Research Article

Improvement of the symptoms of lower urinary tract and sexual dysfunction with tadalafl and solifenacin after the treatment of benign prostatic hyperplasia with dutasteride

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ABSTRACT

Background: The aim of this research is to study the influence of simultaneous taking of tadalafl and solifenacin in standard and double dosage on the lower urinary tract symptoms (LUTS) and sexual dysfunction in men with benign prostatic hyperplasia after the course of dutasteride.

Materials and methods: The research included 326 patients older than 50 years with benign prostatic hyperplasia coupled with LUTS and sexual dysfunction having undergone the course of treatment with dutasteride. After random division into three groups, patients from the Group A (n = 107) got tadalafl 5 mg/d as monotherapy, from the Group B (n = 107) got tadalafl 5 mg/d and solifenacin 10 mg/d, and from the Group C (n = 112) got tadalafl 5 mg/d and solifenacin 20 mg/d. The duration of treatment was 12 weeks. The rating of sexual function was made with the questionnaires International Index of Erectile Function and other.

Results: The results of rating of sexual function with the questionnaires MSHQ-EjD and International Index of Erectile Function correlated among themselves. According to MSHQ-EjD, overall rating of the sexual function increased in each of the three groups (A: 67.9 (12.4)/91.5 (10.4), B: 72.4 (14.5)/102.6 (16.9), P ≤ 0.05; C: 76.6 (16.3)/109.6 (15.6), P ≤ 0.05). The level of hyperactivity symptoms decreased in Groups B and C (B: urgency −2.9 (0.7)/1.1 (0.6), P ≤ 0.05; nocturia 2.7 (1.0)/0.7 (0.5), P ≤ 0.05; C: urgency −2.5 (0.5)/0.8 (0.6), P ≤ 0.05; nocturia −2.8 (0.6)/1.0 (0.5), P ≤ 0.05), and it did not change in the Group A.

Conclusions: The use of tadalafl as monotherapy significantly improves the sexual function but does not affect overactive bladder symptoms. The combination therapy of tadalafl and solifenacin leads to dramatic improvement of sexual function and reversibility of detrusor hyperactivity symptoms.

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1. Introduction

The benign prostatic hyperplasia (BPH) is quite common in national populations and occurs in 20–62% of men older than 50 years in the United States, Europe, China, Russia, Japan, and in countries of South Africa.1–3 The risk of developing BPH in the future for a 46-year-old man is more than 45%.4,5 BPH is characterized by a range of symptoms including weak stream, straining, incomplete emptying; but many authors report nocturia, urgency, a rise of daytime and nighttime frequency of urination, and urge incontinence and sexual dysfunction in men with BPH.6,7 The sexual dysfunction as well as nocturia, urgency, and a rise of nighttime frequency of urination are taken hard by patients, they often lead to depressions, have negative impact on the quality of life related to health.8,9

Modern means of treating BPH with LUTS are represented by α1-adrenergic blockers and 5α-reductase inhibitors (5-ARIs),
recently they have been supplemented with phosphodiesterase Type 5 inhibitors (PDE5-Is) and antimuscarinic drugs. Medications of each class are clinically proven, but still have some insufficiencies and side effects.16,17 The increased pharmacotherapy effectiveness for BPH with lower urinary tract symptoms (LUTS) is usually related to the search for optimal algorithms of combined impact of drugs of different classes on pathological processes. The combination of drugs of different pharmacological classes that vary in medication actions enables to improve the effectiveness and to increase the advantageous effect rate. Meanwhile, the timing of onset of the positive clinical effect is an important criterion of successful treatment in general because of poor adherence both in monotherapy and in combination therapy in men with BPH with LUTS.15-18 In such a situation, in addition to the influence on behavior patterns and patients’ motivation, it makes sense to combine drugs and to calculate dosage to improve the timing and effectiveness of clinical benefit response and to exclude the increase of side effects.

