ARTICLE IN PRESS
+ MODEL
Asian Journal of Urology xxx (xxxx) xxx

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/ajur

Original Article

Efficacy of a combination of dutasteride, tadalafil, and solifenacin in the treatment of previously unsuccessful patients

Kirill Kosilov [a,b,*], Irina Kuzina [a], Vladimir Kuznetsov [c], Olga Barabash [d], Ekaterina Fedorishcheva [c]

[a] *Department of Social Sciences, School of Humanities, Far Eastern Federal University, Vladivostok, Primorsky region, Russian Federation*
[b] *Department of Clinical Medicine, School of Medicine, Far Eastern Federal University, Vladivostok, Primorsky region, Russian Federation*
[c] *Department of Public Health, Pacific State Medical University, Vladivostok, Primorsky region, Russian Federation*
[d] *Department of Physical Culture and Health and Sports Work, Vladivostok State University of Economics and Service, Vladivostok, Primorsky region, Russian Federation*

Received 8 July 2019; received in revised form 15 July 2020; accepted 9 September 2020

KEYWORDS
Lower urinary tract symptoms;
Benign prostatic hyperplasia;
Dutasteride, tadalafil;
Solifenacin;
Sexual function

Abstract *Objective:* To evaluation of the efficacy and safety of simultaneous administration of dutasteride, tadalafil and solifenacin in the treatment of benign prostatic hyperplasia (BPH) with overactive bladder symptoms and lower urinary tract obstruction in previously unsuccessfully treated men.
Methods: Patients in Group A ($n = 97$) received dutasteride 0.5 mg/day, tadalafil 2.5 mg/day, and solifenacin 2.5 mg/day; Group B ($n = 95$) received dutasteride 0.5 mg/day, tadalafil 5 mg/day, and solifenacin 5 mg/day; Group C ($n = 103$) received dutasteride 0.5 mg/day, tadalafil 10 mg/day, and solifenacin 10 mg/day. The functional status of the lower urinary tract was assessed using the International Prostate Symptom Score (I-PSS), Overactive Bladder Questionnaire (OABq), International Index of Erectile Function (IIEF), Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) as well as uroflowmetry.
Results: The total score of the sexual function remained unchanged in Group A of patients 81.3 points *vs.* 80.2 ($p > 0.05$) according to MSHQ-EjD, 61.4 points *vs.* 51.2 ($p > 0.05$) according to IIEF data. The total assessment of symptoms of hyperactivity significantly decreased in Group C according to OABq data after the 4th week of the study (17.5 points *vs.* 26.1, $p < 0.05$) and remained below the baseline until the end of the study (15.2 points).

* Corresponding author. Department of Social Sciences, School of Humanities, Far Eastern Federal University, Vladivostok, Primorsky region, Russian Federation.
E-mail address: oton2000@mail.ru (K. Kosilov).
Peer review under responsibility of Second Military Medical University.

https://doi.org/10.1016/j.ajur.2021.04.002

Please cite this article as: K. Kosilov, I. Kuzina, V. Kuznetsov et al., Efficacy of a combination of dutasteride, tadalafil, and solifenacin in the treatment of previously unsuccessful patients, Asian Journal of Urology, https://doi.org/10.1016/j.ajur.2021.04.002

Conclusions: The simultaneous administration of standard doses of dutasteride, solifenacin and tadalafil for 3 months is safe, effective and can be recommended for patients with BPH to reduce symptoms of obstruction and hyperactivity of the bladder and maintain sexual function.

1. Introduction

The development of the benign prostatic hyperplasia (BPH) is usually associated with a metabolic disorder, hormonal dysfunction, and chronic inflammation. With the presence of at least two of these three processes, the probability of BPH developing is considered to be very high [1,2]. One of the important mechanisms of BPH is an increase of 5alpha-reductase activity and interstitial concentration of dihydrotestosterone, which stimulates the activity of interstitial cells of the gonads, smooth muscles, connective tissue and prostatic epithelium in the presence of estrogens. Metabolic syndrome can lead to atherosclerosis of the microcirculatory channel of the pelvic organs, including the prostate gland and detrusor. It can also be accompanied by an alteration of the nitric oxide-cyclic guanosine monophosphate pathway, an enhancement of RhoA-Rho-kinase contractile signaling, and an increase of afferent adrenergic impulsion level. In addition, the violation of intercellular interaction and local mechanisms of normal growth of glandular tissue of the prostate gland regulation are very important in the pathogenesis of BPH [3—5]. Some of the described processes may be accompanied not only by obstruction, but also by lower urinary tract hyperactivity symptoms (LUTS), and also by sexual dysfunction [6,7]. Patients are concerned not only with weak stream, straining, and incomplete emptying, but also with nocturia, urgency, increased nighttime and daytime frequency of urination, decreased libido and sexual desire, and erectile dysfunction [6,8,9]. In turn, the combination of LUTS and sexual dysfunction can lead to reactive depression, adversely affect the quality of life associated with health, and change the rational behavior [10,11]. Some patients refuse to continue the prescribed treatment having not received a rapid effect of monotherapy, and the development of BPH gets worse [12—14].

Considering that the prevalence of BPH among men over 50 years old is 20%—62%, and the risk of developing BPH for forty-year-old reaches 45%, we can assume that the timely correction of obstructive and hyperactivity symptoms associated with BPH is of great interest of the professional community [15,16]. Currently doctors use alpha1-adrenergic blockers (α1-AB) and 5alpha-reductase inhibitors (5-ARIs) to reduce the volume of the prostate gland. 5-ARIs in the presence of estrogens significantly reduce the concentration of 5alpha-dihydrotestosterone, and inhibit the proliferation of glandular tissue.

One of the most effective representatives of the 5-ARIs line is 1 and 2 isoenzymes 5-ARI—dutasteride. However, it reduces the quality of sperm and inhibits libido along with reducing the volume of the prostate gland. In turn, the deterioration of sexual function can lead to the appearance of reactive depression symptoms and the refusal to continue prescribed therapy [17,18].

