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АНДРОЛОГІЯ

The role of Tadalafil in the treatment of benign prostatic hyperplasia and erectile dysfunction

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SUMMARY

The aim of this study is to investigate the effectiveness of a single 5 mg daily dose of Tadalafil in patients with lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) accompanied by erectile dysfunction (ED). The data of patients who applied to the urology outpatient clinic between 2014 and 2019 and were diagnosed with BPH and ED were retrospectively analysed. Before and after the treatment with 5 mg tadalafil daily for 12 weeks; maximum flow rate (Qmax), average flow rate (Qave), postvoid residual volume (PVR), prostate volume (PV), PSA values, IPSS and IIEF scores of the patients were compared. The mean age of 66 male patients diagnosed with ED and BPH was 48.1±6.9 years. The mean IPSS score of the patients before the treatment was 9.85 which represents moderate LUTS. After the treatment, the mean score decreased to 5.7 which represents mild LUTS. Before the treatment, the mean IIEF score showed mild ED with 18.79. After the treatment, the mean IIEF score increased to 29,9. The treatment statistically significantly decreased ED and increased the IIEF score (p=0.000). While the mean Qmax and Qave were increased statistically significantly (p=0.000). A statistically significant decrease was observed in the mean PVR from 60.1 ml to 37.6 ml (p=0.000). The decrease in PV was not statistically significant (p=0.321). The decrease in PSA values before and after treatment was found to be statistically significant with p=0.046. It has been shown that the daily use of 5 mg Tadalafil alone for 12 weeks can be a preferable treatment option, especially in younger patients with BPH / LUTS and ED.

INTRODUCTION
Вступ

The medical treatment of lower urinary tract symptoms due to benign prostatic hyperplasia (BPH/LUTS), which increases with age and affects life quality dramatically, contains alpha-adrenergic blockers and 5-alpha reductase usages in combination or separately, and it was reported that usage of these medications may cause adverse effects such as dizziness, hypotension and erectile dysfunction (ED) [1, 2]. In clinical practice, usually, BPH/LUTS complaints of the patients are taken as the main concern and thus ED is ignored, and the treatment of BPH/LUTS is administrated in these conditions. As a result, the erectile functions of the patients worsen.

In older ages, BPH/LUTS is considered as an independent risk factor for ED and 70% of the patients are diagnosed with ED [3]. Mechanisms that explain coexistence of BPH/LUTS and ED are: increased Rho-kinase activity or decreased nitric oxide (NO) synthase activity cause decrease in the relaxation of prostatic, bladder and penile smooth muscle; increase in the bladder outer tract obstruction and decrease in erection [1]. Autonomous adrenergic hyperactivity and atherosclerosis are also added to these mechanisms [1]. Inhibition of phosphodiesterase 5 (PDE5) causes relaxation in the smooth muscles mediated by NO/cGMP. In addition, increased cGMP levels provide an antiproliferative effect in prostatic smooth muscle tissue, decrease chronic inflammation in the prostate and bladder, increase perfusion and oxygenation of lower urinary system [4,5]. Based on these mechanisms, although it was showed that selective PDE5 inhibitors sildenafil, tadalafil and vardenafil, which are commonly used in the treatment of ED, are effective on the treatment of BPH/LUTS. However only 5 mg tadalafil per day is approved in the guides of American Urological Association (AUA) and European Urological Association (EUA) [3, 6–8].

In this study, it was aimed to assess the effectiveness of daily single dose of 5 mg Tadalafil treatment on the patients with BPH/LUTS accompanied by ED, which have a common pathophysiology.

