Efficacy of combination of daily tadalafil and solifenacin in patients with storage symptom predominant lower urinary tract symptoms

Depolama semptomu baskın alt üriner sistem semptomu olan hastalarda günlük tadalafil ve solifenasin kombinasyonunun etkinliği

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Özet

Amaç: Depo semptomları baskın olan benign prostat hiperplazi hastalarında tadalafil 5mg+solifenasin 5mg kombinasyonunun alt üriner sistem semptomları (AÜSS) ve erektil fonksiyonlar açısından etkinliğini değerlendirmek.

Gereç ve Yöntemler: Ocak 2019 ile Aralık 2021 tarihleri arasında AÜSS ile başvuran ve depolama semptomları baskın olan 40 yaş üstü erkek hastalar çalışmaya dahil edildi. Hastalara günlük tadalafil 5mg ve solifenasin 5mg tedavisi başlandı. AÜSS için aşırı aktif mesane semptom skoru (OABSS), uluslararası prostat semptom skoru (IPSS) ve erektil fonksiyon için uluslararası erektil fonksiyon indeksi-erektil fonksiyon (IIEF-EF) anketleri kullanıldı. Üç günlük mesane günlüğü ile günlük idrar sıklığı, noktüri, sıkışma ve idrar kaçırma sıklığı analiz edildi. On iki hafta sonra hastaların IPSS, OABSS ve IIEF-EF skorları değerlendirildi.

Bulgular: Hastaların 12 haftalık tedavi öncesi ve sonrası semptom skorları ve mesane günlükleri karşılaştırıldığında, IPSS skorlarında (hem işeme, hem depolama, hem de toplam) anlamlı azalma (her biri için p<0,001), IIEF-EF skorlarında anlamlı artış (p<0.001) ve Qmax değer yükselmesinde anlamlı artış gözlendi. Mesane günlükleri karşılaştırıldığında, tadalafil+solifenasin tedavisi sonrası 12. ayda gündüz işeme sayısı, noktüri sayısı ve sıkışma sayısı azaldı (p<0,001).

Sonuç: Günde 5 mg tadalafil ve 5 mg solifenasin kombinasyonu, depolama semptomları baskın AÜSS/ED olan erkek hastalar için etkili ve güvenli bir tedavidir.

Anahtar Kelimeler: benign prostat hiperplazisi, depolama, tadalafil, solifenasin, erektil fonksiyon

Abstract

Objective: To evaluate the efficacy of tadalafil 5mg+solifenacin 5mg combination in terms of lower urinary tract symptoms (LUTS) and erectile functions in benign prostate hyperplasia patients with predominant storage symptoms.

Material and Methods: Male patients over the age of 40 who presented with LUTS with predominant storage symptoms between January 2019 and December 2021 were included into the study. Daily tadalafil 5mg and solifenacin 5mg treatment were started to the patients. Overactive bladder symptom score (OABSS), international prostate symptom score (IPSS) for LUTS, and international erectile function index-erectile function (IIEF-EF) questionnaires were used for erectile function. Frequency of daily urinary frequency, frequency of nocturia, urgency and urinary incontinence were analyzed with a three-day bladder diary. Twelve weeks later, IPSS, OABSS and IIEF-EF scores of the patients were evaluated.

Results: When the symptom scores and bladder diaries of the patients before and after 12 weeks of treatment were compared, significant decrease in IPSS scores (both voiding, storage and total) (p<0.001 for each), significant increase in IIEF-EF scores (p<0.001), and significant increase in Qmax value elevation was observed. When the bladder diaries were compared, the number of daytime micturitions, the number of nocturia and the number of urgency decreased in the 12th month after tadalafil+solifenacin treatment (p<0.001).

Conclusion: The combination of tadalafil 5mg and solifenacin 5mg daily is an effective and safe treatment for male patients with storage symptoms predominant LUTS/ED.

Keywords: benign prostate hyperplasia, storage, tadalafil, solifenacin, erectile function

The study was approved by Ethics Committee of University of Health and Sciences Şişli Hamidiye Etfal Training and Research Hospital (Approval No: 2089, Date: 2021/06/07). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

In aging men benign prostatic hyperplasia (BPH) is very common and it is a benign enlargement of prostate tissue and is caused by proliferation of prostate epithelial and stromal cells (1). The lower urinary tract symptoms (LUTS) associated with BPH, which greatly affect men's quality of life (QoL), include storage, voiding, and post-voidal symptoms (2). In many studies, it has been reported that nocturia, urgency, increased frequency of day and night urination, sexual dysfunction, and urge incontinence are common in men with BPH, as well as voiding symptoms (3,4).