Some researchers propose to use PDE5-I tadalafil aiming to correct the sexual function when patients taken dutasteride. Tadalafil improves an erection, increases libido, and general satisfaction with sexual function [19]. The combination of these drugs proved to be very effective for patients with obstructive symptoms, but was not successful enough to correct the hyperactivity symptoms [20,21]. In the recent literature, there is also evidence on the appropriateness and safety of prescribing antimuscarinic drugs (AM) to patients with BPH who take dutasteride. However, it is noted that the combination of dutasteride and AM can hardly bring relief to men with severe symptoms of sexual dysfunction [22,23]. As can be seen from the above, the data on attempt to correct BPH with symptoms of obstruction and hyperactivity using a combination of selective inhibitors of 5alpha- reductase and antimuscarinic medications when controlling a sexual function with tadalafil are not presented in the current urological periodicals.

While searching for the optimal combination of drugs that reduce the symptoms of obstruction and hyperactivity in men with BPH, simultaneous administration of tamsulosin, dutasteride, and imidafenacin was proposed which, in the opinion of the authors, "did not cause serious adverse reactions in patients with enlarged prostate" [24]. The mode of action of tamsulosin and dutasteride is different, so the effect of reducing obstruction increases; the purpose of this combination seems rational and justified from this point of view. However, a decrease in the sexual life quality and libido (against the background of dutasteride administration), as well as the maintenance of hyperactivity symptoms can lead to psycho-emotional lability of patients, reactive depression and refusal of further treatment. There are numerous studies, including our own, which indicated a significant decrease in medication adherence, and even a rejection of it in case of the absence of a relatively rapid positive effect [25—27]. Nevertheless, methods for rapid and safe correction symptoms of obstruction and hyperactivity and sexual dysfunction in the dutasteride treatment of BPH are not currently fully studied. When selecting medications, we relied upon data of many investigations that dutasteride may have a faster and long-lasting effect of imaginative expansion of tissues of the prostatic gland compared to other representatives of the group of selective inhibitors of 5-α, and α1-adrenergic blocking agents. This medicinal product is considered to be thoroughly studied but it has a substantial undesired effect in the form of

decrease of sexual dysfunction. At the same time, it doesn't have any observable effect on symptoms of hyperactivity. Therefore, in the number of investigations of recent vintage it is specified that the progression of BPH may be accompanied by detrusor hypoxia and abnormality of autonomous innervation, "afferent noise", which is accompanied by augmenting of symptoms of hyperactivity. This understanding is confirmed by numerous clinical observations, but attempts to control these symptoms using antimuscarinic medications are presented only by very few works. Currently, we are not able to find information about attempts of simultaneous solution of the problem of decrease of symptoms of hyperactivity and maintaining of a sexual function in the scientific databases in case of long-lasting treatment of BPH with dutasteride. Probably this attempt could cause an occurrence of the new treatment strategy in relation to similar patients and increase a patient retention to the conservative therapy of BPH.

Based on these views, literature data and results of previous studies, we hypothesized that simultaneous administration of PDE5-Is and AM in the dutasteride treatment of BPH may be an effective and safe method for correcting the symptoms of obstruction and hyperactivity, as well as preventing the development of sexual dysfunction. Therefore, the aim of this study was to assess the possibility of BPH pathological symptoms treating using combination dutasteride, tadalafil, and solifenacin at different dosages without violating sexual function in patients.

2. Patients and methods

This study was conducted from Mar 1, 2016 to Jan 10, 2017 using the principles of randomization and blinding. In total, 295 men with BPH and symptoms of obstruction and hyperactivity were taken to participate in this study. The criteria for excluding patients from the group were the following reasons: Age 50 years and older, symptoms of obstruction (8 points and higher according to the International Prostate Symptom Score [I-PSS] questionnaire [28]), symptoms of hyperactivity (8 points or higher on the Overactive Bladder Avareness Tool [OAB-AT] [29]), and the volume of the prostate gland more than 35 mL. The average sexual function score on the I-PSS scale in men included to the study was 21.6 points; in 95% of patients the function score corresponded to a range of 12–28 points. The criteria for the inclusion of patients in the group were the following reasons: Prostatic-specific antigen (PSA) level above 10 ng/mL, dementia, terminal cancer, chronic visceral diseases at the stage of prolonged decompensation, overweight or underweight, and taking drugs (alpha1-blockers, selective 5-ARIs, type 5 phosphodiesterase inhibitors, and antimuscarinic drugs) that affect prostate growth, symptoms of hyperactivity or sexual function during the last 6 months before the study. Previous to this term, 94 (31.8%) patients took alpha1-adrenergic blocking agents, 13 (4.4%) patients took selective inhibitors of 5-alpha reductase from 1 to 14 months and discontinued for different reasons not associated with the physician's recommended medication. One hundred and nineteen patients (40.3%) took various AM earlier than 6 months before the start of treatment; this intake usually did not exceed 2 months. Seventy-three (24.7%) patients pointed out the occasional administration of PDE5-I. Socio-demographic and physiological characteristics of patients from each group are presented in Table 1.

All patients were divided into three groups: A, B and C. Patients in each group received dutasteride, tadalafil, and solifenacin. The men from Group A received these drugs in a reduced dose, from Group B in a standard dose, from Group C in an increased dose. Randomization was carried out by blind random sampling using a random number generator. Each patient from these groups was examined prior to the start of this study and had a diagnosis "BPH with symptoms of obstruction and hyperactivity of the bladder". Also, every male from the sample was assigned with a random number corresponding to one of three groups (A or B, or C). A patient with an appropriate diagnosis could have been included into each of three groups, having given written informed consent to participate in the study. The sample size was determined according to the standard formula, including Z-value of the standardized normally distributed random variable. When calculating the volume, the dispersion characteristic of the studied variables, obtained in previous similar studies [6,8,11,12,14], was taken into account. Based on an acceptable sampling error and taking a cutoff level of 95% as a confidence level, we calculated that the minimum number of each of the compared groups could be 87 people. We determined the approximate percentage of patients who discontinue treatment in the combined treatment of urological diseases on the basis of the results of previously conducted similar design studies, including our own studies. Thus, by reference to data on dispersion of the symptoms under examination and on probable number of patients refusing medical treatment for any reasons, at the start of the investigation minimum 94 persons shall be in each group. At the beginning of the experiment, there were 97 people in group A, 95 people in group B, and 103 people in group C. The total number of patients was equal to 295.

