Clinical Center of Vojvodina, Novi Sad
Clinic for Urology[1]
University of Novi Sad
Faculty of Medicine[2]

Case report
Prikaz slučaja
UDK 616.63/.65-085
DOI: 10.2298/MPNS1612379G

EFFICIENCY OF SILDANEFIL MONOTHERAPY IN BENIGN PROSTATIC HYPERPLASIA

NOVA OPCIJA MEDIKAMENTOZNOG TRETMANA BENIGNE HIPERPLAZIJE PROSTATE I SIMPTOMA DONJEG URINARNOG TRAKTA

Dragan GRBIĆ[1], Sasa VOJINOV[1, 2], Dimitrije JEREMIĆ[1, 2], Ivan LEVAKOV, Senjin ĐOZIĆ[1, 2] and Vuk SEKULIĆ[1, 2]

Summary

Introduction. High incidences of benign prostatic hyperplasia and lower urinary tract symptoms have a high socioeconomic importance. There are several published studies which have proved the efficiency of phosphodiesterase type 5 inhibitors in treatment of benign prostatic hyperplasia and lower urinary tract symptoms. However, more studies are needed to make this therapy the standard option for treating benign prostatic hyperplasia and lower urinary tract symptoms. This study was aimed at exploring changes in International Prostate Symptom Score, post voiding residuum and maximal urine flow in benign prostatic hyperplasia and lower urinary tract symptoms patients treated by sildenafil for benign prostatic hyperplasia and lower urinary tract symptoms. **Material and Methods.** This study, which was conducted as a prospective, controlled, opened, randomized study, included 30 patients with benign prostatic hyperplasia and lower urinary tract symptoms. Research was conducted at the Department of Urology, Clinical Center of Vojvodina (November 2011 till November 2012). The inclusion criteria were as following: >45 years of age, International Prostate Symptom Score >3, prostatic specific antigen <10, normal urinalysis. The patients were periodically tested for International Prostate Symptom Score, maximal urine flow, and post voiding residuum. **Results.** Statistically significant changes were found in all parameters: mean International Prostate Symptom Score value improved from 12.8 to 8.6 (32.8% change), mean post voiding residuum value decreased from 49.4 ml to 40.2 ml (18.6% change), mean maximal urine flow value increased from 11.8 ml/s to 12.8 ml/s (8.5% change). **Conclusion.** Treatment of benign prostatic hyperplasia and lower urinary tract symptoms with a continuous low dose of sildenafil seems to be a good treatment choice for the patients with mild to moderate benign prostatic hyperplasia and lower urinary tract symptoms, especially in the patients with concomitant erectile dysfunction. The authors are aware that their study is limited by a small number of patients. Since there are not too many studies on this topic, they believe that their study will contribute to the determination of place and role of this treatment approach.

Key words: Prostatic Hyperplasia; Signs and Symptoms; Lower Urinary Tract Symptoms; Urinary Retention; Treatment Outcome; Sildenafil Citrate; Phosphodiesterase 5 Inhibitors

Sažetak

Uvod. Velika incidencija benigne hiperplazije prostate i simptoma donjeg urinarnog trakta imaju značajnu socioekonomsku važnost. Postoji više objavljenih studija koje dokazuju efikasnost *phosphodiesterase type* 5 inhibitora u tretmanu benigne hiperplazije prostate/simptoma donjeg urinarnog trakta. Neophodno je više studija da bi ova terapija postala standardna opcija u lečenju benigne hiperplazije prostate i simptoma donjeg urinarnog trakta. Cilj studije je utvrđivanje promena u Internacionalnom prostata Simptom Skoru, rezidualnom urinu i maksimalnom protoku urina pri *uroflow* merenju kod pacijenata sa benignom hiperplazijom prostate i simptomima donjeg urinarnog trakta tretiranih sildenafilom. **Materijal i metode.** Studija je sprovedena kao prospektivna, kontrolisana, otvorena i randomizirana, uključivala je 30 muškaraca sa benignom hiperplazijom prostate i simptomima donjeg urinarnog trakta. Istraživanje je sprovedeno na Klinici za urologiju, Kliničkog centra Vojvodine (Novembar 2011 - Novembar 2012). Inkluzioni kriterijumi: >45 godina starosti, Internacionalni prostata simptom skor>3, prostata specifičan antigen <10, sediment urina uredan. Svakom pacijentu su periodično određivani: Internacionalni prostata simptom skor, maksimalni protok urina i rezidualni urin. **Rezultati.** Utvrđene su statistički signifikantne promene u svim parametrima: pad srednje vrednosti Internacionalnog prostata simptom skora sa 12,8 na 8,6 (poboljšanje 32,8%), smanjenje srednje vrednosti rezidualnog urina sa 49,2 ml na 40,2 ml (poboljšanje 18,6%), uvećanje srednje vrednosti maksimalnog protoka urina sa 11.8 ml/s na 12,8 ml/s (poboljšanje 8.5%). **Zaključak.** Tretman benigne hiperplazije prostate i simptoma donjeg urinarnog trakta kontinuiranim niskim dnevnim dozama sildenafila deluje kao korektna terapijska opcija, posebno kod pacijenata as konkomitantnom erektilnom disfunkcijom. Autori su svesni da je studija limitirana malim brojem pacijenata. S obzirom na mali broj postojećih studija, smatramo da naša studija doprinosi određivanju mesta i uloge ove terapijske opcije u lečenju benigne hiperplazije prostate i simptoma donjeg urinarnog trakta.