5-ARI Type 1 and 2 dutasteride reduces the concentration of 5α-dihydrotestosterone and is widely used in clinical practice to reduce the volume of significantly enlarged prostate gland.19,20 However, the gland volume reduction is often followed by suppression of sexual function and semen quality, but symptoms of obstruction especially of hyperactivity decreases slowly and gradually.19,20 Often after the course of dutasteride, the reduction of gland volume and the restoration of functional status of lower urinary tract are recorded; but as the storage symptoms and sexual dysfunction still remain, a patient refuses medical treatment.

Thus, it seems suitable to search for opportunities of quick and effective treatment of mentioned disorders using the combination of PDE5-Is and modern antimuscarinic drugs. PDE5-I tadalafl improves the oxygenation of LUT, decreases the activity of afferent innervations, and unstraited muscle tonus. But, its main clinical effect is a restoration of erectile function and libido.20 Therefore, solifenacin is a competitive M-cholinoreceptor inhibitor, mainly of M3-subtype. Solifenacin blocks the action of acetylcholine that suppresses overafferentation and leads to reversibility of detrusor hyperactivity symptoms.21,22

There are few and contradicting references to the usage of tadalafl and solifenacin for the purpose of the restoration sexual function and storage symptoms in men with BPH with LUTS after taking dutasteride. Nevertheless, the problem of effectiveness of the restoration of sexual function and LUTS after the treatment with dutasteride remains unsolved nowadays.

With reference to the above, a research objective is to study an opportunity of quick and safe treatment of sexual function and also storage symptoms and voiding symptoms of lower urinary tract in men who underwent treatment with dutasteride using the combination of tadalafl and solifenacin.

2. Patients and methods

The research was performed at Far East Federal University and City Outpatient Clinic No. 3 from January 3, 2016 to January 1, 2018. The research included 326 men older than 50 years, who underwent 3- to 6-month course of monotherapy with dutasteride, and complained of sexual dysfunction coupled with symptoms of obstruction and hyperactivity of lower urinary tract. Entry criteria were mild symptoms of obstruction [8–19 on the International Prostate Symptom Score (I-PSS)], symptoms of detrusor hyperactivity [more than 8 on the Overactive Bladder Questionnaire—awareness tool (OABq-AT)] sexual dysfunction according to Men’s Sexual Health Questionnaire—ejaculatory dysfunction (MSHQ-EjD), and the international index of erectile function (IIEF). Exclusion criteria were malignant changes in prostate gland tissue, the volume of the prostate gland more than 45 ml, the level of prostate-specific antigen (PSA) more than 10 ng/ml, chronic visceral organs disease at the decapsulation stage, and also taking solifenacin and/or tadalafl together with dutasteride, or in under 6 months before the research.

All patients were divided randomly into three groups. The Group A (n = 107) included men who were prescribed tadalafl 5 mg/d as monotherapy, the Group B (n = 107)—tadalafl 5 mg/d and solifenacin 10 mg/d, and the Group C (n = 112) tadalafl 5 mg/d and solifenacin 20 mg/d. Taking into account an approximate expected time of the onset of the effect, the duration of observation was 3 months.15,21-23 Basic sociodemographic and physiological characteristics of patients are represented in Table 1. Statistically significant diversity of variables, when comparing average values, was not detected.

At the beginning of the research, to prove the diagnosis and to determine the level of sexual dysfunction and disorder of lower urinary tract, an ultrasound test of prostate gland was performed to all patients.24,25 Uroflowmetry,26 PSA test, and survey according to MSHQ-EjD, IIEF,27 as well as I-PSS28 and OABq-AT.29 Besides, during the research, all patients filled in diary voiding daily to monitor diversity of variables,30 and also once every 2 weeks they filled in the questionnaires MSHQ-EjD, IIEF, I-PSS, and OABq-AT. At the end of therapy, all patients were examined similar to that at the start. The questionnaires MSHQ-EjD and IIEF partially duplicate each other, but the first one describes libido, general sexual satisfaction more detailed and enables to assess the quality of sexual life in its entirety, meanwhile the second one pays more attention to erectile dysfunction and orgasm. On this basis, the study considered simultaneous use of questionnaires relevant and enabling to assess disorders of sexual function more objectively, and considered it not burdensome for patients.