In accordance with the design of this study, the time interval of 12 weeks from the start of the study was taken as the primary endpoint. In the primary endpoint, the main clinical effects were evaluated the state of sexual function and symptoms of hyperactivity with minimal, standard, and elevated doses of solifenacin and tadalafil. We chosed the minimum time as a secondary endpoint when a significant decrease in symptoms of hyperactivity was noted. Since the efficacy and safety of each drug were well studied [15–21], as well as taking into account the recommendations of the ethics committee, we did not form a placebo group in this study. A control group included patients who received standard doses of drugs recommended by manufacturers.

The design of the study is presented in Fig. 1. Patients in all three groups received dutasteride at the standard dosage (d0.5 mg/day) recommended by the manufacturer. At the same time, to study the possibility of simultaneous correction of the symptoms of hyperactivity and reduction of sexual function, Group A patients ($n = 97$) received low doses of tadalafil 2.5 mg/day and solifenacin 2.5 mg/day, in accordance with previously obtained data on the use of these drugs in flexible doses [30,31]. Group B patients ($n = 95$) received these drugs in standard doses (tadalafil 5 mg/day and solifenacin 5 mg/day). Group C patients ($n = 103$) received the elevated doses (tadalafil 20 mg/day

Table 1 Physiological and socio-demographic characteristics in men with benign prostatic hyperplasia and lower urinary tract symptoms ($n = 295$).

Variable	Group A ($n = 97$)	Group B ($n = 95$)	Group C ($n = 103$)
Age, mean (SD), year	62.3 (10.5)	66.4 (12.4)	67.3 (14.2)
Married, *n* (%)	61 (62.9)	73 (76.8)	70 (68.0)
Professionally active, *n* (%)	35 (36.1)	45 (47.4)	32 (31.1)
City areas, *n* (%)	78 (80.4)	57 (60.0)	68 (66.1)
Education, *n* (%)			
Secondary	19 (19.6)	17 (17.9)	13 (12.6)
Vocational	31 (31.9)	17 (17.9)	34 (33.0)
Higher	47 (48.4)	61 (64.2)	56 (54.4)
Experience of taking, *n* (%)			
α1-AB (monotherapy)	34 (35.0)	19 (20.0)	21 (20.4)
5-ARIs (monotherapy)	14 (14.4)	25 (26.3)	31 (30.1)
PDE5-Is (monotherapy)	9 (9.3)	14 (14.7)	18 (17.5)
AM (monotherapy)	45 (46.4)	64 (67.4)	42 (40.8)
Various of combinations	19 (19.6)	27 (28.4)	58 (56.3)
MSHQ-EjD score sum, *n* (%)	75.8 (9.1)	80.2 (11.4)	68.5 (5.9)
IIEF score sum, *n* (%)	55.2 (7.1)	51.2 (7.8)	47.3 (8.8)
Prostate volume, mL, *n* (%)	44.5 (5.5)	39.8 (7.4)	38.9 (7.7)
Level of PSA, ng/mL, mean (SD)	3.7 (2.1)	4.2 (1.4)	4.6 (1.2)
Uroflowmetry, *n* (%)			
PVR, mL	46.9 (7.6)	50.3 (12.1)	42.4 (8.5)
Q_{aver}, mL/sec	9.1 (2.7)	9.5 (2.6)	8.9 (1.7)
Q_{max}, mL/sec	13.0 (3.4)	12.3 (5.0)	12.1 (2.4)
I-PSS score sum, mean (SD)	20.4 (4.5)	21.0 (3.5)	22.1 (3.8)
OABq-AT score sum, mean (SD)	25.6 (5.4)	28.7 (3.6)	26.1 (5.2)
Diary of voiding, *n* (%)			
Daytime frequency, episodes	9.7 (1.5)	8.8 (0.7)	9.2 (1.3)
Nighttime frequency, episodes	2.3 (1.4)	2.1 (1.0)	2.4 (0.9)
Urgency, episodes	1.7 (0.7)	1.9 (0.4)	1.9 (0.5)
Incontinence, episodes	0.4 (0.4)	0.4 (0.2)	0.3 (0.2)

I-PSS, International Prostate Symptom Score; OABq-AT, Overactive Bladder Questionnaire Awareness Tool; PSA, prostatic-specific antigen; MSHQ-EjD, Men's Sexual Health Questionnaire-ejaculatory dysfunction; IIEF, the International Index of Erectile Function; PVR, post void residual urine volume; Q_{aver}, average flow rate; Q_{max}, maximum flow rate; α1-AB, alpha1-adrenergic blockers; 5-ARIs, 5alpha-reductase inhibitors; AM, antimuscarinic drugs; PDE5-Is, phosphodiesterase type 5 inhibitors; SD, standard deviation.

and solifenacin 10 mg/day) [32,33]. The safety and efficiency of tadalafil and solifenacin in reduced and elevated doses in comparison to standard doses have been previously proven.

At the start and finish of the study, all patients was underwent ultrasound examination of the prostate gland. They had a study level of prostatic-specific antigen (PSA), and uroflowmetry (UF) was performed. Also, all men were interviewed using questionnaires the International Prostate Symptom Score (I-PSS), Overactive Bladder Awareness Tool (OAB-AT), Men's Sexual Health Questionnaire (MSHQ-EjD) and International Index of Erectile Function (IIEF). Questionnaires were repeated every 2 weeks using MSHQ-EjD, IIEF, OABq-AT, I-PSS and UF; patients filled voiding diary on a daily basis [34,35].

The I-PSS questionnaire is an international score for assessing symptoms of prostate disease. During the survey, patients were asked to answer each of the seven closed and one open question; the result was interpreted as follows: From 8 to 19 points—moderate severity, more than 20 points—severe degree of violations. UF was carried out in a standard configuration with the determination of the average volumetric and average maximum speed of urination, delay at the start, and the total time of urination. In the urination diary, which was filled in by the patients on a daily basis throughout the study, the patient had to reflect the time of each urination, the volume of urine excreted, episodes of urination urgency, episodes of urinary incontinence, and information about drinking balance. The information about taking medications and side effects was additionally entered in the diary voiding.