Ključne reči: hiperplazija prostate; znaci i simptomi; simptomi donjeg urinarnog trakta; retencija urina; ishod lečenja; sildenafil; PDE5 inhibitori

Corresponding Author: Dr Dragan Grbić, Klinički centar Vojvodine, Klinika za urologiju, 21000 Novi Sad, Hajduk Veljkova 1-7, e-mail: d_grbic@yahoo.com

Abbreviations

BPH – benign prostatic hyperplasia
LUTS – lower urinary tract symptoms
PDE – phosphodiesterase
PDE5 – phosphodiesterase type 5
IPSS – International Prostate Symptom Score
PVR – post voiding residuum
Qmax – maximal urine flow
PSA – prostatic specific antigen
UA – urinalysis
ED – erectile dysfunction
NO – nitro oxide
cGMP – cyclic guanosine monophosphate
NOS – nitric oxide synthase
nNOS – neuronal nitric oxide synthase
eNOS – endothelial nitric oxide synthase
iNOS – immune cell nitric oxide synthase
Ca++ – calcium
DRE – digital rectal examination
FDA – Food and Drug Administration
DHT – dyhidrotestosterone

Introduction

Benign prostatic hyperplasia symptoms (BPH) result from: 1) mechanical obstruction - intrusion of enlarged, hyperplastic prostatic tissue into the urine pathway (bladder neck, urethra) and from 2) dynamic obstruction - hyper stimulated adrenergic receptors of smooth muscle and collagen of bladder neck and prostate leads to dynamic obstruction of urine flow. Drugs of choice for mechanical obstruction are 5α-reductase inhibitors, whereas alpha blockers would be the most appropriate therapy for dynamic component of BPH.

Phosphodiesterase type 5 inhibitors (PDE5) are a group of drugs (sildenafil, tadalafil, vardanafil) that are widely used as a standard treatment for erectile dysfunction (ED) and some of them for pulmonary hypertension as well (sildenafil and tadalafil).

The efficiency of PDE5 inhibitors in benign prostatic hyperplasia and lower urinary tract symptoms (BPH/LUTS) treatment is nowadays being widely studied. Their mechanism of action is by inhibiting autonomous stimulation of smooth muscle and collagen (inhibition of dynamic obstruction). The mechanism of PDE5 inhibitors action involves the nitro oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway. NO is an important non-adrenergic, non-cholinergic neurotransmitter in the human body. It is involved in transmission of neural signals in the urinary tract as well. NO is produced from amino acid L arginine under the influence of nitro oxide synthase (NOS). In human body they are classified by tissue origin as: neuronal NO synthase (nNOS), endothelial NO synthase (eNOS) and NO synthase of immune cells origin (iNOS).

Once NO has been produced, it goes into the cells and stimulates the synthesis of cyclic guanosyn monophosphate (cGMP) by enzyme guanylyl cyclase. cGMP activates protein kinase, ion channels, and cGMP binding phosphodiesterase which leads to the relaxation of smooth muscles by decreasing concentration of intracellular Ca++ and desensibilisation of contractile proteins [1]. The effect of cGMP is discontinued by PDE isoensyme which catalyzes the hydrolysis of cGMP into the inactive form. PDE5 inhibitors inhibit PDE isoenzyme and increase the concentration and activity of intracellular cGMP and thus, decrease the tonus of smooth muscle of detrusor, prostate and urethra. Eleven different PDE esterases have been discovered so far, among which are PDE esterases 4 and 5 predominant in the transitional zone of human prostate, bladder and urethra [2, 3]. It is possible that NO is involved in micturition also by the inhibition of reflex pathways in the spinal cord [4].