α1-adrenergic blockers (alpha blockers), phosphodiesterase type-5 inhibitors (PDE-5 inh.), 5α reductase inhibitors (5ARI) and antimuscarinic/beta-3 adrenergic agents are used in the medical treatment of LUTS due to BPH [5,6]. With the combined use of these drugs, their efficacy increases, and their side-effect profile expands. Timing the treatment efficacy well and adjusting the doses of medical treatments to predict possible side effects increases the success of combination therapy [7].

Tadalafil, a PDE 5 inhibitor, specifically degrades cGMP and restores its smooth muscle relaxant effect. Tadalafil positively affects the lower urinary system (i) by decreasing the smooth muscle tone in the prostate, urethra, and bladder neck, (ii) by increasing the lower urinary tract blood flow by decreasing the vascular smooth muscle tone, (iii) by inhibiting the bladder afferent nerve activity (C- and Aδ-fibers). and (iv) reduction of inflammation and fibrosis through inhibition of interleukin-8 and Rho-kinase [8-10].

Solifenacin, an antimuscarinic agent, is a muscarinic receptor blocker that predominantly acts on the M3 subtype. It reduces bladder detrusor hyperactivity by suppressing acetylcholine activation [11]. As with all anticholinergic medications, dry mouth and constipation are most common side effects of solifenacin. In addition, it requires careful use in BPH patients because of the risk of voiding difficulty and increasing the post-void residual urine [12].

Currently, the study evaluating the effect with the combination of PDE5-inhibitor and antimuscarinic drugs is limited. The aim of present study was to evaluate the efficacy of tadalafil 5mg+solifenacin 5mg combination in terms of LUTS and erectile functions in BPH patients with predominant storage symptoms.

MATERIAL AND METHODS

Ethics approval of the study was obtained from the Instutional Ethical Reviewer Board, approval number 2089. Male patients over the age of 40 who presented with LUTS with predominant storage symptoms between January 2019 and December 2021 were included in the study. Demographic data of the patients were recorded. International prostate symptom score (IPSS), overactive bladder symptom score (OABSS) for LUTS, and international erectile function index-erectile function (IIEF-EF) questionnaires were used for erectile function. Frequency of daily urinary frequency, frequency of nocturia, urgency and urinary incontinence were analyzed with a three-day bladder diary. Post void residual urine volume and prostate volume (PV) (PVR) were measured by transabdominal ultrasound. Prostate specific antigen (PSA) value (ng/mL) of the patients was recorded. Maximum urine flow rate (Qmax) was evaluated with uroflowmetry.

The patients were started on daily tadalafil 5mg and solifenacin 5mg treatment. Twelve weeks later, IPSS, OABSS and IIEF-EF scores of the patients were evaluated. Bladder diary, uroflowmeter and PVR measurements were recorded. Change and satisfaction rates were compared before and after 12 weeks of treatment. Side effects observed during the treatment were noted.

Inclusion criteria: patients with mild to moderate erectile dysfunction (IIEF-EF between 12 and 21), patients with IPSS score >7, patients with Q max <15.

Exclusion criteria: PVR>50 ml, bladder neck sclerosis, neurogenic bladder, urethral stricture, active urinary tract infection, history of prostate cancer, use of 5ARI, nitrate use, history of unstable angina pectoris, history of renal hepatic failure, narrow-angle glaucoma patients, patients with myasthenia gravis.

The IPSS questionnaire is an inquiry form consisting of 7 questions [13]. The score obtained from each question in the scale is between 0-5. The total score is between 0-35 and scores of 7 and above are interpreted in favor of LUTS.

The IIEF-EF inquiry form includes questions 1-5 and 15 of the IIEF, which consists of 15 questions [14]. A maximum of 30 points can be obtained in the survey, which is organized according to five-point Likert scoring. 1st,3,5th of IPSS. While the questions are about excretion 2.,4. And 7. Questions are about the storage function. A total score of 21 and below was evaluated in favor of ED [15]. Turkish validation made by Turunç et al. [16].

OABSS is a 4 -question survey used to evaluate the extremely active bladder symptoms [17]. A total of 0-15 points can be obtained from the questionnaire and 3 points and above are indicated as OAB. Language validation was made by Culha et al. [18].

Statistical Analysis

Data analysis was done with SPSS 25.0 (IBM, USA). The homogenity of datas were evaluated with the Kolmogorov-Smirnov test. The comparison the parameters before and after the treatment performed with Paired-samples t-test and Fisher's exact test. Significant p value was determined as $p<0.05$.