The obtained data were processed with standard package of statistical analysis Statistics 6.0 (StatSoft Inc.,Tulsa, Oklahoma, USA). To compare the differences between average values among the groups and in one group at the different stages of therapy, this study used the one-tailed dispersion test (analysis of variance) and the Tukey–Kramer method. Spearman ρ was used to study the curves correlation, describing changes of variables over time. The level of statistical differences P ≤ 0.05 considered to be sufficient to reject the null hypothesis. Data received for statistical processing were depersonalized by assigning each case a random number.

Thirty-one people discontinued participation in the study (9.5%), 14 people dropped out of the Group A [10 (3.1%) of them because of lack of positive effect, 2 (0.6%) because of side effects (vertigo, vision disorder), and 2 (0.6%) without giving any reason]. Nine people (2.7%) left the Group B [5 of them (1.5%) because of lack of expected effect, 3 (0.9%) because of undesired side effects (dry mouth), and 1 because of recurrence of chronic diseases]. Lastly, 10 people dropped out of the Group C [7 of them (2.4%) because of unbearable side effects and 3 (0.3%) without giving any reason]. Therefore, in total, 12 people dropped out because of undesired side effects and it amounts to 3.6%. Moreover, during the therapy, 48 people (14.7%) complained of various side effects; however, they were short-term and did not affect patients’ behavior.

During the research, ethical standards, passed in the Declaration of Helsinki with additions passed in Seoul, were fully accomplished. Each participant certified the study personnel of his informed consent to participate in the experiment. The local ethics committee approves the design of the study.

3. Result

Table 2 provides evaluations of various domains MSHQ-EjD and IIEF in patients taken tadalafl as monotherapy, or coupled with
MSHQ-EjD data. Composite scores, received from the evaluation according to the questionnaire IIEF correlate with erectile function in patients. The results of sexual function therapy they were at a high level and showed a normal initial state (values of overall satisfaction and libido did not differ from the initial ones). Evaluation of orgasmic function, satisfaction with intercourse got significantly higher after the therapy. The tendency of reversibility of hyperactivity symptoms in Groups B and C is also confirmed by OABq-AT data. Average number of obtained scores of urgency decreased in the Group B. Average number of obtained scores of nighttime frequency of urination decreased in the Group B from 4.6 (1.2) to 1.5 (1.4), and in the Group C from 3.9 (1.3) to 1.9 (0.5) (P ≤ 0.05 in both cases). According to the data of diaries of urination, the number of urgency episodes and nighttime frequency of urination in these groups significantly decreased too (P ≤ 0.05 in all cases). At the same time, the daytime frequency of urination decreased in all groups. According to the data of uroflowmetry, in patients of Groups B and C, post void residual urine volume significantly decreased; also, average flow rate of urination increased in these groups.

Fig. 1 shows the change of average number of scores of erectile, ejaculatory functions, and sexual life satisfaction for the whole period of the research. Erectile function slightly improved, but different doses of solifenacin after the therapy with dutasteride. Average values of “satisfaction” and “ejaculation” according to the questionnaire MSHQ-EjD got higher (P ≤ 0.05) in all three groups. Values of erectile domain did not change (P ≥ 0.05), but before the therapy they were at a high level and showed a normal initial state of erectile function in patients. The results of sexual function evaluation according to the questionnaire IIEF correlate with MSHQ-EjD data. Composite scores, received from the final survey in each group, were significantly higher than at the start (P ≤ 0.05). Evaluation of orgasmic function, satisfaction with intercourse got significantly higher in all three groups. However, in the Group A, values of overall satisfaction and libido did not differ from the initial ones (P ≥ 0.05). There were not significant differences between values of erectile domain before and after the therapy.