This study was aimed at assessing any changes in voiding parameters: International prostate symptom score (IPSS), post voided residuum (PVR) and maximal urine flow (Qmax), which were assessed at the start of the study before treatment, at the middle of study and at the end of three-month period during which the patients were on sildenafil treatment.

Material and Methods

This research was conducted as a prospective, controlled, opened and randomized study, which included 30 men with BPH/LUTS. It was done at the Clinic for Urology, Clinical Centre of Vojvodina in one year time frame (November 2011 until November 2012). The inclusion criteria were: >45 years of age, IPSS >3, PSA <10, normal urinalysis (UA), digital rectal examination (DRE) with no suspicion of cancer. The exclusion criterion was having a contraindication for using PDE5 inhibitors.

Assessment of Parameters of Voiding

Each study participant underwent physical examination (digitorectal examination, brief neurological examination) during the first visit and completed the IPSS questionnaire form. The IPSS questionnaire has seven questions which are the same as American Urological Association Symtpom index (AUA-SI) plus the eighth question known as a bother score, which is designed to estimate disease specific quality of life (QoL). Each question can yield 0-5 points, the minimal and maximal number of points being 0 and 35, respectively. Based on the first seven questions and severity of symptoms all patients were classified into three groups: group I – the patients with mild symptoms (0-7 points), group II – the patients with moderate symptoms (8-19 points) and group III – the patients with severe symptoms (20-35 points). Each participant had to have at least 3 or more points to qualify for the study. Once patients had been qualified for the study, the assessment of Q max and PVR was performed. For the assessment of Qmax, Uroflow study had to be done by means of Solar urodynamic machine – Medical Measurements Systems (the Netherlands). Each participant was asked to urinate at least 150 ml of urine to have valid uroflow study and Q max value determined. The patients were left alone in the examination room (to prevent social inhibition of micturition*)* and used the

previously activated Uroflow device. The patient urinated in standing position with the comfort height level of urinal (should the urinal be too high, it would be uncomfortable for the patient to urinate and the results of the study would not be valid). Once the patient finished urinating, PVR immediately was determined by means of the Ultrasound – SIEMENS – Sonoline Prima with convex abdominal ultrasound probe of 3.5 MHz. Having passed all examinations and tests, and thus satisfied inclusion criteria, the patient was given a six-week supply of 1x25 mg of siledenafil to have enough up to the next checkup. At the first checkup six weeks after the introduction of treatment, the same procedures (IPSS, PVR and Qmax) were repeated in the same manner and under the same conditions. The patients were provided with another six week supply of sildenafil at a dose of 1x25 mg per a day and then came for the second, i.e. the last checkup and underwent the same diagnostic procedures (IPSS, PVR and Qmax) under the same conditions.

Results

The research results are given in **Tables 1-3.**

Discussion

Benign prostatic hyperplasia results in the enlargement of the prostate and may lead to the reduced urinary flow from the urinary bladder. BPH is considered to be a normal part of aging in men and it is hormonally dependent on the testosterone and dyhidrotestosterone (DHT) production. It is estimated that 50% of all men at the age 60 have the histological form of BPH. This percentage goes up to 90% at the age of 85 [5].

The administration of PDE5 inhibitors for BPH/LUTS treatment was officially approved by Food and Drug Administration (FDA) in the USA three years ago. However, there are still contradictory data regarding the efficiency level of BPH/LUTS treatment by PDE5.