MATERIALS AND METHODS
Матеріали і методи дослідження

Patients diagnosed with BPH and ED between 2014 and 2019 are reviewed retrospectively. Patients whose BPH/LUTS severity was determined according to International Prostate Symptom Score (IPSS), ED status was determined according to International Erectile Function Index-5 (IIEF); who underwent uroflowmetry test, transrectal ultrasonography (USG) and abdominal USG; and who used daily single dose of 5 mg of tadalafil for 12 weeks were included. Patients who underwent a surgery due to BPH; have urinary system infection, urethral stricture, prostatic cancer, diabetes mellitus and any neurologic conditions; have been using alpha adrenergic-blocker, 5-alpha reductase inhibitors, anticholinergics,antidepressants,and antipsychotics were excluded. The first examinations and maximum flow rate (Qmax) and mean flow rate (Qave) acquired by uroflowmetry, postvoid residual (PVR) urine volume measured by abdominal USG, prostatic volume (PV) measured by transrectal USG, prostate specific antigen (PSA) levels, IPSS and IIEF scores after 12 weeks of the treatment were compared (table 1). Severity of LUTS is categorized as mild (0–7), moderate (8–19) or severe (20–35) according to IPSS. Severity of ED is categorized as mild (17–21), mild-moderate (12–16), moderate (8–11) or severe (5–7) according to IIEF-5 score.

This study was conducted under the guidance of the Declaration of Helsinki, on 18.01.2021, with

TABLE 1. Statistics of the variables before and after the treatment

	Before the treatment Mean (min–max)	After the TreatmentMean (min–max)	P
IPSS	9.85 (4–15)	5.7 (2–13)	0,000
IIEF	18.79 (6–25)	26.9 (17–30)	0,000
Qmax	11.9 (7–18)	15.5 (8–50)	0,000
Qave	6.6 (3–11)	8.8 (4–12)	0,000
PVR	60.1 (25–120)	37.6 (0–75)	0,000
PV	34.53 (20–52)	33.8 (2–52)	0,321
PSA	0.9 (0–3)	1.1 (0–3)	0,046

Note: IPSS – International Prostate Symptom Score, IIEF – International Erectile Function Index-5, Qmax – Maximum flow rate, Qave – Average flow rate, PVR – Postvoid residual urine volume, PV – Prostate volume, PSA – Prostate specific antigen.

the approval of the ethics committee with the number of TUTF–BAEK 2021/5.

Statistical Analysis. All data were analysed with IBM SPSS (SPSS Inc., Chicago, IL, USA). Symptom scores are shown as minimum, maximum and mean. Wilcoxon Test was used in the IPSS, IIEF, Qave, PMR and PSA variable, to determine statistical significance between non-homogenous distributed groups. For continuous variables (Qmax and PV), Student's T-test was used to compare two groups.

RESULTS AND DISCUSSION
Результати та їх обговорення

Sixty six patients were included the study and mean age was 48.1±6.9. While mean IPSS score of patients before the treatment was 9.85, which represents moderate LUTS, after the treatment mean score was 5.7, which represents mild LUTS, ($p<0.000$). Mean IIEF score of the patients before the treatment was 18.79, which represents mild ED, and it has raised to 29.9 after the treatment. The difference between the mean IIEF scores was statistically significant ($p=0.000$). While mean Qmax of the patients before the treatment was 11.9 mL/s, after the treatment mean Qmax was increased statistically significant to 15.5 mL/s ($p=0.000$) and mean Qave value was increased statistically significant from 6.6 mL/s to 8.8 mL/s ($p=0.000$). PVR urine volume was decreased statistically significant from 60.1 mL to 37.6 mL ($p=0.000$). Mean PV was measured as 34.5 mL before the treatment and as 33.8 mL after the treatment. The difference between mean prostatic volumes was not statistically significant ($p=0.321$). The difference between PSA values before and after the treatment was statistically significant ($p=0.046$) (table 1, figure 1).

This study showed that statistically significant improvement in IPSS, IIEF, Qmax, Qave, PVR levels with daily single dose 5 mg tadalafil for 12 weeks treatment on the patients with concomitant moderate BPH/LUTS and mild ED, and tadalafil can be used as a single-agent therapy.

IPSS. Tadalafil causes relaxation on bladder neck, prostate, and urethra smooth muscles by strengthen the effects of cGMP and NO, which increase after PDE5 inhibition, in the pelvic tissues. At the same time, perfusion and oxygenation increase in the lower urinary tract due to vasodilatation. This result was supported in our study, as in other studies in the literature, which argued that the IPSS score improved significantly with these effects [9–12].

In meta-analyses, when IPSS was evaluated according to storage and voiding symptoms subgroups, voiding symptoms showed significant improvement in all studies, whereas there were conflicting results in storage symptoms [10, 13, 14]. Although subgroup analysis was not performed in our study, it was shown that voiding quality markers such as Qmax and PVR improved significantly.