Table 3 provides functional status of lower urinary tract before and after the treatment. Average values of symptoms of obstruction at the end of the research did not significantly differ from the initial level. At the same time, storage symptoms distinctly decreased in Groups B and C. According to the data of I-PSS, the level of urgency significantly decreased after the therapy. The tendency of reversibility of hyperactivity symptoms in Groups B and C is also confirmed by OABq-AT data. Average number of obtained scores of urgency decreased in the Group B. Average number of obtained scores of nighttime frequency of urination decreased in the Group B from 4.6 (1.2) to 1.5 (1.4), and in the Group C from 3.9 (1.3) to 1.9 (0.5) (P ≤ 0.05 in both cases). According to the data of diaries of urination, the number of urgency episodes and nighttime frequency of urination in these groups significantly decreased too (P ≤ 0.05 in all cases). At the same time, the daytime frequency of urination decreased in all groups. According to the data of uroflowmetry, in patients of Groups B and C, post void residual urine volume significantly decreased; also, average flow rate of urination increased in these groups.

### Table 1
Sociodemographic, physiological characteristics, and parameters associated with health in men with benign prostatic hyperplasia and lower urinary tract symptoms (n = 326).

| Parameters                                  | Group A (N = 107) | Group B (N = 107) | Group C (N = 112) |
|----------------------------------------------|-------------------|-------------------|-------------------|
| Mean or N (SD or %)                          | Mean or N (SD or %) | Mean or N (SD or %) |
| Age                                          |                   |                   |                   |
| Married                                      |                   |                   |                   |
| Widowed/single                                |                   |                   |                   |
| Rural areas                                  |                   |                   |                   |
| Education                                    |                   |                   |                   |
| Secondary                                    |                   |                   |                   |
| Vocational                                   |                   |                   |                   |
| Higher                                       |                   |                   |                   |
| MSHQ-EjD, score sum                          |                   |                   |                   |
| IIEF, score sum                              |                   |                   |                   |
| OABq-AT, score sum                           |                   |                   |                   |
| Level of PSA (ng/mL)                         |                   |                   |                   |
| Uroflowmetry                                 |                   |                   |                   |
| PVR (mL)                                     |                   |                   |                   |
| Qmax (mL/sec)                                |                   |                   |                   |
| Diary of voiding                             |                   |                   |                   |
| Daytime frequency                            |                   |                   |                   |
| Nighttime frequency                          |                   |                   |                   |
| Urgency                                      |                   |                   |                   |
| Episodes of incontinence                     |                   |                   |                   |
| Prostate volume (mL)                         |                   |                   |                   |

### Table 2
Change in MSHQ-EjD and IIEF at the start and after treatment in men with benign prostatic hyperplasia (n = 326).

| Observation period | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment |
|--------------------|------------------|-----------------|------------------|-----------------|------------------|-----------------|
| MSHQ-EjD (in scores) |                  |                 |                  |                 |                  |                 |
| Overall rating     | 67.9 (12.4)       | 91.5 (10.4)*    | 72.4 (14.5)      | 102.6 (16.9)*   | 76.6 (16.3)      | 106.6 (15.6)*   |
| Erectile domain    | 13.9 (2.9)        | 16.5 (3.1)      | 12.7 (3.4)       | 14.6 (2.5)      | 14.0 (4.1)       | 16.3 (1.5)      |
| Ejaculation        | 19.5 (3.1)        | 25.4 (2.1)*     | 18.2 (2.2)       | 24.4 (1.5)*     | 17.4 (2.5)       | 25.3 (2.3)*     |
| Satisfaction       | 34.4 (4.1)        | 49.6 (7.6)*     | 41.5 (8.9)       | 63.6 (9.1)*     | 45.2 (7.4)       | 67.9 (9.4)*     |
| IIEF questionnaire (in scores) |            |                 |                  |                 |                  |                 |
| Overall rating     | 47.2 (4.8)        | 58.6 (4.0)*     | 49.6 (6.7)       | 65.0 (7.3)*     | 49.2 (5.7)       | 66.3 (5.2)*     |
| Erectile domain    | 24.4 (2.6)        | 25.8 (3.7)      | 26.2 (3.4)       | 26.9 (5.4)      | 24.9 (7.3)       | 25.7 (5.2)      |
| Satisfaction with intercourse              | 8.1 (1.3)         | 11.6 (1.5)*     | 6.7 (2.4)        | 12.6 (2.7)*     | 7.8 (2.1)        | 14.5 (2.5)*     |
| Orgasmic function | 5.1 (0.8)         | 7.4 (1.5)*      | 6.0 (1.4)        | 8.9 (0.8)*      | 5.4 (1.4)        | 8.8 (1.3)*      |
| Libido             | 4.7 (1.6)         | 7.1 (3.2)*      | 5.1 (0.8)        | 7.9 (1.1)*      | 5.0 (1.4)        | 8.2 (1.3)*      |
| Overall satisfaction | 4.5 (2.5)        | 6.7 (2.8)       | 5.6 (0.9)        | 8.7 (1.4)*      | 6.1 (1.2)        | 9.1 (1.4)*      |

