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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.

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, 5α-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