It was demonstrated in an animal model study that PDE5 expression in the bladder is androgen-dependent, and in the study of Gacci et al., improvement in IPSS after PDE5 inhibitor treatment was associated with younger age and lower body mass index [15, 16]. Also, our study was conducted on a young sample with mean age of 48, and the result was supported with statistically significant decrease in IPSS. This may explained by the fact that aging decreases PDE5 sensitivity by decreasing the androgen level.

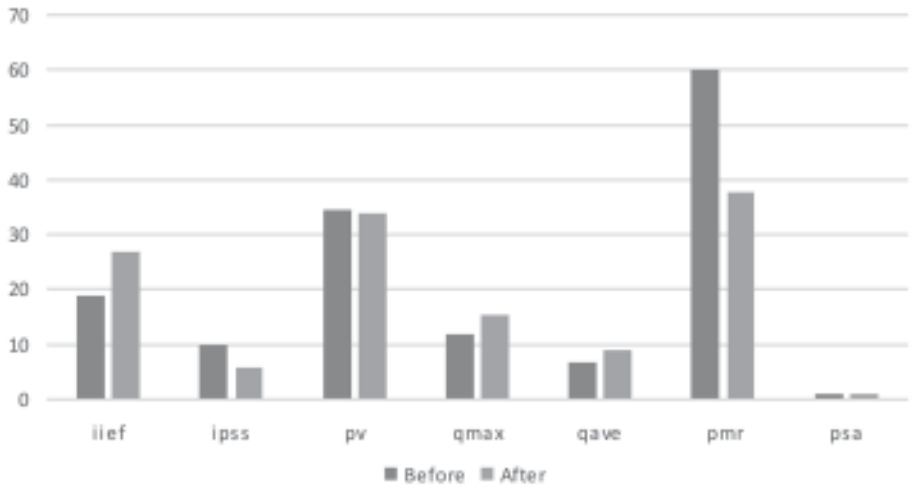

FIGURE 1: Mean variables before and after the treatment.
IPSS – International Prostate Symptom Score, IIEF – International Erectile Function Index-5, Qmax – Maximum flow rate, Qave – Average flow rate, PVR – Postvoid residual urine volume, PV – Prostate volume, PSA – Prostate specific antigen

Qmax and PVR. Contrary to the significant improvements seen in total IPSS with tadalafil 5 mg treatment in the literature, consistent results in Qmax and PVR values have not been reported [10, 12]. In our study, the Qmax value increased statistically significantly after 12 weeks of Tadalafil 5 mg treatment, and it is similar to only the randomized controlled study of Oelke et al., which consisted of 511 patients, in the literature [10]. In vitro studies have shown that inhibition of PDE5 provides relaxation of bladder neck and prostate smooth muscle, and this mechanism explains the contribution of tadalafil to Qmax increase and PVR decrease [10]. In another study, although there was no statistically significant effect of daily 5 mg tadalafil treatment on Qmax and PMR values, when analysed according to age groups, it was reported that Qmax and PMR values improved more in patients under 65 years of age [17]. Our study, in which all patients were under the age of 65, supports these results.

In a study by Takahashi et al., statistically significant improvement was observed in LUTS evaluated at the 12th week, however there was no significant change in Qmax and PMR values [18]. Although the baseline Qmax and PMR values were similar to our study, the difference in recovery after treatment may be due to the insufficient sample size of this study and the difference in the mean age.

IIEF. With the demonstration that all PDE5 inhibitors used in studies improve the IIEF score, it has also been widely used in the treatment of ED seen simultaneously with BPH [6, 9, 16]. In our study, it was observed that the mean IIEF score was 18.79 in the pre-treatment period, while it increased to 26.9 after 12 weeks of tadalafil treatment, and the ED complaints of the patients decreased significantly, which correlates with previous studies [11, 12]. In the study of Takahashi et al. consisting of patients with a mean age of 67 years and patients with severe ED accompanying BPH, it was shown that the IIEF score improved significantly at 4th week, but this effect was not maintained at 12th week [18].