The international OAB-questionnaire (OAB-q) is used for the differential diagnosis of urinary incontinence types and for evaluating the effectiveness of treatment. It contains questions to identify urgent urinary incontinence, stress urinary incontinence, nocturia, and other pathological symptoms of the lower urinary tract. The patient had to fill it out on his own, noting the severity of certain symptoms. The 15-question IIEF contains the domains: Erectile function (Q1,2,3,4,5,15), orgasmic function (Q9,10), sexual desire (Q11,12), intercourse satisfaction (Q6,7,8) and overall satisfaction (Q13,14). Patients with low IEEF scores

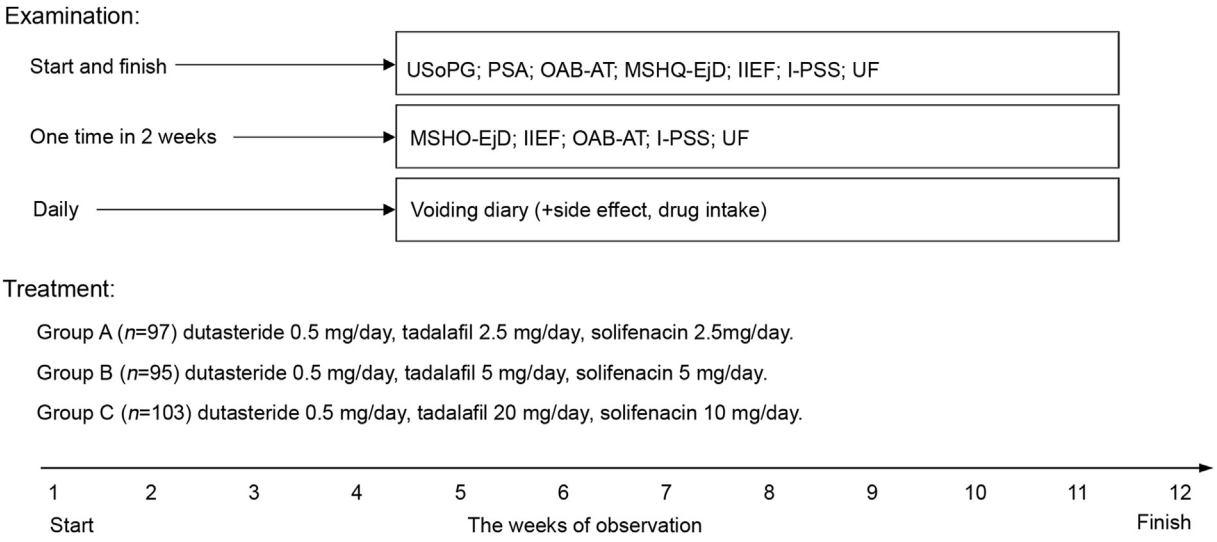

Figure 1 Study design ($n = 295$). USoPG, ultrasound examination of the prostate gland; PSA, prostatic-specific antigen; I-PSS, International Prostate Symptom Score; OAB-AT, Overactive Bladder Awareness Tool; MSHQ-EjD, Men's Sexual Health Questionnaire Ejaculatory Dysfunction; IIEF, the International Index of Erectile Function; UF, uroflowmetry.

(<14 out of 30) in domain A (erectile function) usually need correction and the use of special medicines. The MSHQ-EjD contains the erection scale (three items), ejaculation scale (seven items), and sexual satisfaction scale (six items). It is aimed to study the same functions, but is more concise, and has slightly different wording of questions, which may be important in the study of sexual function in patients with cognitive impairment.

The statistical processing of the data was also carried out using the standard analysis package Statistics 6.0 (StatSoft Inc.StatSoft Inc.,Tulsa, Oklahoma, USA). Evaluation of the variables' differences in different groups and within one group at different stages of treatment was carried out using ANOVAs; the Bonferroni correction was used to correct type 1 errors. Correlation between the curves describing the change of mean population values was performed using the Spearman coefficient. The reliability of the differences between the mean values of the variables in the groups was considered sufficient for $p \leq 0.05$. Each set of variables for a particular participant was assigned a random sequence number using a random number generator.

During the study 29 (9.8%) patients from all groups were withdrawn. Seven (2.4%) patients of Group A were discontinued (6 [2.0%]—due to lack of expected effect; 1 [0.3%]—without any explanation). Seven patients from Group B also refused to continue the study (5 [1.7%]—due to intolerable side effects; 2 [0.7%]—due to exacerbation of chronic diseases). Fifteen patients were withdrawn from Group C (10 [3.4%]—due to intolerable side effects; 3 [1.0%]—due to a lack of expected effect; 1 [0.3%]—due to an exacerbation of a chronic disease; and 1 [0.3%]—for an unknown reason). The most frequent side effects were dry mouth (7 [2.4%]), nausea (3 [1.0%]), headache (3 [1.0%]), and pain in the heart (1 [0.3%]). The number of patients in the primary and secondary endpoint, taking into account the "losses", turned out to be sufficient for the correct comparison of variables.

In total, 61 (20.7%) patients experienced side effects. Dry mouth was noted in 28 (9.5%) cases; 25 (8.5%) patients had headache and dizziness; 8 (2.7%) had other symptoms. Side effects were short-term, disappeared on their own, and did not lead to the refusal of treatment in 46 (15.6%) patients.

Conducting this study, we followed the ethical standards recommended by the Helsinki Declaration, as amended in Seoul (decision of the Ethics Committee of FEFU M-0173.18). Prior to the study, each patient signed a written informed consent. Study design was approved by the local ethics committee.

3. Results

Comparison of the initial average values of variables between groups did not reveal any significant differences between them. The Student's *t*-criteria when comparing the initial average I-PSS values were: $p_{A/B} = 0.071$, $p_{A/C} = 0.077$, $p_{B/C} = 0.069$; UF: $p_{A/B} = 0.091$, $p_{A/C} = 0.087$, $p_{B/C} = 0.089$; OAB-q: $p_{A/B} = 0.083$, $p_{A/C} = 0.091$, $p_{B/C} = 0.088$; Voiding diaries: $p_{A/B} = 0.075$, $p_{A/C} = 0.079$, $p_{B/C} = 0.064$; MSHQ: $p_{A/B} = 0.065$, $p_{A/C} = 0.072$, $p_{B/C} = 0.051$; IIEF: $p_{A/B} = 0.084$, $p_{A/C} = 0.057$, $p_{B/C} = 0.066$.