In our study we have found that the mean value of IPSS improved from 12.8 at the beginning of study to 9.0 (29.6% change) and 8.6 (32.8% change) at the first checkup (six weeks on sildenafil treatment) and at the second/last checkup (after 12 weeks on sildenafil treatment), respectively. In most randomized, placebo controlled studies, which were conducted

Table 1. Mean values for International Prostate Symptom Score, post voiding residual and maximal uroflow for all 30 patients at the beginning of study
Tabela 1. *Srednje vrednosti za Internacionalni prostata simptom skor, rezidualni urin i maksimalni protok urina za 30 pacijenata na početku istraživanja*

30 patients *30 pacijenata*	PVR in ml/*rezidualni urin u ml*	Qmax/*maksimalni protok urina* ml/s	IPSS value/*Internacionalni prostata simptom skor*
Values at the beginning of study *Vrednosti na početku istraživanja*	49,4	11,8	12,8

Table 2. The mean values for IPSS, PVR and Qmax of all patients at the first checkup (six weeks upon starting sildenafil treatment)
Tabela 2. *Prikaz srednje vrednosti Internacionalnog prostata skora, rezidualnog urina i maksimalnog protoka urina pacijenata prilikom prve kontrole (nakon šest nedelja terapije sildenafilom)*

30 patients *30 pacijenata*	PVR in ml/*rezidualni urin u ml*	Qmax/*maksimalni protok urina* ml/s	IPSS value/*vrednost Internacionalnog prostata simptom skora*
Values after six weeks of sildenafil/*Vrednosti nakon 6 nedelja terapije sildenafilom*	41.0	12.6	9.0

Table 3. Mean values for International Prostate Symptom Score, post voiding residual and maximal uroflow for all patients at the end of study (12 weeks after the introduction of sildenafil treatment)
Tabela 3. *Prikaz srednje vrednosti Internacionalnog prostata skora, rezidualnog urina i maksimalnog protoka urina pacijenata prilikom kontrole na kraju studije (nakon dvanaest nedelja terapije sildenafilom)*

30 patients *30 pacijenata*	PVR in ml/*rezidualni urin u ml*	Qmax/*maksimalni protok urina* ml/s	IPSS value/*Vrednost Internacionalnog prostata simptom skora*
Values after twelve weeks of sildenafil/*Vrednosti nakon 12 nedelja terapije sildenafilom*	40.2	12.8	8.6

lately, the efficiency of all three PDE5 inhibitors was observed through IPSS, Qmax and PVR changes [6–15]. Maximal time frame of studies was 12 weeks. In all of these studies, it was concluded that IPSS significantly improved, from 17% up to 35%.

The uroflow/Qmax mean value changed in our study from 118 ml/s at the beginning of study to 126 ml/s (improvement of 0.8 ml/s - 6,8% change) at the first checkup (six weeks on sildenafil treatment) and 12.8 ml/s (improvement of 1.0 ml/s – 8.4% change) and at the second, i.e. last checkup (after 12 weeks on sildenafil treatment). Our findings were not confirmed in most other studies [6–14]: Qmax was not significantly different comparing to placebo.

Changes within the third parameter were also observed in our study: the mean PVR value was 49.4 ml at the beginning of study and during sildenafil treatment it decreased to 41.0 ml (17% change) and 40.2 ml (18.6% change) at the first checkup (six weeks on sildenafil treatment) and at the second, i.e. last checkup (after 12 weeks on sildenafil treatment), respectively. In almost all other studies there were no significant changes of PVR [6–14]. There are few studies with significant improvement of Qmax. The study done by Guler C et al. [15] showed significant improvement in the mean value of Qmax in the patients treated by sildenafil: 29 out of 38 patients (76%) had improvement of Qmax and it was 38% on average (from 11.4 ml/s to 15.7 ml/s), whereas no significant change in Qmax was observed in the controls. A significant Qmax improvement was found in a study done by Guven E et al. as well (from 15.6±6.8 ml to 19.3±7.2 ml/s) [16].

Besides, there are three studies which compared the efficiency of sildenafil monotherapy vs. sildenafil plus alpha blocker (alfuzosin or tamuslosin) combined therapy. There are three studies that compared efficiency of PDE5 inhibitors (sildenafil or tadalafil) with or without alpha blockers (alfuzosin or tamsulosin) [8, 11, 12]. These studies were conducted on a limited number of patients. Their duration was relatively short-up to six or twelve weeks. Treatment with the combination of these drugs led to a bigger improvement in IPSS, Qmax and PVR than when each drug was given as a mono therapy. However, only the study done by Bechar A et al. [11] revealed significant changes in the parameters. The study sample consisted of 27 patients, who were divided into two groups: those receiving only tamsulosin and those treated with tamsulosin plus tadalafil. The authors found a significant change in IPSS in both groups from 18.4 to 12.7 and 10.2. The improvement was bigger in the patients who were treated with tamsulosin plus tadalafil. The improvement was also observed in Qmax and PVR in both groups of patients (Qmax from 9.6 ml/s to 11.7 ml/s and 12.6 ml/s; PVR from 60 ml to 24.8 ml and 21.3 ml). There was no significant difference in these two parameters between the groups.