RESULTS

A total of 132 patients were included in the study. Ten of them were excluded from the study because they were excluded from follow-up, and 1 patient was excluded due to intolerable side effects (constipation), and the study was terminated with 121 patients. The patients' mean age was 47.8±12.3, and the mean BMI was 27.9±8.7 kg/m2. The mean IIEF-EF score of the patients was 13.2±6.3, the mean OABSS was 8.4±2.4, the IPSS-Voiding mean was 5.3±2.2. The mean IPSS-Storage was 13.1±1.7, the mean IPSS total score was 18.4±2.6. The mean PSA value of the patients was 1.1±0.6 ng/ml (Table 1).

When the symptom scores and bladder diaries of the patients before and after 12 weeks of treatment were compared, significant decrease in IPSS scores (both Voiding, Storage and total) ($p<0.001$ for each) significant increase in IIEF-EF scores ($p<0.001$) significant increase in Qmax value elevation was observed.

When the bladder diaries were compared, the number of daytime micturitions, the number of nocturia and urgency decreased in the 12th month after tadalafil+solifenacin treatment ($p<0.001$).

In the PMR measurement, at the end of the 12th week, significantly more residual urine remained in the patients (10.0 (10-30) vs. 20.0 (10-50); $p<0.001$) (Table-2).

Treatment-related side effects were seen in 19% of the patients. Among the patients participating in the study, dry mouth developed in 9 patients (7.4%), constipation in 7 patients (5.8%), dyspepsia in 4 patients (3.3%), and muscle pain in 3 patients (2.5%). Only 1 of these patients could not tolerate the treatment due to constipation (Table-3).

Table 1. Demographic characteristics of the patients

	Mean±SD	Min-Max
Age (years)	47.8±12.3	40-79
BMI (kg/m^2)	27.9±8.7	22.2-36.4
PSA (ng/dL)	1.1±0.6	0.3-3.1
IIEF-EF	13.2±6.3	0-25
OABSS	8.4±2.4	4-14
IPSS-Voiding	5.3±2.2	1-9
IPSS-Storage	13.1±1.7	10-17
IPSS-Total	18.4±2.6	11-22
Qmax	7.3±2.3	3-12
PVR (ml)	14.9±13.2	0-40

***BMI:** body mass index, **PSA:** prostate specific antigen, **IIEF-EF:** international erectile function index-erectile function, **OABSS:** overactive bladder symptom score, **IPSS:** international prostate symptom score, **PVR:** post void residue.*

Table 2. Comparison of data before and after tadalafil + solifenacin treatment

	Before Treatment		After treatment		p value
	Mean	SD	Mean	SD	
IIEF-EF	13.2	6.3	18.9	6.7	<0.001
OABSS	8.4	2.4	3.7	3.1	<0.001
PSA (ng/dL)	1.1	0.6	1.1	0.6	0.954
IPSS-Voiding	5.3	2.2	4.4	1.8	<0.001
IPSS-Storage	13.1	1.7	8.2	3.7	<0.001
IPSS	18.4	2.6	12.6	4.1	<0.001
Qmax	7.3	2.3	8.3	2.9	<0.001
PVR (ml), median (IQR)	10 (10-30)		20 (10-50)		<0.001

IIEF-EF: *international erectile function index-erectile function,* ***OABSS:*** *overactive bladder symptom score,* ***PSA:*** *prostate specific antigen,* ***IPSS:*** *international prostate symptom score,* ***PVR:*** *post void residue*

Table 3. Side effects of the patients

Side Effects	n (%)
Dry Mouth	9 (7.4)
Constipation	7 (5.8)
Dyspepsia	4 (3.3)
Muscle Pain	3 (2.5)

DISCUSSION

The present study showed that, daily tadalafil 5mg and solifenacin 5mg treatment in male patients with storage symptoms predominant LUTS/ED had positive effects on both the LUTS symptom scores of the patients and positive effects on the bladder diary data, while it was effective in restoring erectile functions.

Guidelines recommend the addition of anticholinergic/beta 3 adrenergic agent to alpha blocker therapy in LUTS cases with predominant storage symptoms [19]. In addition, the efficacy and safety of daily use of PDE-5 inhibitors were found to be like alpha-blockers, and use of daily tadalafil 5 mg is recommended in patients with LUTS/ED [20]. In recent years, studies on the use of various combinations in the treatment of BPH/LUTS have been increasing. These combinations include treatments such as alpha blocker + 5α-reductase inhibitors (5-ARI), 5-ARI + PDE-5 inhibitors, alpha blockers, and anticholinergics. There are limited studies in the literature investigating the daily use of tadalafil and solifenacin as a safe and effective treatment [12]. In our study, tadalafil and solifenacin combination therapy was given for 12 weeks to LUTS patients with predominant storage symptoms and ED.