IIEF, the international index of erectile function; I-PSS, International Prostate Symptom Score; MSHQ-EjD, Men’s Sexual Health Questionnaire—ejaculatory dysfunction; OABq-AT, Overactive Bladder Questionnaire—awareness tool; PSA, prostate-specific antigen; PVR, post void residual urine volume; Qmax, average flow rate; Qmax, maximum flow rate; SD, standard deviation.

SD is indicated in parentheses; significance of differences in the same group before and after treatment is denoted as * (P ≤ 0.05).
patients evaluated it as normal before the research. The number of scores of ejaculator function significantly increased after a month of observation; and at the end of the research, it significantly differs from the initial level in all three groups (P < 0.05).

The overall satisfaction of sexual function significantly increased in all groups at the end of the research. However, if the changes in Groups B and C at the end of the research almost did not differ (63.6 vs. 67.9, P > 0.05); then the difference between values in these groups and the Group C was significant. The correlation level between curves describing the change of number of scores of sexual satisfaction was r = 0.93, P ≤ 0.05 in Groups B and C.

The Fig. 2 shows the raise in the percentage of patients who did not have storage symptoms of LUT at different stages of the research. The number of such persons slightly changed (112/13/1, 15.9, P > 0.05) in the Group A after 1, 2, and 3 months of observation. On the contrary in the Groups B and C after each month of observation, their number increased simultaneously and reached 72.9% and 75.9% at the end of the research, respectively.

4. Discussion

The data from literature reviews demonstrate a strong relation and presence of common pathogenesis mechanisms between BPH, LUTS, and sexual dysfunction. Patients evaluated it as normal before the research. The number of scores of ejaculator function significantly increased after a month of observation; and at the end of the research, it significantly differs from the initial level in all three groups (P < 0.05).

The overall satisfaction of sexual function significantly increased in all groups at the end of the research. However, if the changes in Groups B and C at the end of the research almost did not differ (63.6 vs. 67.9, P > 0.05); then the difference between values in these groups and the Group C was significant. The correlation level between curves describing the change of number of scores of sexual satisfaction was r = 0.93, P ≤ 0.05 in Groups B and C.

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It is known that the presynaptic part of the parasympathetic nerve endings contains muscarinic receptors of one to four sub-species, which accordingly have an inhibitory effect on the release of acetylcholine into the intersynaptic space. On the membranes of muscle cells, norepinephrine secreted from synaptic terminals interacts with β3-adrenergic receptors, relaxing the detrusor. Acetylcholine counteracts adrenergic effects through M2 receptors, and causes contraction of muscle fibers by activating M3 receptors. At the same time, solifenacin is a specific competitive inhibitor of m-cholinergic receptors, mainly of the M3 subtype, due to which it reduces the tonus of the smooth muscles of the urinary tract.