The Fig. 2 presents the results of comparing the severity of the symptoms of obstruction in men with BPH from different groups before and after the course of treatment according to I-PSS and UF data. There were no significant differences between the assessment of symptoms at the start and after the study in Group A.

In patients from Group B significantly decreased daytime frequent urination (from 2.6 to 1.3 episodes, $p < 0.05$), urgency (from 2.9 to 1.4 episodes, $p < 0.05$), nocturia (from

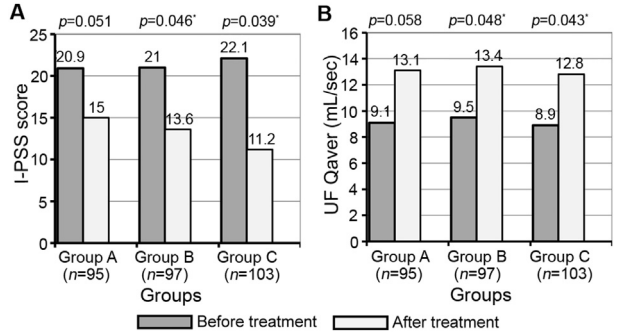

Figure 2 Symptoms of obstruction lower urinary tract in patients with benign prostate hyperplasia before and after treatment ($n = 295$). (A) I-PSS before/after treatment, total score; (B) UF before/after treatment, Qaver, mL/sec. I-PSS, International Prostate Symptom Score; UF, uroflowmetry. * Differences are statistically significant.

2.7 to 1.5 episodes, $p < 0.05$). In patients from Group C significantly decreased the assessment of symptoms of obstruction: from 22.1 to 11.2 point. The average volume flow rate of urine after treatment significantly increased in Group C (12.8 *vs.* 8.9 mL/s, $p < 0.05$) and in Group B (13.4 *vs.* 9.5 mL/s, $p < 0.05$). The results of hyperactivity symptoms are presented in Fig. 3. The assessment of symptoms of hyperactivity in groups B and C after treatment became significantly lower (Group B: 17.6 *vs.* 28.7 points, $p \leq 0.05$; Group C: 15.2 *vs.* 26.1 points, $p \leq 0.05$). The number of episodes of urgency and nighttime urination significantly decreased after treatment in both these groups, but the number of episodes of urination during the day decreased reliably only in Group C (5.4 *vs.* 9.2 episodes, $p \leq 0.05$).

The assessment of sexual function increased in patients from Group C (according to IIEF—60.7 *vs.* 47.8 points, $p \leq 0.05$; according to MSHQ-EjD—84.8 *vs.* 68.5, $p \leq 0.05$).

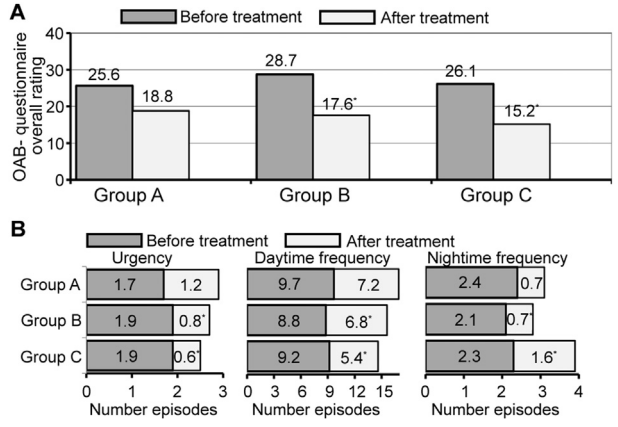

Figure 3 Symptoms of hyperactive lower urinary tract in patients with benign prostate hyperplasia before and after treatment ($n = 295$; Group A: $n = 95$; Group B: $n = 97$; Group C: $n = 103$). (A) OAB- questionnaire, overall rating; (B) Voiding diaries, number episodes. OAB, overactive bladder. * Differences are statistically significant.

The largest increase in the scores was noted in the domain's "erection" and "satisfaction". The assessment of the sexual function did not change significantly in groups A and B according (Fig. 4).

The reverse development of symptoms of obstruction and hyperactivity occurred in different groups at different speeds. A significant decrease of hyperactivity symptoms (OABq-AT) in Group C occurred after 4 weeks of follow-up (17.5 *vs.* 26.1, $p \leq 0.05$); the assessment of these symptoms in the group was 15.2 points at the end of the study. By the end of the treatment, the assessment of hyperactivity symptoms was also significantly lower than the baseline ($p \leq 0.05$) in Group B, but the decrease in scores was more gradual and the differences were evident only at the end of the study. The average numbers of points in Group C patients also decreased by the end of treatment, but the differences were unreliable. The decrease in the average number of points according to the IPSS questionnaire occurred synchronously in all three observed groups. However, significant differences between the assessments at the beginning and at the end of the study were found only in Group C, mainly due to the reduction of the hyperactivity symptoms. Correlation between the curves describing the change in the number of points in all three groups turned out to be high ($r_{A/B} = 0.90$, $p < 0.05$; $r_{B/C} = 0.89$, $p < 0.01$; $r_{A/C} = 0.96$, $p < 0.05$). A significant increase in the total index of sexual function in Group C was detected after 8 weeks of follow-up (81.7 *vs.* 68.5, $p < 0.05$).

4. Discussion

The findings allow us to suggest that simultaneous administration of tadalafil, dutasteride and solifenacin is an acceptable combination for the treatment of BPH with symptoms of bladder hyperactivity. Twenty-seven percent of patients from all groups reported about side effects, but only 5.1% of men had severe side effects and were discontinued; otherwise the symptoms were short-term and there was no need for additional therapy. The most frequent side effects were dry mouth (9.5%), headache and dizziness (8.5%). Side effects were noted in 26 (8.8%) patients from Group A, 23 (7.8%) patients from Group B, and 12 (4.1%) patients from Group C. The percentage of side effects when taking a combination of drugs did not exceed the sum of the percentages of side effects which occur in case of each single drug administration [19,21,23]. This also applies to the percentage of patients with side effects from Group C who took higher doses of tadalafil and solifenacin [33,36,37]. Thus, our data support the opinion of most researchers that increasing the dose of solifenacin and tadalafil, as a rule, does not lead to a significant increase in the number of side effects.

