	3.89 ± 3.84	3.50 ± 1.60	3.94 ± 1.91	0.502**

ANOVA = analysis of variance; BDI = Beck Depression Index; ICIQ-SF = International Consultation on Incontinence Questionnaire—Short Form; IIEF = International Index of Erectile Function.

^a ANOVA test.

^b Kruskal–Wallis test.

were the first to prove that early use of 100 mg sildenafil after RP may conserve intracorporeal smooth muscle content. Several well-designed studies have supported the use of PDE5-Is for penile rehabilitation after this trial [17]. None of these studies have demonstrated higher efficacy of penile rehabilitation with PDE5-Is as compared to the on-demand administration schedule. Pavlovich et al [18] demonstrated that erectile functions did not differ between patients using sildenafil either nightly nor on demand after BNSRP. Another prospective, randomized study demonstrated that on-demand vardenafil was found to be more efficient than its daily use in advancing erectile function [19]. In our recent study, tadalafil administered three times per week was found to be more effective than its on-demand use in improving erectile function after BNSRP. We chose tadalafil among all PDE5-Is in our study. Because the longer half-life of tadalafil preferences to this drug the suitable pharmacokinetic profile for its use in penile rehabilitation. The Scheduled Use versus on-demand Regimen Evaluation (SURE) study, which included 4262 patients—the largest study population, indicated that tadalafil is effective and well tolerated irrespective of whether it is used on demand or three times per week. Furthermore, a large number of patients (42.2%) preferred the three times per week treatment [20].

As we mentioned previously, post RP, ED is a common problem. This wide range can be explained by the differing forms of consideration in clinical trials. There are significant differences with respect to the surgical technique used as well as the number of surgeons involved. BNSRP was performed in all patients; however, although previous studies involved many surgeons, in our study all operations were performed by only one surgeon.

In the current study, drug administration began immediately after catheter removal and we suggested that patients in the on-demand group might begin sexual intercourse 4 weeks after the surgery.

The effects of PDE5-Is in UI has been a current issue as well as ED. It is known that elevated levels of cGMP may inhibit smooth muscle apoptosis or collagen deposition. Effects of vardenafil on bladder overactivity were derived from preclinical studies on human and rat bladder smooth muscle cells [21]. Here, we investigated the effects of tadalafil administration on not only erectile function but also urinary continence status after BNSRP. Thus, considering all these points, our trial is one of the rare studies in the literature that evaluated these two factors together in a penile rehabilitation program after BNSRP.

The neurotrophic impact of PDE5-Is may be notable in the afferent suburothelial plexus of the trigon and bladder neck [22]. Besides, membranous urethral blood flow may be one of the targets of the PDE5-I-mediated sphincter contraction [23]. Age, obesity, and diabetes mellitus can also be taken into account as markers of patients' vascular and neurogenic statuses. These factors might be associated with poor pelvic vascular status, thus leading to a reduction in pelvic and sphincteric blood flow. All these variables were analyzed in detail in our study and a homogeneous distribution among the groups was maintained.

UI is a well-known complication of RP and occurs in 2–87% of patients after surgery [24]. Moreover, it remains one of the most boring sequelae influencing quality of life after RP and affects 1–25% of patients [25,26].

There are several studies in the literature on the treatment of post-RP incontinence. Several studies have investigated the influence of behavioral therapy on UI after RP; limited data are available on the impact of medical therapy on UI after the surgery [27,28]. One of the agents used in medical treatment of UI after RP includes PDE5-Is, and the number of studies dealing with this subject is increasing. Gacci et al [6] demonstrated that the strong correlation between continence and sexual recovery in vardenafil nightly group compared with the placebo group after BNSRP with small number of patients. In our study, which enrolled 112 patients, no correlation was observed between continence and erectile function at 12 months after the surgery. Another study interestingly showed ED prior to RP as a prognostic factor for UI after surgery [29]. Our study did not evaluate this situation because patients with moderate or

Table 4 Adverse events of treatment groups.

	Group 1 (n = 38)	Group 2 (n = 40)	p ^a
	n (%)	n (%)	
No adverse event	22 (57.8)	30 (75)	0.737
Flushing	6 (15.8)	4 (10)	0.737
Headache	6 (15.8)	4 (10)	0.737
Dizziness	2 (5.3)	0 (0)	0.737
Dyspepsia	2 (5.3)	2 (5)	0.737

^a Chi-square test.

severe ED prior to the surgery were excluded from the study.

Urodynamic studies should provide beneficial information about UI. However, urodynamic testing is invasive, difficult, and expensive. Therefore, validated questionnaires can be used to record the incontinence. The ICIQ-SF was recommended by the International Continence Society [30] and validated in a Turkish population in 2004 [31]. The consideration of its internal consistency demonstrated that the ICIQ-SF provides repeatable and reliable data [30]. We used this form to assess the urinary continence status after BNSRP. There was no significant difference between the treated groups and the control group with respect to the ICIQ-SF scores at 12 months after the surgery, unlike some previous studies. However, incontinence was significantly higher in the three times per week group than in the on-demand or control group at 6 weeks after the surgery. We could not explain this interesting finding with any pathophysiological mechanism.

In our study, both routes of administration of tadalafil were well tolerated. Headache was the most common side effect, along with flushing. A meta-analysis also revealed that headache was the most frequently reported adverse effect of PDE5-Is [32].

A limitation of our study is the lack of a placebo arm. Furthermore, the duration of the current trial was 12 months. Additionally, drug administration began immediately after the surgery (after removal of catheter). Therefore, not all patients would experience post-RP ED and incontinence. Thus, the consideration of the efficacy of tadalafil for ED and incontinence might have some biases due to inclusion of some patients without ED and incontinence prior to the surgery. Despite these limitations, the present study represents a relatively large prospective report trying to evaluate the association between different routes of PDE5-I administration and erectile function—urinary continence recovery in patients treated with BNSRP.

Conclusion

ED and UI will continue to be important problems for patients undergoing RP. PDE5-Is have become the first-line treatment for ED after localized treatment for prostate cancer. However, there is not sufficient evidence to recommend the use of PDE5-Is for post-RP incontinence. We conclude that tadalafil 20 mg three times per week is an efficacious and well-tolerated treatment option for ED post RP. However, neither tadalafil on demand nor tadalafil three times per week can improve continence recovery after BNSRP. For practical application of PDE5-Is to treat post-RP ED and incontinence, more randomized, placebo-controlled clinical trials with a larger population of patients are required, to investigate variables such as time of initiation of treatment, duration of treatment, dosage required, and selection of the most efficacious drug.

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