Tadalafil, with its mechanism of action, shows improvements in both urodynamic results and symptom scores and in monotherapy in patients with LUTS/ED. Unlike alpha-blockers, tadalafil acts to increase nitric oxide and cGMP activity, triggering detrusor muscle relaxation and eliminating functional obstruction [8,21]. In our study, significant improvements were found in the IPSS-Excretion related scores according to the initial symptoms of the patients. In addition, the significant increase in Qmax also shows the effect of tadalafil on functional obstruction.

Although the effect of alpha-blockers on LUTS-storage symptoms is not clear, it has been shown to affect storage symptoms by inhibiting urethral smooth muscle contraction [22]. Tadalafil, on the other hand, improves storage symptoms by reducing vascular smooth muscle tonicity, increasing blood flow in the pelvic region, and inhibiting affer-

ent nerves that stimulate the bladder [9,10]. In addition, its use together with solifenacin, an anticholinergic agent that inhibits bladder detrusor contractions, shows that there were significant improvements in the storage symptoms of the patients in our study. In addition, he defends the hypothesis that the decrease in the number of nocturia is also the effect of combined use.

Although the use of anticholinergics in combination with alpha-blockers has shown greater benefit for storage symptoms than alpha-blocker monotherapy, the incidence of voiding difficulty and increased residual urine is increased due to detrusor inhibition [23]. In the study of Urakami et al, they detected 16% urinary retention in the group receiving tamsulosin and solifenacin, and they found that PMR increased from 19 ml to 61 ml after 3 months of treatment [12]. In our study, although the PMR volumes of the patients receiving tadalafil and solifenacin were statistically significant (16 vs 20, $p<0.001$), no patient with clinical urinary retention was detected. This shows that the effect of tadalafil on LUTS storage functions is realized by a different mechanism than alpha-blockers and does not cause urinary retention.

Changes in nitric oxide levels in the pelvis and prostate and the neurogenic effect of this change; smooth muscle contractility, increase adrenergic tone in autonomic hyperactivity/metabolic syndrome, upregulation of the rho kinase / endothelin pathway induced by obstruction resulting in increased smooth muscle tonicity, and coexistence of ED in LUTS patients due to pelvic atherosclerosis in metabolic syndrome [24-26]. Concomitant treatment of these two symptoms by a single agent was investigated, and daily use of tadalafil was found to improve both LUTS and ED in LUTS/BPH patients [27-28]. Especially with the improvement in erectile functions, its effect on LUTS-storage symptoms at least as much as an anticholinergic makes its use widespread. It is known that tadalafil has an effect of 17-35% on IPSS scores [29]. However, this decrease is reduced in patients with predominant storage symptoms. In our study, tadalafil was used together with solifenacin, an anticholinergic, and approximately 40% improvement was achieved in the storage symptoms of the patients. In addition, a significant increase was achieved in the IIEF-EF scores of the patients.

Depending on the combined agents used, the incidence of side effects was found to be 19%. Concomitant use of tadalafil with alpha-blockers may decrease blood pressure and therefore caution should be exercised during its use [30]. However, dizziness or lightheadedness due to low blood pressure was not detected in the use of solifenacin together with tadalafil. dry mouth and constipation, which are the most common side effects, are thought to be due to solifenacin. However, only one patient was excluded from the study due to side effects.

There are some limitations of the study. The first of these is the lack of long-term follow-up of the patients. Another limitation is that tadalafil and solifenacin were not evaluated in separate groups and a comparison could not be made. The combination of tadalafil with an alpha-blocker group is also not included. Conducting the study as a single arm is also among the limitations. However, the information obtained at the end of the study will shed light on the future and will be the precursor of future randomized placebo-controlled studies.

CONCLUSION

The combination of tadalafil 5mg and solifenacin 5mg daily is a safe and effective theraphy for male patients with storage symptoms predominant LUTS/ED. Especially in patients suffering from storage functions, this combination therapy will be a good alternative if resistance is encountered in monotherapy. Prospective randomized controlled studies with large participation are needed to evaluate the efficacy of daily tadalafil+solifenacin treatment.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

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

Ethical Approval

The study was approved by University of Health and Sciences Şişli Etfal Training and Research Hospital Clinical Research Ethics Committee (Approval Number: 2089, Date: 2022/06/07) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Hacıislamoğlu A, Data acquisition; Hacıislamoğlu A, Data analysis and interpretation; Yavuzsan AH, Drafting the manuscript; Hacıislamoğlu A, Yavuzsan AH, Critical revision of the manuscript for scientific and factual content; Hacıislamoğlu A, Yavuzsan AH, Statistical analysis; Yavuzsan AH, Supervision; Hacıislamoğlu A, Yavuzsan AH.

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