However, the main purpose of this study was to investigate the possibilities of rapidly reducing hyperactivity symptoms and preserving sexual function during the dutasteride treatment of BPH. We managed to establish that in patients who previously had an unsatisfactory experience of treatment, the appointment of standard doses of tadalafil, dutasteride and solifenacin ensures a smooth, gradual decrease of the hyperactivity symptoms. A significant reduction of most of the hyperactivity symptoms

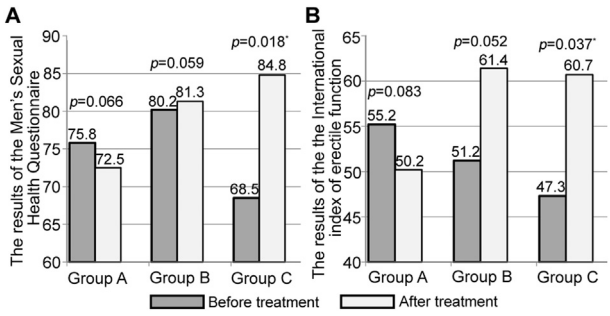

Figure 4 Symptoms of sexual dysfunction in patients with benign prostate hyperplasia before and after treatment ($n = 295$; Group A: $n = 95$; Group B: $n = 97$; Group C: $n = 103$). (A) The results according to the Men's Sexual Health Questionnaire; (B) The results according to the International index of erectile function. * Differences are statistically significant.

was noted at the 6–8 weeks' follow-up. The data obtained are similar to the results of other studies [20,21,24], but allow us to suggest that a 2-month delay in the effect, despite maintaining a normal sexual function, may adversely affect the motivation of health behaviors and medication adherence.

The detrusor hyperactivity symptoms significantly decreased among patients who received increased doses of tadalafil and solifenacin (Group C) at the 4th week of observation already. This is a very important result, in our opinion, that the rapid reverse development of obsessive, irritating hyperactivity symptoms, such as nocturia, urgency, and high nighttime and daytime frequency of urination, can have a favorable psychological effect and significantly increase medication adherence. In addition, this group was the only one in which patients noted improvement in sexual function (except for the ejaculation domain), and significant differences in MSHQ-EjD were revealed at the 8th week of follow-up. However, we could not confirm a significant increase in sexual function in this group according to IIEF.

Double control of the results when using different instruments (questionnaires) confirms their reliability [17,18]. The results of a study of changes in the symptoms of hyperactivity and obstruction using different tools have also been consistent. Thus, data on the level of urethral obstruction obtained using the I-PSS were fully confirmed by the results of UF: At the end of the study, both methods showed a statistically significant decrease in pathological symptoms in groups B and C, and their moderate (not statistically significant) decreases in Group A. The explanation of the fact that with equal doses of dutasteride the result was not the same may be attributed to the additional action of other drugs, in particular, by an improvement in detrusor microcirculation while taking standard and increased doses of solifenacin. We obtained the highest level of correlation between the results of the study of hyperactivity symptoms using OAB-q and diaries of urination, which was quite rationally explainable, given the closeness of most of the questions used by both tools. However, if OAB-q allowed us to assess the functional state of the LUT from the point of view of the subjective perception of the patient, then diaries of urination allowed us to formally register pathological symptoms in real time. The identity of the data obtained by these tools allowed us to obtain additional confirmation of the changes that occurred under the influence of treatment.

The tendency to decrease the symptoms of obstruction corresponded to the effectiveness of dutasteride which was described in the recent literature. In particular, there is evidence of a decrease in the size of the prostate gland and a reliable decrease in obstruction after the 6–9 month of regular intake of this drug [17,38]. We did not set out to further investigation of the effectiveness of this drug in our short-term study, which was well confirmed by numerous trials. However, we managed to find out that the simultaneous administration of tadalafil, dutasteride and solifenacin in elevated doses leads, in addition to the expected gradual decrease of the LUTS of obstruction, to a rapid reduction in hyperactivity and a rise in sexual function in patients.

Reception of solifenacin in a low dose (Group A) did not lead to a significant decrease in the symptoms of hyperactivity even at the end of the study. The average dose of this drug made it possible to achieve the desired result by 10–12 weeks of the study (Group B). At the same time, when taking an increased dose of solifenacin (Group C), a significant decrease in the symptoms of hyperactivity was noted by the end of the first month of treatment. Such a result is in good agreement with earlier conducted similar researches, including by our research team, and is likely to positively affect the patient's behavioral strategy with regard to adherence to treatment and the exact execution of doctor's prescriptions. Taking the minimum and standard doses of tadalafil allows to maintain a normal level of sexual function (in Group A, a statistically insignificant deterioration was noted). If patients take an increased dose of tadalafil, then despite taking dutasteride, their sexual function significantly improves by the end of treatment (Group C). Taking a standard dose of dutasteride in all three groups gave the expected effect by the end of the observation: The symptoms of obstruction decreased moderately, which was reflected in the test results. Thus, the main result of the study was the confirmation of the assumption made in the working hypothesis that taking an increased dose of solifenacin and a standard dose of tadalafil can avoid the negative effect of dutasteride on sexual function and reduce the symptoms of bladder hyperactivity.

Evaluation of the main clinical effects at the primary endpoint (12 weeks from the start of treatment) revealed that Group A patients did not show a significant decrease in symptoms of obstruction and hyperactivity, and sexual function remained unchanged. In Group B patients, a significant decrease in obstruction and hyperactivity was noted, and no change in the state of sexual function was detected. In Group C patients, a significant decrease in symptoms of obstruction and hyperactivity was accompanied by an improvement in sexual function, including an increase in libido and erectile component. When evaluating the secondary endpoint, it was found that the symptoms of hyperactivity decreased most rapidly in patients of Group C who took an increased dose of solifenacin (without increasing the number of side effects).

Thus, when developing the design of our study we relied upon the idea that α1-adrenergic blocking agents and selective inhibitors of 5-α reductase were medicines with proven efficiency, but the long period was required for achievement of the therapeutic result. An additional point is that their intake inhibits a sexual function and does not ease the symptoms of hyperactivity that follow often BPH. In turns this may lead to weak medication adherence.