The fact that our patients were younger and had a higher initial IIEF score was thought to be the reason for this difference. In contrast, in the study of Porst et al., it was suggested that factors such as age, BMI, BPH/LUTS severity, and alpha-blocker use did not have a statistically significant effect on the change in IIEF results in tadalafil treatment [12]. As a result, these two studies, when evaluated together with our study, show that ED severity before tadalafil treatment in BPH/LUTS patients may be a determining factor in the improvement in IIEF score.

PV and PSA. There are limited data in the literature for the effect of tadalafil use on prostate volume and PSA value, and although it prevents smooth muscle proliferation, there is no study showing that it causes lysis and apoptosis [19]. In our study, it was observed that the use of tadalafil did not statistically significantly change the prostate volume, however, it reduced the PSA, albeit slightly, significantly. In the study of Pingge et al., which is the only detailed study in the literature on perfusion and volume of the prostate, no significant difference was found between the prostate volumes measured by transrectal USG at the 4th and 8th weeks of tadalafil treatment, supporting our results [20].

Cost-Effectiveness. Recent trends in the treatment of ED in the world are towards the widespread use of PDE5 inhibitors [9]. Arreola et al.'s study with 2000 ED patients showed that 20 mg tadalafil treatment would have a higher cost for 5 and 10 years compared to 50 mg sildenafil treatments [21]. The most recent study on this subject is Hansen et al. in 2020, 3 different treatment options, 50/100 mg sildenafil, 10/20 mg tadalafil and 10 mg vardenafil, were compared in the treatment of ED complaints of diabetic patients. Sildenafil has been shown to be less costly than tadalafil and vardenafil [22]. The non-reimbursement of the cost of tadalafil treatment by the health systems of the countries is a factor that will affect the continuity of treatment. This increases the importance of cost-effectiveness analysis.

The main limitations of our study that should be considered is being retrospective study, lack of placebo or control group, and a limited sample size.

CONCLUSIONS
Висновки

It has been shown that regular use of 5mg Tadalafil alone for 12 weeks can be a good treatment option, especially in younger patients with BPH/LUTS and ED.

CONFLICT OF INTEREST
Інформація про конфлікт інтересів

The authors declared that there is no conflict of interest.

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РЕФЕРАТ

Роль тадалафілу у лікуванні доброякісної гіперплазії передміхурової залози та еректильної дисфункції

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Метою цього дослідження є дослідити ефективність одноразової 5 мг добової дози тадалафілу у пацієнтів із симптомами нижніх сечовивідних шляхів (СНСШ) внаслідок доброякісної гіперплазії передміхурової залози (ДГПЗ), що супроводжується еректильною дисфункцією (ЕД). Ретроспективно проаналізовано дані пацієнтів, які звернулися амбулаторно до уролога в період з 2014 до 2019 р. з діагнозом ДГПЗ та ЕД. До та після лікування 5 мг тадалафілу на добу протягом 12 тижнів. Порівнювали максимальну швидкість потоку (Qmax), середню швидкість потоку (Qave), об'єм залишкової сечі (PVR), об'єм передміхурової залози (PV), значення ПСА, показники IPSS та IIEF пацієнтів. Середній вік 66 пацієнтів чоловічої статі з діагнозом ЕД та ДГПЗ становив 48,1±6,9 року. Середня оцінка IPSS пацієнтів до лікування становила 9,85, що представляє помірну СНСШ. Після лікування середній бал знизився до 5,7, що означає легку СНМП. До лікування середній бал за IIEF показав легку ЕД з 18,79. Після лікування середній бал за IIEF збільшився до 29,9. Лікування статистично достовірно зменшило ЕД та підвищило бал за IIEF (p=0,000). Тоді як середні Qmax і Qave були статистично достовірно збільшені (p=0,000). Статистично значуще зниження середнього PVR від 60,1 мл до 37,6 мл (p=0,000). Зниження PV не було статистично значущим (p=0,321). Зниження значень ПСА до

та після лікування виявилося статистично значущим із p=0,046. Було показано, що щоденне застосування 5 мг тадалафілу окремо протягом 12 тижнів може бути кращим варіантом лікування, особливо у молодих пацієнтів з ДГПЗ/СНСШ та ЕД.

Ключові слова: доброякісна гіперплазія передміхурової залози; імпотенція; тадалафіл.