It is also known that in the pathogenesis of OAB, disturbances in microcirculation in the detrusor and chronic inflammatory processes play an important role. It is assumed that a decrease in smooth muscle tonus under the influence of solifenacin restores, at least in part, normal microcirculation and increases oxygen access both to the detrusor receptor apparatus and to the conducting afferent and efferent pathways and intramural ganglia. Perhaps the restoration of normal trophism of the local area of the nervous system related to the detrusor is one of the processes leading to the rehabilitation of the evacuation function of the detrusor and a decrease in post void residual.

Some studies analyzing the action of solifenacin show no decrease in post void residual.33,34 However, there are recent studies confirming the results of the present study.35 Nevertheless, the authors understand the need for further in-depth study of this issue, which, perhaps, will make possible a clearer and more comprehensive explanation of the paradoxical decrease in post void residual associated with solifenacin.

Patients from Groups B and C who got standard and extra dose of solifenacin apart from tadalafil, changes in urodynamic and sexual function were somewhat different. The criteria of ejaculator and orgasmic functions, satisfaction and overall value of sexuality improved too in these groups. Besides, patients of these groups

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**Fig. 1.** Changes in indicators of Men’s Sexual Health Questionnaire in men with benign prostatic hyperplasia and lower urinary tract symptoms, who received combined treatment by dutasteride and solifenacin. Group A (N = 107)—acceptance of tadalafil 5 mg/d; Group B (N = 107)—acceptance of tadalafil 5 mg/d and solifenacin 10 mg/d; and Group C (N = 112)—acceptance of tadalafil 5 mg/d and solifenacin 20 mg/d.
evaluate the function of sexual desire much higher. However, the storage symptoms including urgency, nighttime frequency of urination/nocturia decreased dramatically in the patients of these groups if compared with the Group A. Significant decrease of these symptoms level occurred after 1 month of therapy. Furthermore, till the end of the research, the level of these symptoms in Groups B and C continued to decrease, but the average values did not differ. The number of patients with absence of hyperactivity was significantly higher after 2 and 3 months of observation if compared with the Group A, but also did not dramatically differ in these groups among themselves. The achieved results correlate with data of Maeda et al., who says that assigning of solifenacin after the therapy with dutasteride may lead to the improvement of LUT persistent symptoms.

On analyzing the results, the authors noticed that erectile function values, in spite of 3-month therapy with tadalafil, did not significantly improved. However, the erectile component of sexual function was almost not affected in many patients of this research after the course of dutasteride therapy. Patients complained of suppressed libido, sexual satisfaction, reduced sperm volume, and body fatigue. These functions restored because of tadalafil. Therefore, the absence in changes of erectile function is seemed to be normal.

In this research, the authors did not study remote results of combined therapy of LUT persistent symptoms after the cancellation of medications. They suppose that long simultaneous tadalafil and solifenacin therapy may cause additional side effects and lack of adherence to treatment because of cognitive disorders in men older than 65 years. These circumstances certainly limit the importance of this study. They also did not study the monotherapy of sexual disorders and LUTS with doubled solifenacin. However, there are single notes indicating that even standard doses of this medication are effective after taking dutasteride. These problems can be a direction to further researches.

To the authors mind, the obtained data can make a contribution to the assessment of effectiveness and safety of combined treatment of LUTS and sexual dysfunctions in patients with BPH after the basic therapy with dutasteride and can be helpful to practicing urologists, andrologists, endocrinologists, sexologists, and physicians of related areas.

5. Conclusion

Monotherapy with tadalafil in men with BPH and LUTS after dutasteride enables to decrease the sexual dysfunction except the storage symptoms of LUT. Sexual satisfaction in groups having assigned combined therapy significantly increases than in groups having assigned monotherapy with tadalafil. Combined therapy with tadalafil and solifenacin dramatically decreases urgency, nighttime frequency of urination, and nocturia; however, the average value of remaining symptoms of obstruction does not change. Combined therapy with tadalafil and solifenacin also reduces the number of people with LUTS. The effectiveness of standard and doubled dose of solifenacin assigned together with tadalafil to control the storage symptoms and sexual dysfunction does not significantly differ.

Compliance with ethical standards

This research was funded by the authors at their own expense.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest

All authors have no conflict of interest to declare.

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