In light of this we have assigned the task: To give a course of combination treatment aimed at quick reduction of annoying symptoms of hyperactivity and maintenance of normal sexual function of patients concurrently with institution of dutasteride. As a result of the study carried out we found that in the course of the treatment of BPH with dutasteride, simultaneous application of standard doses of tadalafil allowed maintaining a normal sexual function in the majority of patients, and the application of high doses of solifenacin resulted in positive decrease of symptoms of hyperactivity by the end of the first month of observation. Moreover, the number of undesired effects is not increased as compared with their usual level; that is, there is no cumulative effect in respect of undesired effects.

The similar combination of medications was used in the clinical study for the first time ever. The successful result of observation allows to suggest that similar treatment strategy may be considered to be effective and safe in respect of patients with BPH accompanied by symptoms of obstruction and hyperactivity and has important advantage over existing strategies. From our point of view, concurrent use of three medications of different pharmacological classes may be a more successful treatment strategy as compared with surviving ones and be useful in clinical practice.

This study has some limitations. We did not study the effect of the combination on the basis of the severity of LUTS and the violation of sexual dysfunction. We also did not evaluate the long-term results of the study. The study of the possibility of long-term correction of sexual dysfunction and symptoms of hyperactivity may be the subject of further observations that develop the obtained result. The use of a combination of three drugs probably has a limitation in elderly patients, as well as men with a high index of comorbidity. A direct study of the correlation between the efficacy of the combination of tadalafil, dutasteride and solifenacin, and medication adherence was also not included in the design of this study. These questions require further studying. In addition, we consider it interesting and promising area of research to compare the effectiveness of pharmacological and surgical methods of treating BHP with symptoms of obstruction and hyperactivity, as well as a combination of these methods to optimize the treatment and rehabilitation algorithm of such patients. The total duration of observation over efficiency and safety of use of the proposed treatment strategy with respect to possible remote outcomes and refusal of the part of patients from the treatment shall make up not less than 6—12 months and shall be carried out for more patients.

Nevertheless, the results make it possible to recommend this combination of drugs for the treatment of BPH with symptoms of bladder hyperactivity without increasing the risk of sexual dysfunction.

5. Conclusion

Simultaneous administration of dutasteride, tadalafil, and solifenacin in standard doses for 3 months is accompanied by a gradual decrease of the obstruction symptoms and a significant decrease symptom of hyperactivity within 6—8 weeks, without changing sexual function. Simultaneous administration of elevated doses of these drugs can reliably reduce the symptoms of hyperactivity within the first 4 weeks from the start of treatment, and obstructive symptoms within 12 weeks without increasing side effects. The assessment of sexual function in patients is significantly increased. Simultaneous administration of dutasteride, tadalafil and solifenacin in reduced doses does not lead to significant changes in the function of lower urinary tract. The use of a combination of standard doses of dutasteride, solifenacin, and tadalafil for 3 months in patients with BPH can reliably reduce the symptoms of obstruction and hyperactivity of the bladder while maintaining sexual function and does not lead to an increase in the frequency of side symptoms. At the same time, taking an increased dose of solifenacin can reliably reduce the symptoms of hyperactivity by the end of 1 month of administration, which can be of great importance for patient adherence to treatment.

Author contributions

Study design: Kirill Kosilov, Vladimir Kuznetsov.
Data acquisition: Irina Kuzina.
Data analysis: Irina Kuzina, Ekaterina Fedorishcheva, Kirill Kosilov.
Drafting of manuscript: Kirill Kosilov.
Critical revision of the manuscript: Olga Barabash.

Conflicts of interest

The authors declare no conflict of interest.

References

[1] Vignozzi L, Rastrelli G, Corona G, Gacci M, Forti G, Maggi M. Benign prostatic hyperplasia: a new metabolic disease? J Endocrinol Invest 2014;37:313—22.
[2] Aaron LT, Franco OE, Hayward SW. Review of prostate anatomy and embryology and the etiology of benign prostatic hyperplasia. Urol Clin North Am 2016;43:279—88.
[3] Gacci M, Eardley I, Giuliano F, Hatzichristou D, Kaplan SA, Maggi M, et al. Critical analysis of the relationship between sexual dysfunctions and lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol 2011;60:809—25.
[4] Shih HJ, Huang CJ, Lin JA, Kao MC, Fan YC, Tsai PS. Hyperlipidemia is associated with an increased risk of clinical benign prostatic hyperplasia. Prostate 2018;78:113—20.
[5] Kanai A, Andersson KE. Bladder afferent signaling: recent findings. J Urol 2010;183:1288—95.
[6] Rosen RC. Assessment of sexual dysfunction in patients with benign prostatic hyperplasia. BJU Int 2006;97:29—33.
[7] Spångberg A, Dahlgren H. [Benign prostatic hyperplasia with bladder outflow obstruction. A systematic review]. Lakartidningen 2013;110:682—5 [Article in Swedish].