Conclusion

Treatment of benign prostatic hyperplasia and lower urinary tract symptoms with continuous low dose of sildenafil seems to be a good treatment choice in the patients with mild to moderate benign prostatic hyperplasia and lower urinary tract symptoms, especially in those patients with concomitant erectile dysfunction. The authors are aware of limited value of this study due to a small number of included patients. However, since there are not too many studies dealing with this issue, we assume that our study may contribute to further determination of the place and role of this treatment approach.

References

1. Kedia GT, Uckert S, Jonas U, et al. The nitric oxide pathway in the human prostate: clinical implications in men with lower urinary tract symptoms. World J Urol. 2008;26(6):603-9.

2. Uckert S, Kuthe A, Jonas U, et al. Characterization and functional relevance of cyclic nucleotide phosphodiesterase isoenzymes of the human prostate. J Urol. 2001;166(6):2484-90.

3. Uckert S, Oelke M, Stief CG, et al. Immunohistochemical distribution of cAMP- and cGMPphosphodiesterase (PDE) isoenzymes in the human prostate. Eur Urol. 2006;49(4):740-5.

4. Andersson KE, Persson K. Nitric oxide synthase and the lower urinary tract: possible implications forphysiology and pathophysiology. Scand J Urol Nephrol Suppl. 1995;175:43-53.

5. Fejsa Levakov A, Mocko Kacanski M, Vuckovic N, Zivojinov M, Amidzic J, Ilic Sabo J. The exspression and localization of estrogen receptor beta in hyperplastic and neoplastic prostate lesions. Vojnsanit Pregl. 2015;72(10):906-13.

6. Mulhall JP, Guhring P, Parker M, et al. Assessment of the impact of sildenafil citrate on lower urinarytract symptoms in men with erectile dysfunction. J Sex Med. 2006;3:662-7.

7. McVary KT, Monnig W, Camps JL Jr, et al. Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. J Urol. 2007;177(3):1071-7.

8. Kaplan SA, Gonzalez RR, Te AE. Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. Eur Urol. 2007;51(6):1717-23.

9. Vojinov S, Marušić G, Levakov I, Popadić-Gaćeša J. Influence of hormonal therapy on the level of prostate specific antigen in patients with advanced prostatic cancer. Med Pregl. 2010;63(7-8):479-82.

10. Roehrborn CG, McVary KT, Elion-Mboussa A, et al. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. J Urol. 2008;180(4):1228-34.

11. Bechara A, Romano S, Casabe A, et al. Comparative efficacy assessment of tamsulosin vs. tamsulosin plus tadalafil in the treatment of LUTS/BPH. Pilot study. J Sex Med. 2008;5(9):2170-8.

12. Liquori G, Trombetta C, De Giorgi G, et al. Efficacy and safety of combined oral therapy with tadalafil and alfuzosin: an integrated approach to the management of patients with

lower urinary tract symptoms and erectile dysfunction. Preliminary report. J Sex Med. 2009;6(2):544-52.

13. Stief CG, Porst H, Neuser D, et al. A randomised, placebo-controlled study to assess the efficacy oftwice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol. 2008;53(6):1236-44.

14. Roehrborn CG, Kaminetsky JC, Auerbach SM, et al. Changes in peak urinary flow and voidingefficiency in men with signs and symptoms of benign prostatic hyperplasia during once daily tadalafil treatment. BJU Int. 2010;105(4):502-7.

Rad je primljen 12. I 2016.
Recenziran 31. I 2016.
Prihvaćen za štampu 3. VII 2016.
BIBLID.0025-8105:(2016):LXIX:11-12:379-383.

15. Guler C, Tuzel E, Dogantekin E, et al. Does sildenafil affect uroflowmetry values in men with lower urinary tract symptoms suggestive of benign prostatic enlargement? Urol Int. 2008;80(2):181-5.

16. Guven EO, Balbay MD, Mete K, et al. Uroflowmetric assessment of acute effects of sildenafil on the voiding of men with erectile dysfunction and sympotomatic benign prostatic hyperplasia. Int Urol Nephrol. 2009;41(2):287-92.