[8] Hanuš T, Zámečník L, Doležal T, Karmazínová Z. Occurrence of overactive bladder in patients with benign prostatic hyperplasia in the Czech Republic. Urol Int 2011;86:407–13.
[9] Wang Y, Bao Y, Liu J, Duan L, Cui Y. Tadalafil 5 mg once daily improves lower urinary tract symptoms and erectile dysfunction: a systematic review and meta-analysis. Low Urin Tract Symptoms 2018;10:84–92.
[10] Pietrzyk B, Olszanecka-Glinianowicz M, Owczarek A, Gabryelewicz T, Almgren-Rachtan A, Prajsner A, et al. Depressive symptoms in patients diagnosed with benign prostatic hyperplasia. Int Urol Nephrol 2015;47:431–40.
[11] Jeong WS, Choi HY, Nam JW, Kim SA, Choi BY, Moon HS, et al. Men with severe lower urinary tract symptoms are at increased risk of depression. Int Neurourol J 2015;19:286–92.
[12] Nichol MB, Knight TK, Wu J, Barron R, Penson DF. Evaluating use patterns of and adherence to medications for benign prostatic hyperplasia. J Urol 2009;181:2214–21.
[13] Kosilov K, Loparev S, Kuzina I, Shakirova O, Zhuravskaya N, Lobodenko A. The effective tool for self-assessment of adherence to treatment in patients with benign prostatic obstruction and overactive bladder symptoms. Aging Male 2017;20:39–44.
[14] Kosilov K, Loparev S, Kuzina I, Shakirova O, Zhuravskaya N, Lobodenko A. Long-term adherence to antimuscarinic drugs when treating overactive bladder in the older: subjective reason and objective factors. Investig Clin Urol 2017;58:109–16.
[15] Egan KB. The epidemiology of benign prostatic hyperplasia associated with lower urinary tract symptoms: prevalence and incident rates. Urol Clin North Am 2016;43:289–97.
[16] Chughtai B, Forde JC, Thomas DD, Laor L, Hossack T, Woo HH, et al. Benign prostatic hyperplasia. Nat Rev Dis Prim 2016;2:16031. https://doi.org/10.1038/nrdp.2016.31.
[17] Drobnis EZ, Nangia AK. 5α-Reductase inhibitors (5ARIs) and male reproduction. Adv Exp Med Biol 2017;1034:59–61.
[18] Chung BH, Roehrborn CG, Siami P, Major-Walker K, Morrill BB, Wilson TH, et al. Efficacy and safety of dutasteride, tamsulosin and their combination in a subpopulation of the CombAT study: 2-year results in Asian men with moderate-to-severe BPH. Prostate Cancer Prostatic Dis 2009;12:152–9.
[19] Gacci M, Andersson KE, Chapple C, Maggi M, Mirone V, Oelke M, et al. Latest evidence on the use of phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. Eur Urol 2016;70:124–33.
[20] Schauer I, Madersbacher S. Medical treatment of lower urinary tract symptoms/benign prostatic hyperplasia: anything new in 2015. Curr Opin Urol 2015;25:6–11.
[21] Oelke M, Martinelli E. [Pharmacological treatment of benign prostatic hyperplasia]. Urologe 2016;55:81–94 [Article in German].
[22] Chung DE, Te AE, Staskin DR, Kaplan SA. Efficacy and safety of tolterodine extended release and dutasteride in male overactive bladder patients with prostates >30 g. Urology 2010;75:1144–8.
[23] Auffenberg GB, Helfand BT, McVary KT. Established medical therapy for benign prostatic hyperplasia. Urol Clin North Am 2009;36:443–59.
[24] Yamanishi T, Asakura H, Seki N, Tokunaga S. Efficacy and safety of combination therapy with tamsulosin, dutasteride and imidafenacin for the management of overactive bladder symptoms associated with benign prostatic hyperplasia: a multicenter, randomized, open-label, controlled trial. Int J Urol 2017;24:525–31.
[25] Felicilda-Reynaldo RF. A review of anticholinergic medications for overactive bladder symptoms. Medsurg Nurs 2013;22:119–23.
[26] Kosilov K, Loparev S, Kuzina I, Shakirova O, Zhuravskaya N, Lobodenko A. Treatment compliance of working persons to high-dose antimuscarinic therapies: a randomized trial. Ther Adv Urol 2016;8:239–48.
[27] Kosilov K, Loparev S, Ivanovskaya M, Kosilova L. Additional correction of OAB symptoms by two anti-muscarinics for men over 50 years old with residual symptoms of moderate prostatic obstruction after treatment with Tamsulosin. Aging Male 2015;18:44–8.
[28] Ruffion A, Marionneau N, Taïeb C, Perrin P. Comparison of the response to I-PSS according to the mode of administration of the questionnaire: by the doctor or self-assessment by the patient. Prog Urol 2005;15:1080–4.
[29] Coyne KS, Margolis MK, Bavendam T, Roberts R, Elinoff V. Validation of a 3-item OAB awareness tool. Int J Clin Pract 2011;65:219–24.
[30] Kosilov K, Loparev S, Ivanovskaya M, Kosilova L. Comparative effectiveness of combined low- and standard-dose trospium and solifenacin for moderate overactive bladder symptoms in elderly men and women. Urol Int 2014;93:470–3.
[31] Chen H, Wang F, Yu Z, Zhang Y, Liu C, Dai S, et al. Efficacy of daily low-dose tadalafil for treating overactive bladder: results of a randomized, double-blind, placebo-controlled trial. Urology 2017;100:59–64.
[32] Kosilov K, Kuzina I, Kuznetsov V, Gainullina Y, Kosilova L, Prokofyeva A, et al. Cognitive functions and health-related quality of life in men with benign prostatic hyperplasia and symptoms of overactive bladder when treated with a combination of tamsulosin and solifenacin in a higher dosage. Aging Male 2018;21:121–9.
[33] Ricardi U, Gontero P, Ciammella P, Badellino S, Valentino F, Munoz F, et al. Efficacy and safety of tadalafil 20 mg on demand *vs.* tadalafil 5 mg once-a-day in the treatment of post-radiotherapy erectile dysfunction in prostate cancer men: a randomized phase II trial. J Sex Med 2010;7:2851–9.
[34] Singh G, Lucas M, Dolan L, Knight S, Ramage C, Hobson Ph. Minimum standards for urodynamic practice in the UK. Neurol Urodyn 2010;29:1365–72.
[35] Parsons M, Amundsen CL, Cardozo L, Vella M, Webster GD, Coats AC. Bladder diary patterns in detrusor overactivity and urodynamic stress incontinence. Neurourol Urodyn 2007;26:800–6.
[36] Chun JY, Song M, Han JY, Na S, Hong B, Choo MS. Clinical factors associated with dose escalation of solifenacin for the treatment of overactive bladder in real life practice. Int Neurourol J 2014;18:23–30.
[37] Kosilov KV, Loparev SA, Ivanovskaya MA, Kosilova LV. Comparative effectiveness of combined high-dosed trospium and solifenacin for severe OAB symptoms in age-related aspect. Urol Int 2014;93:470–3.
[38] Homma Y, Gotoh M, Kawauchi A, Kojima Y, Masumori N, Nagai A, et al. Clinical guidelines for male lower urinary tract symptoms and benign prostatic hyperplasia. Int J Urol 2017;24:716–29.